An exploration of deprescribing barriers and facilitators for older patients in primary care in Ireland – the potential role of the pharmacist

Christina Råe Hansen MPharm

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Head of School

Professor Stephen Byrne

Supervisors

Professor Stephen Byrne

Professor Denis O'Mahony

Professor Patricia M. Kearney

Doctor Laura J. Sahm

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Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism.

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List of abbreviations

ACE	Angiotensin Converting Enzyme
ACOVE	Assessing Care Of Vulnerable Elders
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
ANZCTR	Australian New Zealand Clinical Trials Register
aOR	Adjusted Odds Ratio
ATC	Anatomical Therapeutic Chemical
BCT	Behaviour Change Techniques
BCTTv1	Behaviour Change Technique Taxonomy version 1
BMI	Body Mass Index
BNF	British National Formulary
CA	Content Analysis
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DPS	Drug Payment Scheme
DRP	Drug-Related Problem
GEE	Generalized Estimating Equations
GI	Gastrointestinal
GMS	General Medical Scheme
GP	General Practitioner
HMR	Home Medicine Review

HRQoL	Health-Related Quality of Life
HSE	Health Service Executive
ICTRP	International Clinical Trials Registry Platform
INR	International Normalised Ratio
IQR	Inter Quartile Range
ISRCTN	International Standard Registered Clinical/social sTudy Number
LTC	Long-Term Care
MAI	Medication Appropriateness Index
MeSH	Medical Subject Headings
MIMS	Monthly Index of Medical Specialties
MRP	Medication-Related Problems
MTM	Medication Therapy Management
MUR	Medicine Use Review
NIC	Net Ingredient Cost
OECD	Organisation for Economic Cooperation and Development
OpenSIGLE	Open System for Information on Grey Literature in Europe
OPERAM	OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly
OR	Odds Ratio
OTC	Over-The-Counter
PD	Pharmacodynamic

PhIP	Pharmacist Independent Prescriber
PIM	Potentially Inappropriate Medicine
PIP	Potentially Inappropriate Prescribing
PK	Pharmacokinetic
PPI	Proton Pump Inhibitor
PPO	Potential Prescribing Omission
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMPT	PRescribing Optimally in Middle-aged People's Treatment
PSI	Pharmaceutical Society of Ireland
QoL	Quality of Life
RCT	Randomised Controlled Trial
SD	Standard Deviation
SENATOR	Software ENgine for the Assessment and optimization of drug and non-drug Therapy in Older peRsons
START	Screening Tool to Alert to Right Treatment
STOPP	Screening Tool of Older People's Prescriptions
STOPPFrail	Screening Tool of Older Persons Prescriptions in Frail adults
TDF	Theoretical Domains Framework
TILDA	The Irish Longitudinal Study on Ageing
UK	United Kingdom

US	United States
WHO	World Health Organization

Publications resulting from this thesis

Hansen CR, Byrne S, O'Mahony D, Kearney PM, Sahm LJ. Qualitative analysis of community pharmacists' opinions on their involvement in reducing potentially inappropriate prescribing. Eur J Clin Pharmacol. 2019;75(2):265-74.

Hansen CR, O'Mahony D, Kearney PM, Sahm LJ, Cullinan S, Huibers CJA, Thevelin S., Rutjes AWS, Knol W, Streit S, Byrne S. Identification of behaviour change techniques in deprescribing interventions: a systematic review and meta-analysis. Br J Clin Pharmacol. 2018;84:2716-28.

Hansen CR, Byrne S, Cullinan S, O'Mahony D, Sahm LJ, Kearney PM. Longitudinal patterns of potentially inappropriate prescribing in early old-aged people. Eur J Clin Pharmacol. 2017;74(3):307-13.

Hansen CR, Cullinan S, Byrne S, O'Mahony D, Kearney PM, Sahm LJ. Challenges of deprescribing in the multimorbid patient. Eur J Hosp Pharm. 2016;24:43-6.

See Appendix I for a list of additional publications, published abstracts, conference attendances and completed postgraduate taught modules.

Thesis abstract

Introduction

The older population, often defined as people aged ≥ 65 years is growing. With older age, the risk of multimorbidity (commonly defined as the presence of ≥ 2 chronic conditions) increases together with the use of a high number of daily medicines or polypharmacy (≥ 5 daily medicines). These are two risk factors of poor health outcomes in older people, putting them at greater risk of experiencing potentially inappropriate prescribing (PIP), adverse drug events (ADEs) and poor quality of life (QoL). To reduce polypharmacy and the associated risk, the number of medications used per patient needs to be reduced by means of carefully considered deprescribing when appropriate. Deprescribing is the process of discontinuing inappropriate medications with the goal of optimising pharmacotherapy and improving health outcomes. Existing research is limited to support the effective and practical implementation of deprescribing. Pharmacists are trained to evaluate PIP and their knowledge and skills may benefit the process of deprescribing. As the majority of prescribing takes place in primary care, it is logical that GPs would liaise with community pharmacists in a collaborative intervention/practice to deprescribe. Therefore, the aim of this thesis was to identify the challenges and potential benefits of deprescribing, and to explore the potential involvement of the community pharmacist in deprescribing.

Methods

A study design comprising both quantitative and qualitative designs was used. Firstly, a narrative literature review summarised the existing qualitative and quantitative literature on healthcare professionals' views on deprescribing (Chapter 2). Secondly, a systematic literature review and meta-analysis was conducted according to the PRISMA guidelines, to determine the effectiveness of existing deprescribing interventions (Chapter 3). Thirdly, to determine if PIP is predominantly a phenomenon of later life or whether it has its origins in early old age, a secondary

data analysis of a population-based primary care cohort of patients aged 60-74 years was done over a continuous five-year period (Chapter 4). Fourthly, total net ingredient cost (NIC) was estimated for the PIMs identified in the same population-based primary care cohort studied in Chapter 4 in the period from 2016 to 2018, and a potential cost reduction of the routine application of the STOPP criteria was determined (Chapter 5). Fifthly, the views of community pharmacists on their role in medication optimisation and reducing PIP was examined in a qualitative interview study (Chapter 6). Finally, the views of general practitioners (GPs) and community pharmacists, on their collaboration and the potential role of the pharmacist in deprescribing, were explored in a qualitative study (Chapter 7).

Results

The narrative review (Chapter 2) included 23 studies. The content analysis identified five broad themes describing the barriers and facilitators of deprescribing in older patients with multimorbidity: *(i) interprofessional relationships, (ii) medication review, (iii) information, (iv) the patient* and *(v) environmental needs.* The systematic literature review (Chapter 3) summarised findings of 31 studies of which 30 studies were included in the behaviour change component (BCT) analysis and 21 were included in the meta-analysis. The meta-analysis showed that deprescribing interventions are effective in reducing the number of drugs and inappropriate prescribing in older people, although the evidence is mixed. BCT clusters more frequently present in studies reporting intervention effectiveness compared to studies reporting no effectiveness were: *goals and planning; shaping knowledge; natural consequences; comparison of behaviour*; *comparison of outcomes; regulation; antecedents; and identity.* A total of 974 participants aged 60-74 years were included in the secondary analysis in Chapter 4 and data from baseline to year 5 of follow-up was studied. The odds of being exposed to potential prescribing omissions (PPOs) and potentially inappropriate medications (PIMs) increased significantly during years of follow-up (OR 1.08, 95% CI 1.07 1.09 and OR 1.04 95% CI 1.03, 1.06, respectively). A higher number of medicines and new diagnoses were associated with the increasing trend in both PPO and PIM prevalence. The cost-

analysis in Chapter 5 was based on the same population studied in Chapter 4 (n=974) but in the period from 2016 to 2018 (year 6 to year 8 of follow-up). The study showed a high prevalence of PIMs (46%-52%) during the study period. The total net ingredient cost of PIMs identified ranged from €87,152.04 at year 6 and €86,112.48 at year 8 of follow-up. The mean cost of PIM per participant per year was between €178.68 - €179.64 during the three years of follow-up. The qualitative interviews (Chapter 6) included a total 18 community pharmacists. Seven domains from theoretical domains framework (TDF) were identified as relevant to PIP reduction and pharmacist involvement: *(i) beliefs about capabilities, (ii) environmental context and resources, (iii) knowledge, (iv) social influences, (v) social professional role and identity, (vi) memory, attention and decision processes,* and *(vii) reinforcement.* In Chapter 7, a total of 26 interviews were conducted with GPs and community pharmacists. The thematic content analysis identified five themes relevant to the role of the community pharmacist in deprescribing: *(i) the GP's role in deprescribing – is there room for a pharmacist?, (ii) working relationship, (iii) the role of the pharmacist in deprescribing, (iv) patients' interaction with the healthcare system,* and *(v) environmental factors*.

Conclusions

The findings presented in this thesis provide a detailed understanding of the potential role of the community pharmacist in deprescribing. The prospective benefits of and the barriers and facilitators to pharmacists involved in this role of deprescribing have also been elucidated. This thesis contributes to the existing literature, through the provision of novel research that demonstrates the need for the community pharmacist support within the context of deprescribing. The community pharmacist is in a favourable position to bring pharmaceutical care closer to the patient through patient counselling and close collaboration with the patient's GP. To integrate the role of the pharmacist with that of the GP in practice, there is a need to consider the mode of pharmaceutical service delivery and to expand the collaboration between community pharmacists and GPs by building on existing

positive experiences of collaboration and clearly define the role and responsibilities of the community pharmacist in deprescribing.

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1 Thesis introduction

1.1 The ageing population

"*Old age isn't so bad, when you consider the alternative*"; this quotation was attributed to Maurice Chevalier, which is relevant to the present time when people are living longer and as a result, the older population is growing. This demographic change is evident nationally and internationally in reports by the Department of Health in the Republic of Ireland [1], the Organisation for Economic Co-operation and Development (OECD) [2] and the World Health Organization (WHO) [3]. Across the OECD countries, including Ireland, the population aged 65 years or older comprised less than 9% of the population in 1960, 17% in 2015 and is expected to comprise up to 28% of the population in 2050 [2]. Looking at the growth characteristics of the population at a more advanced old age (≥80 years), on average nearly 5% of the population was 80 years or older in 2015 across the OECD countries, and is expected to reach 10% or more by 2050 [2]. The two main drivers for the ageing population are increasing life expectancy and decreasing fertility rates [2, 3]. Improved survival of people at younger ages but also at older ages yields the observed longer life expectancy. This is largely the result of the global socioeconomic development that has taken place over the last 50 years with greater access to healthcare, more focus on healthier lifestyles and improved living conditions before and after people enter old age [3].

Longer life expectancy among the older population does not necessarily mean that these extra years are lived in good health [2]. In Europe, the average number of healthy life years in those aged 65 or more, is 9.3 years for men and 9.4 years for women [2]. In Ireland, women aged 65 years or more, have a life expectancy of 21.1 years and men of a similar age have a life expectancy of 18.4 years [1]. Of these extra years, Irish women and men at age 65 have an expected 12.3 / 11.4 healthy life years ahead, respectively [1]. It should be noted that the level of pressure on any healthcare system, attributable to advancing age, will be highly dependent upon the state of health of persons in old age. If people experience these extra healthy life years, they will feel better and enjoy life more, and their contribution to society may

be greater, whether it be within their family, within their local community or society at large [3]. Conversely, decline in health, whether in the form of loss of physical or mental capacity, brings greater challenges and increased need for health and personal care services which adds to the existing pressures on healthcare system resources [3]. Additionally, rising income among the general population increases expectations of higher quality of life in old age, which creates upward pressure on healthcare systems [2].

1.2 Multimorbidity

With advancing age, people are at greater risk of experiencing chronic conditions, and the proportion of people with multiple chronic conditions is expected to increase substantially over the coming decades [4-6]. Multimorbidity is the coexistence of multiple chronic conditions in an individual. The threshold for number of coexisting chronic conditions to constitute multimorbidity varies according to the definition used (see **Table 1-1**).

Table 1-1 Terms and definitions

Term	Definition and description of the term
Multimorbidity	Multimorbidity is the coexistence of multiple chronic conditions in an individual. The threshold for number of coexisting chronic conditions to constitute multimorbidity varies according to the definition used, from ≥2 condition [7-9] to ≥3 conditions [7]. The most commonly used definition defines a threshold of ≥2 chronic conditions [7-9]. Variations in definitions used and populations studied have provided prevalence estimates of multimorbidity ranging from 12.5% in people aged ≥18 years to 95% in older people aged ≥65 years [7, 10, 11].
Polypharmacy	Polypharmacy has been defined as the concomitant use of several different drugs by an individual [12-15]. Currently, no formally accepted numerical threshold for polypharmacy exist. Polypharmacy is sometimes referred to as the concurrent use of four or more regular medicines [15, 16] but more often the use of five or more regular medicines [12-14, 17-19]. The use of 10 or more regular medicines is often referred to as "*excessive polypharmacy*" or '*hyper-polypharmacy*' or '*major polypharmacy'* [12, 18, 19]. An alternative definition of polypharmacy is the use of more medications than are medically necessary [20], and the term polypharmacy often has a dual meaning in that it can mean the use of multiple medicines or the use of too many medicines.

Multimorbidity is associated with increased healthcare utilisation, greater levels of functional decline, reduced quality of life (QoL) and higher treatment burden [4, 11, 21, 22]. Treatment of chronic conditions comprises eight of the top eleven causes of hospital admissions in the United Kingdom (UK) and is a large burden to the UK healthcare system [23]. In Europe, 70%-80% of healthcare expenditure is related to managing chronic conditions [23]. In Ireland, the mean number of primary care consultations and hospital out-patient visits increase significantly with increasing numbers of chronic conditions [11] and multimorbidity comprises a significant

amount of the total healthcare costs for primary and secondary care among Irish patients aged ≥50 years [11].

When people become ill, one of the mainstays of management and treatment is medication, and thus the selection of appropriate pharmacotherapy in the older population is crucial [24, 25]. The coexistence of numerous chronic conditions in a single multimorbid patient challenges the traditional approach taken to treating individual conditions separately [9]. Having multiple chronic conditions and seeing multiple providers often results in a large number of medications and several different dosage regimens. This may be inconvenient and/ or difficult for the patient to manage [25, 26]. A higher number of medicines may further result in a higher risk of unsafe, or suboptimal, drug combinations, drug interactions and adverse drug events (ADEs) [26, 27]. Ironically, once an ADE has occurred, the response from the physician may be to prescribe another medication to ameliorate the ADE, a situation that is generally referred to as a "*prescribing cascade*" i.e. the prescribing of an additional medicine to offset an adverse effect of another [26]. A daily use of multiple medicines is thus a common phenomenon among multimorbid older people.

1.3 Polypharmacy

1.3.1 Prevalence

With the increasing number of multimorbid older people, the prevalence of polypharmacy (see definition in **Table 1-1**) among older people is also growing as well as the incident ratio over time [13, 14, 28]. Prevalence estimates of polypharmacy (≥5 daily medicines), and hyper-polypharmacy (≥10 daily medicines), have been reported across the world, with some estimates presented in **Table 1-2**.

Table 1-2 Prevalence of polypharmacy across countries (literature search in PubMed using search terms *polypharmacy, prevalence, cross-sectional.*

Country	Population age	Polypharmacy ≥5 medicines (% of study population)	Hyper-polypharmacy ≥10 medicines (% of population)
Sweden [12]	≥65 years	44%	12%
Spain [13]	≥65 years	22%	0.6%
Switzerland [17]	40-81 years	11%	1.4%
England [18]	≥50 years	35%	11%
Australia **[29]**	≥65 years	-	39%
The Netherlands **[30]**	≥20 years	27%	-
Canada **[28]**	45-69 years	32%	-
Ireland **[31-33]**	≥65 years	60%	22%
	45-64 years	30%	8%
	41-90 years	32%	22%
	≥65 years	46%[§]	14%[§]

[§]Polypharmacy was defined as 6-10 daily medicines and excessive polypharmacy was defined as ≥11 daily medicines.

In Ireland, several estimates of polypharmacy prevalence have been published, some of which are reported in **Table 1-2**. A report based on Irish national data has summarised that more than one in four (28%) people aged 52 years or older take five or more daily medicines with a higher prevalence among the older patient groups as illustrated in **Figure 1.1**. This prevalence of polypharmacy in Ireland has been significantly increasing from 22% in 2010 to 28% in 2013 [1]. Other studies reporting on Irish data have shown similar high prevalence estimates of polypharmacy, particularly in the older patient cohort (aged ≥65 years): the study by Moriarty et *al.* [34] showed that over the 15 year-period from 1997 to 2012, the percentage of people aged 65 years and older using polypharmacy (≥5 medicines) increased from 18% to 60% [34]. The study also reported a similar trend for excessive polypharmacy (≥10 medicines) increasing from 2% to 22% for the same time period and age group. Furthermore, this study showed that polypharmacy is not just the burden of the older population but is also present in the age group 45-64 years as well with similar

increasing trends from 1997 to 2012. In 1997, 8% of people aged 45-64 years took ≥5 medicines daily. In 2012, this number had increased to 30% [34].

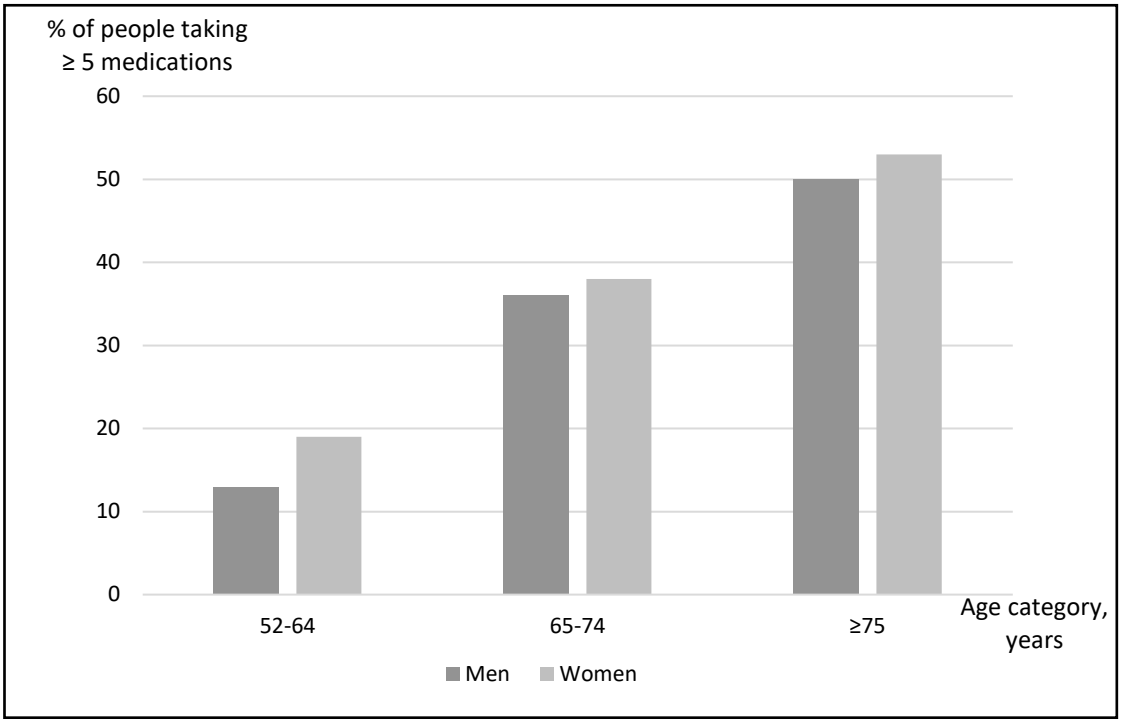

Figure 1.1 Percentage of men and women aged 52 years or older who are taking five or more medications in Ireland in 2012. The figure reports on data from The Irish Longitudinal Study on Ageing (TILDA) Wave 2 in 2012. TILDA participants were 52+ years in Wave 2 [1]

Groups of patients more likely to be exposed to polypharmacy are people with dementia and those with severe/profound intellectual disability (ID): the study by Walsh *et al.* [35] reported a prevalence of polypharmacy (≥5 medicines) in 84% in people with dementia compared to 77% in those without dementia [35]. The study by O'Dwyer *et al.* [32] reported that 47% of those aged 41 to 90 years with polypharmacy (5-9 medications) had severe/profound ID and 29% of those with severe/profound ID reported excessive polypharmacy (10 or more medicines). In contrast, less than 5% of those living independently were exposed to excessive polypharmacy [32].

1.3.2 Factors associated with polypharmacy

Several different parameters have been associated with the increase in polypharmacy prevalence and are summarised in **Table 1-3**.

Table 1-3 Factors shown to be positively associated with increasing prevalence of polypharmacy

Factor associated with increasing prevalence of polypharmacy	Description
– Chronic conditions and number of medicines	A higher number of chronic diseases and older age are both strongly, and positively, correlated with a higher number of daily medicines [12, 17, 18]. One study has shown that for each additional chronic disease there is on average a 0.95 increase in the number of daily drugs (95% CI 0.94-0.96) [12].
– Gender	Some studies have associated female gender with increasing prevalence of polypharmacy [12, 13, 17-19, 34].
– Obesity	Obesity and/or having a higher body mass index (BMI) have been shown to be positively associated with an increasing prevalence of polypharmacy [13, 17, 18].
– Smoking. – Being alone (divorced, separated or widowed.) – Having poorer self-rated health. – Having lower wealth and/or living in deprived areas.	Prevalence of polypharmacy has been positively associated with: smoking [17]; being alone (divorced, separated or widowed) [18]; having poorer self-rated health [18]; having lower wealth and/or living in deprived areas [18, 19].

1.3.3 Potential consequences of polypharmacy

Polypharmacy has been associated with numerous negative outcomes such as: drug-drug interactions, adverse drug reactions (ADRs), risk of falls, hospitalisation, poor

functional status, medication non-adherence, morbidity and mortality [12, 17, 20, 36]. The increased risk of ADEs in older adults with polypharmacy is the result of a number of factors, principally:

1. Higher number of medicines comes with a higher risk of drug-drug interactions.
2. Age-related physiological changes make older people more prone to ADEs as described in **Table 1-4.**
3. High prevalence of multimorbidity, described previously, associated with older age, increases the risk of drug-disease interactions [12].

In addition, polypharmacy is believed to cause unnecessary health expense to both the patient and the healthcare system, due to extensive drug sales and higher levels of adverse outcomes with a need for further drug treatment and healthcare utilisation [14, 20]. Polypharmacy has been shown to increase the overall medical care costs by up to 30% [20].

Previously, polypharmacy implied potentially inappropriate prescribing (PIP), but this is not necessarily true if the prescribed drugs have an appropriate clinical indication [36]. The use of multiple drugs in an individual can be both rational and safe and polypharmacy is also believed to provide major health benefits for older patients with multimorbidity [14]. However, healthcare providers must be aware of the fact that polypharmacy is a strong determinant of PIP in older people [37]. Ensuring appropriate polypharmacy is of considerable importance to ensure patient safety and to contain medication costs within the healthcare system [37, 38].

Table 1-4 Age-related physiological changes pertaining to pharmacokinetic and pharmacodynamic function.

Pharmacokinetic changes		
Absorption	i.	Decreased acidity and function of mucosal cells in the stomach is believed to potentially affect the absorption of some drugs that require an acidic environment [26].
	ii.	Altered motility of the gastrointestinal (GI) tract may negatively affect the absorption of oral medications, but the effects are proposed to be minimal due to the large surface area of the GI tract [26].
Distribution	i.	Reduction in total body water resulting in a smaller distribution volume and thus a higher and potentially toxic concentration of some drugs.
	ii.	Increase in the body fat percentage, which may prolong the effects of lipophilic drugs while prolonging the elimination half-life.
	iii.	Reduction in serum albumin resulting in less drug binding to serum proteins and more drug circulating in the serum with increasing risk of toxicity [26, 39].
Metabolism	i.	Hepatic blood flow and liver mass decreases with age and results in decreased first pass metabolism, resulting in more drug available in the bloodstream [39].
Elimination	i.	Renal function decreases with age resulting in prolonged half-life, and higher concentrations, of drugs or

Pharmacokinetic changes		
		metabolites. As most drugs are eliminated through the renal system, renal function should be a primary consideration when prescribing for older people [26, 39].
Pharmacodynamic changes		
Sensitivity	i.	Physiological changes to the organ systems of an older person are generally considered to increase sensitivity to drugs, and therefore, reduced doses are generally recommended when prescribing medications to this group [26, 39].

1.4 Potentially Inappropriate Prescribing (PIP)

1.4.1 Definition

Potentially inappropriate prescribing (PIP) comprises potentially inappropriate medicines (PIMs) and potential prescribing omissions (PPOs) and encompasses a number of suboptimal prescribing practices (see **Table 1-5**).

Table 1-5 Suboptimal prescribing practices described by the terms potentially inappropriate medicines (PIMs) and potential prescribing omissions (PPOs)

PIP	Suboptimal prescribing practices	
PIMs	(i)	Prescribing of a medicine in which the risk outweighs the benefit when there is a safer and/or more effective alternative available to treat the same condition [29, 40-42].
	(ii)	Prescribing of a medicine without a clear evidence-based indication [37].
	(iii)	Prescribing of a medicine that is not cost-effective [37].
	(iv)	Prescribing of medicine for longer periods than clinically indicated [29].Prescribing of medicine for longer periods than clinically indicated [29].
	(v)	Use of medicines that are likely to cause drug-drug interactions or drug-disease interactions [29].Use of medicines that are likely to cause drug-drug interactions or drug-disease interactions [29].
PPOs	(i)	Omissions of clinically indicated medications [41]. Omissions of clinically indicated medications [41].

1.4.2 Prevalence

Prevalence estimates of PIP vary greatly across countries, healthcare settings and studies with reported ranges of 2.9% to 38.5% [43], 11.5% to 62.5% [44], and 14.0% to 23.5% [45]. In Ireland, the PIM prevalence has been estimated to be 36% in the acute hospital setting [37] and 64.8% in the community setting [46] whilst the PPO prevalence has been reported to be 56.6% among the community-dwelling older Irish population [46]. This puts Ireland in a comparable situation to Northern Ireland [38] and Italy [47] with regards to PIP prevalence.

1.4.3 Adverse outcomes

Exposure to PIP puts older people at greater risk of drug-related morbidity and mortality and PIP has been linked to poorer health outcomes for the patients [37].

PIP has been associated with increased risk of ADEs among older people [48]. In Ireland, the likelihood of experiencing an ADE has been shown to increase significantly with PIP prevalence among older people, with 94% of people exposed to PIMs experiencing an ADE compared to 71% for those unexposed to PIMs [49].

Healthcare services utilisation is another important consequence of PIP prevalence among older people. In Ireland, Cahir *et al.* [49] reported a two-fold increased risk in the rate of visits to the hospital emergency department (IRR 1.85, 95% CI 1.32, 2.58) for those exposed to ≥2 PIPs [49]. Similarly, the study by Lau *et al.* [50] showed that older people prescribed PIM, have a 30% higher risk of being hospitalised, and a 21% higher risk of mortality, compared to those who are not [50].

Reducing polypharmacy and PIP in primary care may thus help lower the burden of ADEs, improve patient health outcomes and QoL whilst reducing healthcare utilisation and associated costs to the healthcare system, such as reduced prescribing budgets [49]. However, new strategies are needed.

1.4.4 Strategies to reduce PIP - the pharmacist

Pharmacist-led interventions have been suggested as an effective way of reducing PIP [51-53]. In 2012, a Cochrane review [54] concluded that medication reviews of patients conducted in close collaboration between pharmacists and physicians resulted in reductions in inappropriate prescribing either through substitution with appropriate medicines or discontinuation of PIMs [54, 55]. The Pharmacist-led Information technology Intervention (PINCER) trial [56] conducted in general practice in the UK, demonstrated these positive outcomes of a pharmacist support intervention. Participants in the intervention arm were at significantly lower risk of hazardous prescribing and inadequate blood-test monitoring of medicines compared to the control patients. In the PINCER trial, the intervention patients received a pharmacist-led information technology intervention (PINCER) composed of feedback, educational outreach and pharmacist support. The general practice received computer-generated prescribing feedback, and the pharmacist then met with the general practice team to discuss the feedback. The pharmacist was also available to support the practice team after the meeting [56]. Similarly, in Ireland,

the Optimizing Prescribing for Older People in Primary Care (OPTI-SCRIPT trial) [40] demonstrated that a multi-faceted pharmacist-led intervention in general practice reduces PIP. In this trial, pharmacists used academic detailing to coach GPs to review medicines together with their patients. The GPs were also given pharmaceutical treatment algorithms to further support the medicines reviews by suggesting alternative therapies to a PIP drug. At the end of the study, the percentage of patients with PIP was lower for the intervention group (52%) compared to the control group (77%), and the mean number of PIP drugs was also lower in the intervention group (0.7) than the control group (1.18) [40].

Integrating pharmacists into multi-disciplinary teams has been suggested as an effective method to reduce the Medication Appropriateness Index (MAI) scores in both the primary and secondary care settings [52, 53]. In the General-Practitioner-Pharmacist-Collaboration (GPPC) study [57] from New Zealand carried out in people aged ≥65 years, community pharmacists conducted a clinical medication review and met with the patient's GP to discuss recommended medication changes. Even though only 40% of pharmacist recommendations were implemented, the study showed that the mean MAI scores had improved significantly at 6 months of follow-up in the intervention group compared to the control group, and the difference in MAI-scores between the two groups was significantly different. In the intervention group the mean number of changes per patient was 3.1 at 6 months compared to 1.6 in the control group. The majority of changes in the intervention group comprised the discontinuation of a medicine (32%) whereas initiation of a medicine was the primary change in the control group (39%). This also resulted in a significantly higher number of initiated medicines in the control group compared to the intervention group [57]. The PINCER, OPTI-SCRIPT and GPPC trials all demonstrated that collaboration between general practitioners and pharmacists is a potential means of reducing hazardous and inappropriate prescribing..

With the increasing complexity of medicines management in the multimorbid older patient, the role of the pharmacist is more important than ever. In turn, greater emphasis is being placed on the integration of pharmacists to enhance patient access to healthcare services, minimise ADEs and help prevent drug-related hospital

admissions. The increasing demands for healthcare have created an opportunity for pharmacists to attain a more central role in medicines management [58, 59]. Today, pharmacists have gained a larger role in the provision of medicines management worldwide with the Home Medicine Review (HMR) in Australia [60], the Medication Therapy Management (MTM) services in USA [61] and the Medicines Use Reviews (MURs) in the UK [62], Italy [63]and New Zealand [64]. However, these reviews are not meant to be clinical reviews and prescribing appropriateness is not generally considered in these reviews, as pharmacists do not have clinical information available to them.

The role of the community pharmacist in Ireland is currently a role of managing the safe supply and rational use of medicines within the community setting. Community pharmacists are trained and expected to screen for potential interactions with other medicines (i.e. prescription, over-the-counter, herbal supplements etc.), to identify and help prevent adverse effects and to ensure that patients know how to take their medication correctly [65].

In recent years, the community pharmacy profession in Ireland has undergone a significant change. The Pharmacy Act 2007 introduced a new modern system for the profession underpinned by the Code of Conduct and the Core Competency Framework outlining the competencies expected of a practising pharmacist [65]. Following this Pharmacy Act in 2007 was the provision for new services to be directly available to patients from their community pharmacists. These services include; administering seasonal influenza vaccinations and emergency hormonal contraception. A new legislation from 2015 expanded the vaccination programme and allowed community pharmacists to administer emergency medicines to patients in life-threatening situations (including epinephrine (adrenaline), salbutamol, glyceryl trinitrate, glucagon and naloxone). Since 2010, all community pharmacies have a designated patient consultation room, which has enabled a more direct patient care in the pharmacy and has created a space for patients to discuss their medication with their pharmacist. Other innovations to community pharmacy practice in Ireland includes anticoagulation services in collaboration with the hospital haematologist [65]. Monitoring of disease

progression is a key part of chronic disease management, and these anticoagulation clinics in community pharmacies have been successful in Ireland, although on a smaller scale compared to New Zealand [66, 67]. These clinics have proven useful in moving services from the hospital setting to the primary care setting to increase patient access and reduce costs to the healthcare service [66, 67].

Today, in Ireland, changes to a prescription must be made by the medical practitioner, dentist or registered nurse prescriber. Legislation supporting pharmacist prescribing has been implemented in the UK, Canada and New Zealand with the aim to improve patient access to care, enhance safe and rational use of medicines and to utilise the source of the pharmacists [68]. A new legislation in Ireland from 2015 allowing trained pharmacists to supply and administer certain prescription only medicines to patients in the event of an emergency highlights the role that the pharmacist can play in directly treating the patients in the community in Ireland as well. These new responsibilities of the pharmacist role demonstrate that while pharmacists may have been over qualified and underutilised, the Government has realised their potential to support safer use of medicines and patient care [65].

Despite these services being available, further evidence is needed on clinical outcomes and the acceptability of these services to all stakeholders. In the UK, the MUR service has been available since 2005, but the value and acceptance of this service to the public has not yet been established [69]. In addition to patient barriers, the successful uptake of MURs is challenged by a lack of awareness among GPs of this service but also a lack of evidence supporting the effectiveness of MURs [69]. Overall, there is evidence to suggest that the involvement of pharmacists in reducing PIP is of benefit to patient care but barriers still persist to the successful integration of this pharmacist support [54, 70].

1.5 Deprescribing

1.5.1 Deprescribing - a new term

Since polypharmacy and PIP is a result of a large number of daily medicines taken by a patient, the solution to overcome this inappropriate use of medicines appears simple: reduce the number of medications a person takes through '*deprescribing*'

[71]. Deprescribing is a relatively new term that focuses the attention on stopping medications to improve outcomes and reduce risks of adversity relating to medication use [55]. Deprescribing is defined as '*the process of withdrawal of inappropriate medication by a healthcare professional with the goal of managing polypharmacy and improving outcomes*' [71]. The process aims to avoid denying safe and effective treatment to people whilst simultaneously eliminating the risks of people receiving unnecessary treatment which is unlikely to benefit them or may increase the risk of harm [72]. This definition describes the true meaning of deprescribing, namely to undo the prescribing of a medication by discontinuing it. However, this may be a reductive definition. It could be said that reducing the dosage or frequency of a medication or switching to a safer medication are actions undertaken with the specific purpose of eliminating the risks of people receiving unnecessary treatment and thus belongs to the deprescribing process as well.

Deprescribing is a complex process of eliminating inappropriate medication usage by weighing up the risks and benefits of a medication in an individual patient but it is equally a process that may benefit from taking into account patients' individual care goals, functional status and life expectancy [73].

In practice, the process has been described as follows:

(1) consider all medications currently taken by a person and the indication for each medication,

(2) identify and prioritise the medication(s) to be targeted for deprescribing. This step should be guided by patient characteristics (e.g. age-related changes and multimorbidity) and the medication used (pharmacokinetic and pharmacodynamic characteristics) [74],

(3) discontinue the medication, which should include planning the process and communicating with the patient and liaising with other healthcare providers, and

(4) monitor the patient for beneficial and harmful effects of stopping the medication [67, 70].

1.5.2 The need to deprescribe

There are many reasons why medications should be deprescribed, including but not limited to: (i) lack of efficacy, (ii) increased risk of medication-related problems, and (iii) low levels of medication adherence [72, 74]. In particular, the older patient population is an important group for consideration of deprescribing. As older people often have multiple comorbidities with a concomitantly high number of daily medicines, there is an increased concern for this patient group about the heightened risk of medication-related adversity, and deprescribing medications in this population seems a reasonable first step [75].

1.5.3 Safety and effectiveness of deprescribing

A literature search on deprescribing (search terms 'deprescriptions' [MeSH term] and 'deprescribing') identified studies aiming to deprescribe in specific therapeutic areas. Proton pump inhibitors (PPIs) is a drug class receiving attention in deprescribing. Guidelines in dyspepsia management recommend that patients treated with PPIs should have their doses reduced to the lowest effective dose or return to self-care [76]. Similarly, the Screening Tool of Older People's Prescriptions (STOPP) recommends stopping or reducing the dose of PPIs at full therapeutic dosage for more than 8 weeks in older people (aged ≥65 years) if used for uncomplicated peptic ulcer disease or erosive peptic oesophagitis [77]. Despite these recommendations, PPIs are continued in the long term in patients, which may result in unnecessary side effects, pill burden or unnecessary high costs [76]. An interventional study from the UK examined the effects of a nurse-led educational support programme and rescue therapy for rebound symptoms offered to patients prescribed PPIs [76]. At 12 months post-intervention, 75% (6249) of patients reduced dosage or dosing frequency or discontinued PPIs. The study also showed that PPI prescriptions had gone from nearly 90,000 to 46,000, however, simultaneously, the number of prescriptions for alginate had gone up from 2,400 to 6,700. The study demonstrated that PPIs can be safely withdrawn from patients or in some cases, substituted to a safer drug, i.e. alginate [76].

Another study tested the effectiveness of a clinical pharmacist-led programme that included tapering instructions, patient education and follow-up

[78]. Patients included in this study were taking a PPI long term for gastroesophageal reflux disease without esophagitis or without a clear indication. Clinical pharmacists then identified candidates for PPI deprescribing. Only 126 patients were assessed for eligibility in the study and of these, only 22 patients agreed to participate and attempt to have their PPIs discontinued or dose reduced. The study showed a high success rate of 86% (19 patients) having their PPI completely discontinued post-intervention and only 5% (1 patient) being unable to reduce dose or discontinue the PPI [78]. Hence, this study showed that PPIs can be deprescribed successfully, but the study was limited due to its small number of participants and short duration of follow-up.

Other studies have targeted deprescribing of benzodiazepines [79]. The use of benzodiazepines in the older patient is of particular concern due to their age-related physiological changes and the significant side-effect profile of benzodiazepines. Consequently, benzodiazepines are commonly described as potentially inappropriate medicines (PIMs) and both benzodiazepines and hypnotic 'Z'-drugs are recommended to stop in people aged ≥65 years in the STOPP tool due to their sedative effects [77]. Despite this, benzodiazepines are frequently prescribed to older people for the treatment of insomnia, anxiety and delirium. It has been estimated that between 5% and 33% of older people are taking benzodiazepines to treat sleep disorders. Known side-effects of benzodiazepines are cognitive impairment, delirium, dizziness, insomnia and increased falls risk [79]. One study conducted in hospitalised patients attempted to deprescribe benzodiazepines by applying an intervention consisting of a structured medication review, patient educational material, patient counselling and post-discharge communication of the deprescribing intervention to the patient's primary care physician. Only 12 patients were included in this study of whom 11 had deprescribing initiated. At study completion (3 months after enrolment), benzodiazepines were successfully deprescribed for six patients and a 50% dosage reduction was achieved in the remaining five patients. During the withdrawal process, seven patients experienced worsening of anxiety symptoms, withdrawal symptoms or a fall. Four patients required substitution of the benzodiazepine with an antidepressant and one patient

required substitution to an antipsychotic whilst one patient required a return to original dose of the benzodiazepine. This study highlighted the difficulties of deprescribing benzodiazepines, and that consideration must be given within the withdrawal process to the option of substituting the benzodiazepine to a more appropriate medication, such as antidepressants as done in the study. Despite the fact that this study did not show a reduction in the total number of medications per patient, it did show an improvement in prescribing by substitutions to safer medications, which, as suggested by the study itself, could be of equal value to the patients [79].

Another study also looked at the feasibility of deprescribing benzodiazepines and hypnotic 'Z'-drugs in patients taking these inappropriately for a longer duration than the prescribed period. A clinical pharmacist conducted a comprehensive medical review and identified potentially inappropriate benzodiazepines or 'Z'-drugs used for more than 4 weeks. Shared decision making of deprescribing with the patient and the department psychiatrist was then done. Based on this and the deprescribing algorithm for benzodiazepines published by Pottie *et al.* [80], a withdrawal plan was developed and initiated. Patients were then monitored for withdrawal symptoms or returning of symptoms. The study was conducted in in- and outpatients of the Department of Psychiatry in a hospital in India. A total of 109 patients were included in the study. Of these 109 patients, the use of benzodiazepines was deemed inappropriate in 99 patients. Of these 99 patients, 33 patients were started on dose reduction and seven patients were prescribed their benzodiazepine on an emergency basis. Amongst the 33 patients who were started on dose tapering, 27 were completely discontinued and six were advised to continue the tapered dose. Two people experienced withdrawal symptoms. The study showed that benzodiazepines and hypnotic 'Z'-drugs can be deprescribed however the evidence is weak considering the small number of participants and the lack of follow-up in the study [81].

The studies mentioned above have shown that deprescribing interventions can be used to successfully discontinue inappropriate use of certain medication such as PPIs and benzodiazepines. However, it is important to consider the risk of

recurrence of the medical condition or withdrawal effects when stopping a medication as this may require restarting of the medication or prescribing of another medication to relieve the symptoms. This in turn may affect the true effect of a deprescribing intervention on the total number of medicines a patient is taken. Furthermore, the durations of follow-up in some of the studies may have been too short to detect medications later restarted, which again, may have impacted the true effect of deprescribing on the number of drugs prescribed to a patient. Additionally, studies were limited by small sample sizes which may have compromised the generalisability of the findings. Small sample sizes may limit inferences depending on how representative the study population is of the target population.

In addition to deprescribing interventions targeting specific drugs or drug classes, deprescribing interventions across settings and drug classes have been shown to be effective in reducing the total number of medications and reduce inappropriate medication use. A systematic review by Page *et al.* [71] summarised the results of 116 studies on the effectiveness of deprescribing interventions targeting single and multiple medications. The included studies comprised a mix of RCTs and comparative studies and reported results for a total of 34,143 participants. The review identified that deprescribing reduced both the total number of medications and number of PIMs in the intervention groups, and deprescribing was not associated with a significant increase in adverse drug withdrawal events. This highlights that deprescribing is safe and effective in reducing the number of inappropriate medicines. Looking at clinical outcomes, deprescribing did not significantly affect mortality across studies. However, a subgroup analysis did show that mortality was significantly reduced in patient-specific interventions compared to educational interventions. Deprescribing interventions however did not result in significant changes of the incidence of ADEs, cognitive function, quality of life nor risk of falls. Hence, this review summarized the growing body of research on deprescribing but also highlighted that deprescribing interventions have not proven themselves effective in improving clinical outcomes [71].

Another systematic review by Johansson et al. [82] included 25 studies (RCTs, cluster RCTs and nonrandomised controlled trials) including a total of 10,980

participants. Only three of the included studies demonstrated a substantial change in the number of drugs taken. The analyses of all-cause mortality and hospitalisations showed that the interventions to reduce polypharmacy had no effect on either, all-cause mortality or, hospitalisation rates. Based on these findings, the authors of the review concluded that the overall evidence of the effectiveness of interventions to reduce polypharmacy is very limited [82].

A Cochrane review [16] including 12 studies with a total of 22,438 older patients further adds to the findings of the previous aforementioned literature reviews [71, 82]. Interventions included in the Cochrane review demonstrated a reduction of inappropriate prescribing and improvements in the appropriateness of polypharmacy similar to the other two literature reviews. The difference in hospitalisations observed varied from (i) no difference, to (ii) a non-significant difference and (iii) a significant difference between the included studies depending on the methods of assessment. No difference in health-related quality of life (HRQoL) was seen in the studies. The findings of this Cochrane review highlighted that evidence exists that deprescribing intervention are effective in reducing inappropriate prescribing but that it remains unclear if these interventions improve hospitalisations and quality of life [16].

The findings of these systematic literature reviews highlight that when one seeks to determine the effect of deprescribing on improved clinical outcomes, the evidence is mixed. Heterogeneous study designs of deprescribing interventions have hampered direct comparisons of the effectiveness of such interventions but as it shows, no RCT has confirmed a significant reduction in mortality among participants receiving a deprescribing intervention and most deprescribing interventions have failed to show a statistically significant reduction of hospitalisations, ADEs or falls. More evidence is needed from high-quality RCTs to determine the clinical outcomes of deprescribing in multimorbid older populations. However, such trials will require thousands of participants, and conducting these trials in practice will be challenging. Instead, the clinical benefits of deprescribing are expected to arise from reducing doses or discontinuing PIMs and minimising the use of polypharmacy – outcomes for which deprescribing has proven effective. Reducing the total number of medications

and inappropriate prescribing in a patient, should be considered as stand-alone outcomes worth achieving in that the patient's treatment burden and unnecessary costs are reduced, which makes deprescribing an area worthwhile to investigate further.

Recently, attempts at creating an evidence-base for deprescribing, such as with the European Union funded trials SENATOR [83] and OPERAM [84] have begun in earnest. These two trials have investigated the effect of the routine application of the STOPP criteria and the Screening Tool to Alert to Right Treatment (START) to the medication lists of hospitalised, older people (aged ≥65 years) using computerised decision support systems. The results of these trials, when published, may thus add useful data to the effectiveness and safety of the deprescribing process. [83, 84].

1.5.4 Guiding deprescribing

There are few evidence-based guidelines on deprescribing as part of medicines management in multimorbid older people [55]. In contrast to prescribing, which is guided by robust evidence from RCTs, deprescribing is often guided empirically due to the common exclusion of this process in clinical trials [74]. In addition, clinical guidelines are usually developed based on evidence from trials that tend to list older people with multiple comorbidities as exclusion criteria, which limits their transferability to this population [72, 74]. Furthermore, current clinical guidelines often have a single-disease focus and rarely take [55, 74] into consideration the complexity of treatment in multimorbid patients [26, 85, 86]. GPs have reported feeling obliged to adhere to clinical guidelines in medicines management, and a high number of medications can thus easily be reached when guidelines to treat individual conditions are followed unquestioningly by physicians prescribing for patients with multiple comorbidities [26, 72].

As part of the process to meet the needs for deprescribing guidelines, a number of tools and criteria have been developed, but only some have been validated to date. Of these, some of the most widely referenced and used are the Beers criteria [87-91], the STOPP tool [77], PROMPT criteria [92], the Medication Appropriateness Index (MAI), STOPPFrail tool [93] and the CEASE deprescribing

framework [94]. These tools and criteria have their limitations when used to assess medication appropriateness in individual patients. These tools, to different extents, fail to consider the multiple factors affecting the appropriateness of a medication in an individual patient, such as severity of the disease, advanced age and life-expectancy, multi-morbidity, physical and mental capacity, care goals and personal preferences. This highlights the complexity of deprescribing due to this individualised context that requires a nuanced approach exceeding that of the current tools and guidelines. However, guidelines provide a more systematic framework for assessing appropriateness of medicines and guiding steps towards successful discontinuation [95].

A Canadian group has developed evidence-based deprescribing guidelines for a number of specific drug classes including proton pump inhibitors (PPIs), benzodiazepines, antipsychotics, antihyperglycemics, cholinesterase inhibitors and memantine [80, 96-99]. These guidelines are supported by algorithms to guide healthcare providers through the process of discontinuing one of the abovementioned drug classes in patients. In clinical practice, the use of these deprescribing guidelines seems beneficial but data from RCTs are needed to confirm their applicability to practice [100].

1.5.5 Patient-involvement in deprescribing

While the abovementioned guidelines on deprescribing provide guidance on the identification of medication to be deprescribed and the management, they are mainly targeted at the healthcare professional, and to some extent excluding the patient perspective. Suggested by Barnett *et al.* [101] deprescribing would benefit from the addition of a more patient-centered approach and they have published a guide to support patient-involvement in practice. This guide divides the process into seven steps and provides explanation of the purpose of each step, things to consider, actions to take and questions to ask the patients in order to undertake deprescribing safely [101]. This patient-centered deprescribing is in line with the published evidence. Tannebaum *et al.* [102] tested the effectiveness of a direct patient education about drug harms on benzodiazepine therapy discontinuation among

older people (aged ≥65 years) receiving long-term benzodiazepine therapy. The study showed that a benzodiazepine discontinuation rate of 27% was found in the intervention group compared to only 5% in the control group, at 6 months after the intervention [102]. In the study by Krol *et al.* [103] a simple information leaflet was developed to provide information on dyspepsia medication and to suggest stopping or reducing long-term PPI use with the help of the GP. Suggestions were made to the patient to seek help from the GP for stopping the PPI or reduce its use. At 20 weeks after the intervention, 15% of patients had stopped taking PPIs or were taking a lower dose compared to baseline [103]. Patient-involvement in deprescribing thus seems to be an enabler to successful deprescribing, and the patient has been suggested as a barrier and facilitator of deprescribing [104]. Summarized in studies by Reeve *et al.* [104, 105] greater involvement of patients in the deprescribing process is associated with greater patient willingness to have a medication stopped. The majority of older people (88%) and their caregivers (84%) are willing to have a medication stopped if deemed possible by the prescribing doctor [105]. However, a number of barriers and facilitators affect this willingness. Hope for future benefits and experiencing improvement when taking a medication are reasons reported for not wanting to have a medication deprescribed. For some patients, taking the medication gives them a feeling that they are doing something for their health and gives a sense of comfort [104]. Patients have also reported feeling pressured by their family, caregivers or healthcare professionals to taking a medication and believe that if a prescription is reissued by the prescriber, that this is done with an express for the patient to continue taking the medication. Previous negative experiences of stopping a medication and fear of recurrence of previous conditions also make patients less open to deprescribing. However, reported enablers to deprescribing are the inconvenience of taking a high number of medications and the cost of same [104].

A main patient barrier to deprescribing is the lack of time and support from the primary care physician both during the initiating conversation about deprescribing, instructions on the process and follow-up after the medication has stopped. The study concluded that interventions designed to overcome patient barriers should include a plan for the actual cessation, educating the patient on what

they should do if they experience return of symptoms or withdrawal side-effects. More support of the patient is needed, preferably from their primary care physician. However, with the existing workload on primary care physicians, the study suggested that future interventions should consider a multidisciplinary approach to deprescribing, with primary care physicians being supported by other healthcare professionals [104]. Support from other healthcare professionals to successful patient-centred deprescribing may thus create an opportunity for the community pharmacist to be more involved in patient care.

1.5.6 Strategies for deprescribing - a new role for the pharmacist

Despite increasing efforts, challenges still exist to design deprescribing interventions that will improve important clinical outcomes. Hence, attention should be drawn to the careful selection of the intervention design and to how deprescribing can be successfully implemented within routine clinical practice [72, 100, 106]. This should be informed by an understanding of the components underlying an effective intervention as well as the barriers to the implementation of such intervention.

As the majority of prescribing takes place in primary care, it makes sense that GPs would liaise with community pharmacists as part of a collaborative strategy on deprescribing. Discontinuing medicines requires careful consideration of pharmacology and patient characteristics, and pharmacists have the knowledge, training and several competencies to assess appropriateness of medicine use versus potential risks and benefits of discontinuation [55, 72, 75]. Community pharmacists represent an important support resource for prescribers and can provide information on appropriate medicine use, drug-drug interactions and ADRs [107]. In addition, community pharmacists are an accessible source of healthcare in the community and are in a key position to take more responsibility for medicines management and patient care which may be of benefit to patient-centred deprescribing [74]. The focus of the community pharmacist is currently changing from a drug-focus to a patient care-focus with a suggested beneficial role in reducing PIP [52, 53, 58, 59].Therefore, there is a potential to evaluate the role of the community pharmacist in supporting the deprescribing process. As described, community pharmacists in Ireland do not

have prescribing authority for either supplementary or independent prescribing. This raises the question if community pharmacists should deprescribe in the true meaning of the term? Ultimately, the responsibility of deprescribing lies with the person responsible for prescribing, in Irish community practice, the GP. However, supporting the GP by providing pharmacological input, identifying potential inappropriate medicines to be stopped and monitoring the cessation of a medication may allow new responsibilities to be managed by community pharmacists with the purpose of enhancing safe and successful deprescribing in the primary care setting in Ireland. There is a need to investigate the potential for a clearly defined role for a community pharmacist to input into the deprescribing process.

1.6 Aims and objectives

The concept of deprescribing is relatively new, and the role of the pharmacist in medicines management is evolving but requires a stronger research evidence base. In this thesis, the potential role of the community pharmacist to give input into deprescribing will be explored, along with the barriers and facilitators to the integration of the pharmacist's supportive role in deprescribing. The work conducted in this thesis is expected to provide a framework from which to make recommendations for pharmacists and policymakers to help facilitate the integration of pharmacists into the deprescribing process. Additionally, the findings of this thesis are expected to generate a series of key implications for interprofessional collaboration and education for pharmacists and GPs to promote the delivery of safe and effective deprescribing. Finally, the combined work in this thesis could help inform the design and implementation of future deprescribing interventions and contribute to the growing discussion about deprescribing and the role of the pharmacist.

The overall aim of this thesis was to identify the challenges and potential benefits of deprescribing and to explore the potential involvement of the community pharmacist in deprescribing.

The thesis objectives were:

i. To identify the barriers and facilitators to deprescribing as viewed by healthcare professionals.
ii. To examine the effectiveness of deprescribing interventions.
iii. To determine the long-term prevalence of inappropriate prescribing in early old aged people.
iv. To assess the potential cost-avoidance of using explicit criteria to reduce potentially inappropriate prescribing in primary care.
v. To explore the views of the community pharmacist and the GP on pharmacist involvement in deprescribing.

2 Challenges of deprescribing in older patients with multimorbidity, from healthcare professionals' perspectives - a narrative review

2.1 Chapter description

It was decided to synthesise the current literature on deprescribing, and the challenges to deprescribing as viewed by healthcare professionals. This was done with the aim to identify knowledge gaps to be explored in depth. This review helped informed the research questions for the next research chapters. I conducted the literature search, screened the retrieved literature for eligibility, summarised the study findings in a narrative synthesis and wrote the chapter and submitted it for publication. The other authors of this chapter and publication reviewed the chapter and gave their input and advice during the study.

2.2 Publication

The work of this chapter has been published as Raae-Hansen C, Byrne S, O'Mahony D, Kearney P, Sahm L, Cullinan S. Challenges of deprescribing in the multimorbid patient. *European Journal of Hospital Pharmacy.* 2017; 24:43-46. Doi: 10.1136/ejhpharm-2016-000921 (Appendix II).

2.3 Introduction

Multimorbidity and associated polypharmacy are among the biggest risk factors for inappropriate medication use, ADRs, ADEs and morbidity leading to hospitalisations [108, 109]. Discontinuation of medication is one of the most common recommendations following medication review in older people despite having a low probability of being implemented in practice [110, 111]. Strategies are urgently needed to facilitate the implementation of deprescribing among patients with multimorbidity. The deprescribing process includes some or all of the following elements; a review of current medications, identification of medications to be discontinued, a discontinuation regimen, involvement of patients, and a review with follow up [112].

Among the solutions proposed to reduce the number of medications per patient, are various screening tools that support prescribers in their decision-making, such as Beer's Criteria [87] and Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START criteria) for potentially inappropriate prescribing (PIP) [77]. Despite the evidence that these PIP screening tools reduce potentially inappropriate medication use, little is known about their specific utility in patients with multimorbidity and limited life expectancy [113].

Deprescribing can be a difficult task for practitioners in many categories of patients but is further complicated in older persons due to the need to consider age-related changes in pharmacokinetics and pharmacodynamics [114]. Therefore, despite existing guidelines on safe withdrawal of most drugs, healthcare professionals must also take account of the patient's age and multimorbidity in the deprescribing process. There is a need to tailor the deprescribing process to the needs of the multimorbid, older patient based on sound clinical recommendations. The aim of this narrative review was to explore the viewpoints of healthcare professionals on the challenges and practicalities of deprescribing in older patients, and to establish the evidence base to suggest appropriate deprescribing.

2.4 Methods

2.4.1 Literature search

The PubMed, CINAHL and Academic Search Complete databases were searched for primary, original literature in English published between January 2006 and February 2019. In all three databases, the word 'deprescribing' was used to search for relevant literature. The deprescribing process was perceived as being a component of polypharmacy management, and an additional literature search in the same three databases was performed with the medical subject headings (MeSH) term 'polypharmacy' combined with 'elderly' and the truncations of 'physician' and 'practitioner' using the Boolean operators. A 'snowballing' approach was used to identify additional literature through the screening of the reference lists of the primary literature and the reference lists of these as well. In addition, the reference lists of literature reviews relevant to deprescribing and polypharmacy management were hand-searched [106, 115-117].

2.4.2 Study selection

The retrieved literature was screened for eligibility according to pre-specified inclusion- and exclusion criteria based on the citation titles followed by a review of their abstracts. The inclusion and exclusion criteria for this review are outlined in **Table 2-1**. Full manuscripts of the articles that appeared eligible for inclusion were read for further assessment for inclusion in this review.

Table 2-1 Inclusion- and exclusion criteria used to identify eligible literature for inclusion in this narrative review

Inclusion criteria	Exclusion criteria
(i) Original primary research; (ii) Articles published in English; (iii) Articles published in 2006-2019; (iv) Articles that contain data on healthcare professionals' views on deprescribing and polypharmacy management in older patients.	(i) Articles about specific drugs, drug classes, treatments and conditions; (ii) Articles not specific to the topic of healthcare professionals' views on deprescribing and polypharmacy management in older patients; (iii) Reviews; (iv) Case studies, framework; (v) Comments, posters, editorials, brief reports.

2.4.3 Study appraisal and synthesis

The purpose of this narrative review is to summarise in a narrative format the findings of the literature on healthcare professionals' views on deprescribing. The findings of each study included were not pooled or combined as in systematic reviews or meta-analyses, and it was not deemed necessary to formally assess the study quality. Instead, data were extracted and categorised according to country, study design, data collection method, type and number of participants, and the focus i.e. whether this was specified as deprescribing or more generally on polypharmacy management in older patients. The findings of the included studies were grouped according to similarity in a thematic analysis [118].

2.5 Results

2.5.1 Search results

From the literature searches in the three databases, a total of 1,569 citations were retrieved after the removal of duplicates. Based upon the title and abstract screening of the citations, 1,522 articles were excluded. Another 27 articles were excluded after reading the full-texts. Reasons for exclusion of the articles are presented in **Table 2-2**.

The remaining 20 articles were eligible for inclusion in this review, and from the reference lists of these another three eligible articles were identified. The flow chart of literature acquisition is outlined in **Figure 2.1**.

Table 2-2 Reasons for the exclusion of articles from this narrative review and the number of articles excluded.

Reason	Articles excluded (n)
Topics specific to drugs, drug classes, treatment and conditions	252
Reviews	119
Case studies and framework	33
Commentaries, letter to the Editor, editorials, brief reports and perspectives	123
Not specific to deprescribing or polypharmacy management in older patients	181
Not about healthcare professionals' views on deprescribing or polypharmacy management	841

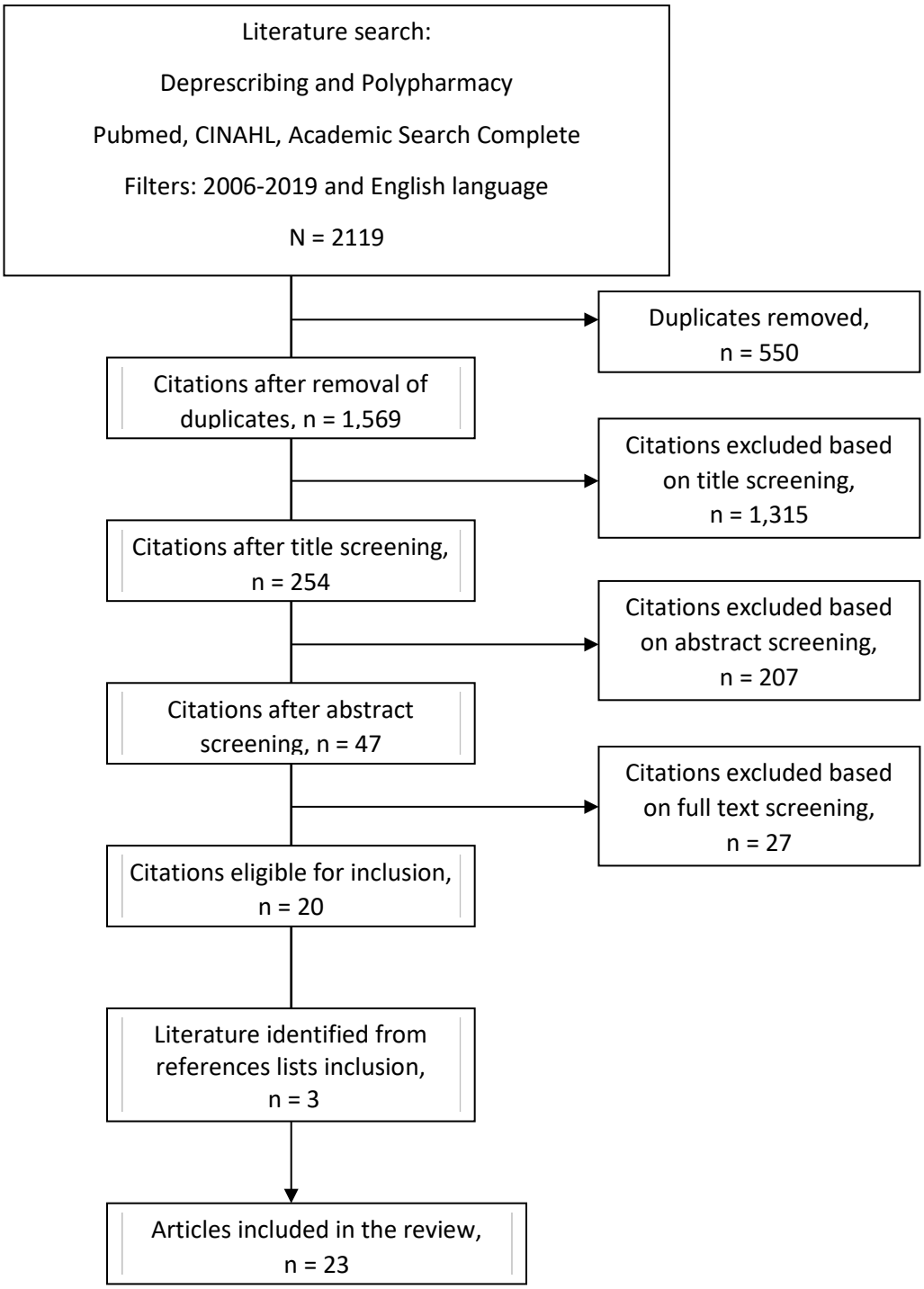

Figure 2.1 Flow diagram of the acquisition of literature for inclusion in this narrative review.

2.5.2 Study characteristics

A total of 23 articles were included in this review; 17 reported on deprescribing, and the remaining six reported on medicines management, i.e., deprescribing was not the main focus in these latter studies. All the included studies focussed on the older patient population. The characteristics of the included studies are presented in **Table 2-3**.

Table 2-3 Characteristics of the included studies in the narrative literature review

Study, year	Country	Study design	Data collection	Participants, (n)	Focus
Ailabouni *et al.* [119], 2016	New Zealand	Qualitative	Semi-structured interviews	General Practitioners (GPs), (n=10)	Deprescribing
AlRasheed *et al.* [120], 2018	Saudi Arabia	Qualitative	Focus groups	Family medicine physicians (n=15)	Deprescribing
Anderson *et al.* [121], 2017	Australia	Qualitative	Focus groups	GPs (n=32) and consultant pharmacists (n=15)	Deprescribing
Anthierens *et al.* [122], 2010	Belgium	Qualitative	Semi-structured interviews	General practitioners, (n=65)	Polypharmacy management
Djatche *et al.*[123], 2017	Italy	Quantitative	Survey	Primary care physicians (n=160)	Deprescribing
Farrell *et al.* [124], 2015	Canada	Quantitative, Modified Delphi approach	Expert panel discussion and three surveys (inclusive of free-text responses)	Pharmacists (55-68%), family physicians (11-17%), geriatricians (9-12%), nurse practitioners /13-16%). (n=64, n=53, n=47)[§]	Deprescribing
Fried *et al.* [125], 2011	United States of America	Qualitative	Focus groups	Physicians (90%), nurse practitioners (5%), Physician assistant (n=1) pharmacist (n=1), (n=40)	Polypharmacy Management
Hansen *et al.* [126], 2019	Ireland	Qualitative	Semi-structured interviews	Community pharmacists (n=18)	Deprescribing
Harriman *et al.* [127], 2014	Canada	Quantitative	Survey	Family physicians, (n=30)	Deprescribing

Study, year	Country	Study design	Data collection	Participants, (n)	Focus
Jubraj *et al.* [128], 2015	United Kingdom	Quantitative	Survey incl. free-text Responses	Foundation Year 1 (FY1) doctors, (n=20)	Deprescribing
Laursen *et al*. [129], 2018	Denmark	Qualitative	In-depth, semi-structured interviews	GPs (n=14)	Polypharmacy management
Moen *et al.* [130], 2010	Sweden	Qualitative	Focus groups	General practitioners, (n=31)	Polypharmacy management
Nadarajan *et al.* [131], 2017	Singapore	Quantitative	Survey	Senior hospital doctors (n=34), junior hospital doctors (n=56)	Deprescribing
Ní Chrónín *et al.* [132], 2015	Australia, New Zealand	Quantitative	Survey	Geriatricians† (84%), trainees† (16%), (n=134)	Deprescribing
Nixon *et al.* [133], 2016	Denmark	Qualitative	Semi-structured interviews	GPs (n= 24)	Deprescribing
Palagyi *et al.* [134], 2016	Australia	Qualitative	Focus groups Semi-structured interviews	Nine focus groups with residents* (n = 25), relatives (n = 16) and staff members* (n = 19). One focus group with GPs** (n = 8). Pharmacists (n = 4)	Deprescribing
Pype *et al.* [135], 2018	Belgium	Qualitative	Semi-structured interviews	GPs (n=11)	Deprescribing
Schuling *et al.* [70], 2012	The Netherlands	Qualitative	Focus groups	Experienced general practitioners (GPs)‡,(n=29)	Deprescribing
Shemeili *et al.* [136], 2015	Abu Dhabi	Qualitative	In-depth semi-structured Interviews	Physicians (26%), pharmacists (48%), nurses (26%), (n=27)	Polypharmacy management

Study, year	Country	Study design	Data collection	Participants, (n)	Focus
Sinnige *et al.* [137], 2016	Netherlands	Qualitative	Focus groups	GPs (n=12)	Polypharmacy management
Sweta *et al.* [138], 2019	India	Quantitative	Survey and interviews[a]	Medical practitioners (n=422)	Deprescribing
Turner *et al.* [139], 2016	Australia	Qualitative	Focus groups	GPs (n=19), nurses (n=12), pharmacists (n=14), residents (n=11)	Deprescribing
Wallis *et al.* [140], 2017	New Zealand	Qualitative	Semi-structured interviews	Primary care physicians (n=24)	Deprescribing

[†]Geriatricians and geriatrician trainees refer to specialist physicians/trainees caring for older patients. [‡]Experienced defined as a minimum of five years' experience. [§]The number of participants varied in the three consecutive surveys, survey 1, 2, and 3, respectively. *Residents (i.e. patients) and staff members belonged to long-term care facilities in New South Wales, Australia. **The GPs included in the study all provided regular medical care to residents of long-term care facilities in New South Wales, Australia. [a]Interviews were based on the tool "Perceptions, Attitudes and Challenges of Physicians towards Deprescribing" which asks the interviewee to answer the questions based on prespecified options, which yields quantitative data similar to what is obtained from a questionnaire

The included studies displayed similar themes on the factors influencing deprescribing. Additional factors associated with management of polypharmacy were identified, e.g. drug selection, drug initiation. However, for this literature review I focussed solely on the factors influencing the discontinuation/deprescribing of medications as part of the management.

2.5.3 Study findings

From the content analysis approach to the study findings, five broad themes were identified as challenges to deprescribing in older patients with multimorbidity: (i) interprofessional relationships, (ii) medication review, (iii) information, (iv) the patient and (v) environmental needs. The main findings within each theme are described in **Table 2-4**.

Table 2-4 Summary of the main findings of the thematic analysis

Theme	Main finding(s)
Interprofessional relationship	Too many prescribers in the treatment of multimorbid older patients adds to the complexity of deprescribing. Poor communication between healthcare professionals, lack of experience with deprescribing and a reluctance to interfere with the decisions made by other healthcare professionals are challenging the decision-making process of deprescribing. With GPs as the responsible profession for overall medicines management including deprescribing, pharmacists were a welcomed support.
Medication reviews	Not having a comprehensive medication review and not understanding the motives of a prescriber to change a patient's medication are barriers to the decision-making process of deprescribing.
Information	Current prescribing guidelines are too disease-specific to treat multimorbidity, they are lacking the evidence-base to be applied to the older population, and they are excluding

Theme	Main finding(s)
	guidance on deprescribing. These limitations, together with limited access to guidelines are barriers described to the deprescribing process.
Patient	Successful deprescribing is challenged by i) patients withholding of important information to make an informed deprescribing decision, ii) their willingness to stop a medication, iii) their acceptance of the GP's role and iv) the difficulties experienced by the prescriber when engaging in a conversation with the patient about deprescribing.
Environmental needs	Lack of time, financial resources, education and decision support systems are needed to overcome the deprescribing barriers pertaining to the working environment.

2.5.3.1 *Interprofessional relationship*

In the treatment of multimorbid older patients, the involvement of several healthcare professionals is common; this was highlighted as an important factor in 12 of the studies reviewed [70, 119, 122, 124, 127, 130-132, 134-136, 138]. The involvement of multiple prescribers was reported by three studies [70, 119, 129] to result in individual prescribers following his/her specialty treatment guideline(s), and to dominate the patient's treatment with their own particular focus. Similarly, Shemeili *et al*. [136] and Pype *et al.* [135] described how some physicians believed that they were solely responsible for the medicines management within their specialty, and that the overall management was the responsibility of others.

In principal, the primary care physicians welcomed the help of pharmacists to support them in polypharmacy management, and most pharmacists were in favour of the suggested clinical role for them in treating multimorbidity [119, 120, 129, 131, 136, 138]. However, the perceived value of a pharmacist's recommendations varied between the GPs in the study by Palagyi *et al*. [134], and was determined by the perceived relationship between the medical and the pharmacy profession. The junior doctors in Jubraj *et al*. [128] felt that GPs and consultants were the main healthcare

professionals responsible for deprescribing, followed by senior house officers (SHOs), pre-registration junior doctors and pharmacists. In the studies by Anthierens *et al*. [122] and Palagyi *et al*. [134], GPs felt that the responsibility to review the patient's overall health status and quality of life lay within the remit of their profession. Hence, they believed that they have a coordinating role in reviewing the patient's medical treatment, including lowering the doses, quantifying the medication use and reducing the number of inappropriate drugs. However, the GPs in both studies also described the challenges of these tasks which included a heavy workload on top of their regular work commitments [122, 134] as illustrated below:

"It's a great idea to reduce medication if you can do it in a safe manner that's not going to make us have to go out to the nursing homes 55 more times:" [134]

The fear of damaging the professional relationship with the original prescriber [119, 120, 123, 129, 131, 134, 135, 137, 138] and a lack of knowledge about and/or experience with deprescribing [119-121, 129, 131, 135, 140] were other concepts identified within this theme. Level of confidence and a fear of the potential outcomes of discontinuing medication influenced the extent to which prescribers and pharmacists would deprescribe/advice deprescribing [119, 121, 123, 126, 131, 135, 138]. Having experience with deprescribing contributed to higher confidence whilst negative experiences enhanced a tendency to continue with the treatment as prescribed without interfering [121, 135]. The primary concern among the GPs for pharmacist-support in deprescribing was that pharmacists working in the community do not have access to patient information which may limit the clinical importance of their recommendations [119].

Reported challenges to the interdisciplinary management of deprescribing were;

i) difficulties in the determination of ongoing benefit versus harm of a medication initialised by a specialist [124],

ii) lack of knowledge and experience when deprescribing another doctor's recommended medication [119, 120, 129-131, 136, 140], and

iii) poor communication between levels of care resulting in inappropriate prescribing and/or several prescribers treating the same indication [119, 122, 129, 134, 136].

2.5.3.2 *Medication reviews*

Multiple prescribers for the same patient usually result in the lack of a clear overview of the patient's medical treatment [70, 122, 136, 140]. This was further compounded by low levels of interprofessional communication, in particular poor documentation of changes made to a treatment, e.g., initiation, amendments and discontinuation. In turn, this poor documentation was a barrier to deprescribing; as it hindered the understanding of other doctors' motivations for the initiation or continuation of particular treatments [70, 120-122, 134, 136].

Apart from the poor documentation from prescribers involved, the difficulty of gaining a complete and updated list of the patients' medications was a barrier to deprescribing. Shemeili *et al*. [136] reported that the main difficulty with medication review was the need to consult several information sources, e.g., pharmacy, patient, family and GP, to complete the list, coupled with uncertainty as to which source provides the optimal list of drugs taken by the patient. Not knowing which medications should be included on the list, like "as required" (PRN) analgesics or topical medicines was another challenge mentioned [136]. The study by Moen *et al*. [130] described how incomplete information was perceived as a barrier to the decision-making towards active deprescribing in terms of which drugs to discontinue and when. The pharmacists in the study by Palagyi *et al*. [134] further commented on poor acquisition and documentation of patient information from the nurses:

"*It's a matter of educating them [nursing staff] to understand that they don't need to know the medicines… they don't need to know specific details, they need to provide information about that resident that's documented well and correctly so that we can use that information."* [134]

2.5.3.3 *Information*

The lack of an evidence base on the use of a particular drug by older patients was reported in many studies as a limitation to structured deprescribing mainly due to the exclusion of multimorbid older patients in clinical trials [70, 119, 121, 123, 124, 129, 130, 132, 133, 135, 139]. The evidence base was perceived as insufficient with regards to the effect of multiple drug therapies in the older patients [132] and the effects of preventive medication in the oldest patients, with a need for more information about the benefit/risk-ratio of these medications in patients with short life-expectancy [70, 124, 130]. As a result of the lack of evidence, treatment guidelines for this particular patient group are lacking, with the current guidelines perceived to be limited because of:

i) being based on trial data involving younger patient populations [130],

ii) only giving a standardised set of recommended medications per indication regardless of the patient's additional comorbidities [130],

iii) being too disease-specific [125, 140], and

iv) not including recommendations for deprescribing [124, 126, 131, 133, 135, 140].

As a result, prescribers felt under pressure to adhere to prescribing guidelines instead of prioritising the medical treatment and deprescribing where appropriate [70, 122, 130]. This onus, was however not experienced by the majority of the participants (67%) in the study by Harriman *et al.* [127], with 24% being unsure about applicability of prescribing guidelines.

Some studies described a minimal use of existing guidelines to deprescribing explained by limited access to those [120, 121]. Easier access to guidelines was suggested to improve the uptake of those recommendations [120, 121].

2.5.3.4 *Patient*

The patient was described to influence the deprescribing process, through the following pathways:

i) some patients' unintentional withholding of information about ADRs because they attributed these to aging rather than side effects of medicines [70],

ii) some patients being more likely than others to report their symptoms to healthcare professionals other than their GPs, (such as hospital specialists or nurses), resulting in the GP not being fully aware of the actual problems experienced by the patient [70],

iii) patient characteristics, such as cognitive impairment, functional dependency, level of education and old age, hindered the explanation of the patient's issues with their current medication list and the desire for deprescribing [70, 132],

iv) some patients' strong attachment to certain familiar medications and consequent poor inclination to cease these medications [70, 119-122, 129, 131],

v) some patients' demands, wishes and expectations, and those of their families [119, 122, 125, 126, 130, 132, 134, 137, 140], and

vi) some prescribers' reluctance to communicate with patients about their life-expectancy [70, 119, 140].

Patient expectations were believed to result in conflicts between medical treatment desired by the patient versus that of the practitioner in the study by Fried *et al*. [125]. Following this, the prescribers in studies by Moen *et al*. [130] and Anthierens *et al*. [122] thought that the patients shared the responsibility of their medication lists with the prescribers due to their treatment demands and frequent self-medication. The study by Schuling *et al*. [70] reported how the prescribers were reluctant to initiate a discussion about discontinuation of medications with their patients, because of a

fear among patients who may misinterpret deprescribing as a sign of a nihilistic healthcare system losing interest in them due to their old age.

> "*People may then get the feeling, 'Don't I count anymore, am I not important?'"* [70]

Moen *et al.* [130] commented that the challenges in communication with patients were believed to be the factor principally responsible for the continuation of medical regimens for longer than appropriate. The study by Harriman *et al*. [127] and Ailabouni *et al.*[119] reported that some prescribers perceived that it was easier or more reasonable to continue a medication that seems to have no negative effects on the patient rather than to deprescribe it. In contrast, Ní Chróinín *et al*. [132], reported that a driver of deprescribing was the older patients' often limited life-expectancy, with physicians being more likely to deprescribe multiple medicines in patients with increasing dependency and cognitive impairment.

Additional challenges identified within this theme were patients' perceptions of the GP and their perceived lack of knowledge, understanding and awareness of deprescribing and medical therapy in general. Two studies [119, 129] described that some patients perceived specialised prescribers (e.g. hospital physicians and clinical pharmacologists) as being more knowledgeable than their GP and this sometimes disrupted the patient-GP relationships. Patients would not accept the GP's recommendations to the same extent as the recommendations made by specialists [119, 129].

2.5.3.5 *Environmental needs*

Across the studies, factors pertaining to the working environment were reported to influence deprescribing. Lack of time and financial support to review medicines and to deprescribe were perceived barriers across studies [119-121, 123, 126, 131, 137, 140]. Other suggested improvements were education to fill any knowledge-gaps

[126, 129, 131, 138], and to create and advance decision support/computer systems to help facilitate deprescribing [119, 126, 140].

2.6 Discussion

A reluctance to deprescribe was apparent when the 'deprescriber' was not the original prescriber [127, 134]. However, the physicians in the study by Harriman *et al*. [127] denied that this reluctance to deprescribe was due to concerns about damaging their relationships with specialists, as it was perceived to be in the study by Palagyi *et al*. [134]. Similarly, a previous study by Cantrill *et al*. [141] has described how a reluctance to change another practitioner's prescription is due to the fear of causing a 'professional dilemma'. In turn, many GPs feel obliged to continue the medical treatment initiated in hospital without changing or questioning the decision. They also expressed the concern that ignoring the advice from the hospital practitioners would undermine the patient's confidence in the healthcare system [141]. The medical culture described by Moen *et al.* [130] with infrequent contact between GPs and organ specialist is noteworthy. The existence of a tacit agreement not to challenge the motivations for any prescription made by specialists may also add to GPs' reluctance to deprescribe. As described by Sinnott *et al.* [142], poor communication by some hospital specialists with the GPs can hinder the coordination of a patient's medical treatment and thereby result in poor therapeutic oversight with consequent inappropriate medication use.

An interesting finding of this review was the agreement on the GP's role in coordinating the patient's medical treatment. GPs in the studies by Anthierens *et al*. [122], Harriman *et al*. [127] and Palagyi *et al*. [134], all believed that they were responsible for keeping a holistic view of the patient's treatment and to taper and discontinue certain medications, and finally follow the effects of these changes over time. The data from junior doctors in Jubraj *et al*. [128] and from specialist physicians in Shemeili *et al*. [136] suggested that the overall responsibility for polypharmacy management did not rest with specialists, but with GPs and pharmacists.

It is thus interesting to note that there seems to be general consensus about the GPs' role in overall medicine management in multimorbid patients on polypharmacy and the supportive role of pharmacists. Randomised controlled trials [143-145], have shown that pharmacist-led medication reviews do not have a significant effect on reducing hospital admissions or mortality in older patients. However, the medication reviews led by pharmacists have been shown to reduce the number of prescribed drugs and appear to have a positive effect on medication adherence [143-145].

Deprescribing in older patients with multimorbidity was perceived to be particularly hindered by the lack of appropriate and updated guidelines for this patient group. Previous studies by Hughes *et al*. [146] and Boyd *et al*. [147] have criticised current treatment guidelines for being disease-specific and not addressing old age, multimorbid illness and adherence, as well as failure to provide any guidance on achieving patient-centred care. Hence, current disease-specific treatment guidelines are another challenge to deprescribing and there is a clear need for patient-centred guidelines.

The patients themselves were another factor influencing the deprescribing process, with most patients disinclined to discontinue long-term medications [122, 130]. Reeve *et al*. [104] maintain that these patient barriers are the result of disagreement with deprescribing decisions, lack of support from other healthcare professionals, lack of knowledge on how to discontinue certain medications, previous negative experiences with deprescribing and finally, fear of negative clinical and legal consequences of medication withdrawal. Many of the included studies reported how GPs struggled in their communication on this issue with patients and their families, especially at the latter stages of life [70, 125, 130, 136]. This may be a contributing factor to the lack of patient understanding of the appropriateness of deprescribing.

The environment in which deprescribing takes place is too busy to allow for a thorough deprescribing process, and studies highlighted the need for financial support and dedicated time and resources to deprescribe [119-121, 123, 126, 131, 137, 140]. Decision support tools to support deprescribing and computer systems for

shared patient information may be some suggestions to facilitate deprescribing in practice.

Another interesting finding of this narrative review was that studies on deprescribing were limited to a small number of countries. These countries, i.e. Australia, Canada, Denmark, Sweden, the Netherlands and the United Kingdom (UK), have advanced healthcare systems and are at the forefront of ensuring rational medication use [148]. Therefore, it is not surprising that these countries are exploring strategies for deprescribing and are included in this narrative review. Additionally, the reported openness to the pharmacist role in supporting deprescribing may also be linked to the transition of the pharmacist role in these countries. Over the past decades, the role of the pharmacist in these countries has shifted from the traditional medication focus to a more advanced patient care focus. This advancement in the role of pharmacists requires them to be part of the broader health care team, providing better health care for the patients, and contributing to rational medication use [59]. With this shift in the role, clinical pharmacist support and pharmacist-led medication reviews have become integral parts of patient care, in these countries, particularly in the hospital setting [60-63]. In addition, the supportive role of the pharmacist in patient care has shifted from a hospital-only focus to a community setting focus. Pharmacists in the UK [149] and Australia [150] are increasingly entering the general practice teams with the purpose of supporting GPs in medicines management and patient care. Other services such as the administration of certain medicines, e.g. the seasonal influenza vaccine, have also been transferred to community pharmacists in the UK, Australia, Canada, Denmark and New Zealand [151]. This expansion of the pharmacist role in patient care in both hospital and community setting may explain the suggested pharmacy support in deprescribing as a means of overcoming some of the challenges in this review. Similarly, the role of the pharmacist in Ireland has also expanded over the past decades. Clinical pharmacists in Ireland are also entering the hospital setting, and Irish community pharmacists are administering the seasonal influenza vaccine and emergency hormonal contraception [65]. The role of the pharmacist in Ireland is

therefore also evolving and their potential role in deprescribing should thus be investigated.

2.6.1 Limitations

The studies included in this review did not all focus specifically on the deprescribing process. However, each study did deal with medicines management in the older population. Factors influencing medication management in general may differ from the factors specific to deprescribing. To overcome this, data on discontinuation and deprescribing processes within the medication management process were extracted from the studies. The included studies were a mixture of qualitative studies and quantitative studies, and limitations to these study designs may present a bias in the quality of the included studies. Review articles may have provided important sources of information. Despite this, it was decided in this study to only include primary literature on healthcare professionals' views on deprescribing.

2.7 Perspective

With the increasing complexity in the treatment of multimorbid older people, the pharmacist was suggested to offer a potential source of support in deprescribing. Pharmacists have a unique skill set due to their training and knowledge in pharmacology, pharmaceutical chemistry, pharmaceutics and clinical practice and bringing in the 'medication expert' may thus be a strategy to help guiding the deprescribing process. As reported in some of the included studies, GPs have the overall responsibility for medicines management, however we know that GPs already carry a heavy workload. Improving the collaboration between GPs and community pharmacists may lessen this load and enhance deprescribing in primary care settings. However, more research is needed to understand the challenges and benefits of this collaboration and this will be done in the subsequent chapters.

2.8 Conclusion

This narrative review of the literature has shown that the challenges of deprescribing in older patients are compounded by the need to manage the shared treatment of multiple conditions by several prescribers from different specialities based on disease-specific guidelines without evidence on the older, frailer, multimorbid patient population. The findings highlight a need to improve the interdisciplinary approach to the treatment of older patients with multimorbidity to ensure that the patient is managed holistically and not merely treated for the individual conditions that the multimorbid patient has, according to evidence-based guidelines.

Based on the findings of the narrative reviewed literature, the following areas of focus for achieving beneficial deprescribing are highlighted:

- more evidence and guidelines on effective deprescribing practices in the older patients,
- standardised procedures for medication reviews and systematic approaches to deprescribing,
- practical and user-friendly tools for medication reviewing,
- improved intra- and inter-disciplinary communication and documentation, including more pharmacist support and clarification of the roles and responsibilities of deprescribing and medication reviewing.

3 Identification of behaviour change techniques in deprescribing interventions: a systematic review and meta-analysis.

3.1 Chapter description

In chapter 2, the challenges and facilitators of deprescribing as viewed by healthcare professionals were identified. It was then decided to examine the published evidence of deprescribing interventions. A meta-analysis was done to assess whether previous interventions had been effective in reducing the number of medicines or inappropriate prescribing. Additionally, in order to understand how these interventions changed the behaviours of the participants to enhance deprescribing, a behaviour change technique analysis was performed.

3.2 Publication

The work of this chapter has been published as Hansen CR, O'Mahony D, Kearney PM, Sahm LJ, Cullinan S, Huiber CJA, Thevelin S, Rutjes AWS, Knol W, Streit S, Byrne S. Identification of behaviour change techniques in deprescribing interventions: a systematic review and meta-analysis. *British Journal of Clinical Pharmacology.* 2018; 84:2716-28. Doi: 10.1111/bcp.13742 (Appendix III)

3.3 Introduction

Older people i.e. above the age of 65 are more vulnerable to medication-related harm and inappropriate prescribing than younger chronically medicated people [152, 153]. Age-related physiological changes contribute to iatrogenic vulnerability in older people, as does multimorbidity and frequent use of multiple medications i.e. polypharmacy [19, 55, 82, 124, 152, 154]. Physiological vulnerability, multimorbidity and polypharmacy represent complex challenges in the care of older people and often exclude them from participating in clinical trials [82, 85, 155, 156]. Therefore, some prescriptions in multimorbid older people are without a clear-cut evidence base to support them and inappropriate prescribing is highly prevalent [34, 46, 157]. Excessive inappropriate prescribing in older people has turned the focus of current research towards deprescribing - the systematic process of identifying and discontinuing drugs in patients for which real and potential harms outweigh the benefits [94]. Making informed decisions to deprescribe with the goal of reducing inappropriate prescribing and improving patient outcome is hampered by a lack of evidence regarding the effects of medication withdrawal in older people and is further challenged by prescriber- and patient-related factors [104, 115].

Research has demonstrated safety and efficacy of deprescribing in older people (aged ≥65 years) [71] whilst reluctance of prescribers to deprescribe a medication commenced by another prescriber is described as well [158]. Although evidence suggests that pharmacist involvement and patient-centred interventions are effective, the best approach to engage and support prescribers in deprescribing remains unclear [52, 53, 104, 106, 159, 160]. Previous reviews examining the effects of deprescribing interventions on clinical outcomes call for a better understanding of successful implementation of deprescribing [71, 82, 106, 158].

This systematic literature review focussed on interventions that were expected to change the behaviours of both healthcare professionals and patients towards successful and safe deprescribing. Within the clinical context of patient care, there is a need to ensure that behaviour change is a part of any intervention design in order to maximise the likelihood that prescribers act upon recommendations [161-164]. Recent advances in behavioural science have provided valuable insights into the components of complex interventions. The Behaviour Change Techniques (BCTs)

taxonomy version 1 (BCTTv1) [165] is designed to assist in the identification of BCTs of effective interventions. A BCT is defined as "an observable, replicable, and irreducible component of an intervention designed to alter or redirect causal processes that regulate behaviour" [166]. It is anticipated that a clear description of BCTs will clarify the essential content of these complex interventions in a consistent way so as to assist in future replication of effective interventions [167]. The application of the BCT taxonomy to deprescribing is novel. This review was designed to complement previous reviews [71, 82, 106] on deprescribing by offering a broader analysis of behaviour change techniques in deprescribing interventions.

The aims of this systematic review are: (i) to identify BCTs used more frequently in interventions that are effective in reducing the number of daily drugs and inappropriate prescribing, (ii) to describe other characteristics of deprescribing interventions, and (iii) to determine intervention impact on drug use, prescribing appropriateness and Medication Appropriateness Index score in meta-analyses.

3.4 Methods

A systematic search of the primary, secondary and grey literature to identify randomised controlled trials (RCTs) on deprescribing was undertaken on December 14, 2016 and again on February 25, 2019 to identify newly published literature. This chapter will report the combined search of literature and findings. This systematic review was reported according to the PRISMA guidelines for systematic reviews and meta-analyses [168] (see PRISMA checklist in Appendix IV), and was registered with Prospero (record no. CRD42016037730, see Appendix V).

3.4.1 Search strategy

The search strategy was designed in conjunction with an experienced medical librarian who was trained in systematic review methodology. A combination of text words and subject headings (such as MeSH terms) related to the intervention was used, without restriction to publication date or language (**Table 3-1**).

Table 3-1 Search terms used

Population	Intervention	Outcome	Filters
Aged, aged 80 and over, adult*, older people, elderly	Deprescriptions, deprescri*, discontinu*, reduc*, ending, stopping	Drug prescriptions, polypharmacy, inappropriate prescribing, prescription*, inappropriate prescriptions, medication*, medicine*	Clinical trial, controlled clinical trial, randomised controlled trial

The following electronic bibliographic databases were searched: MEDLINE, EMBASE, Web of Science and Academic Search Complete. Grey literature was searched via the Google Scholar® search engine and from screening reference lists of included studies as well as relevant systematic reviews. Additional searches were done in the System for Information on Grey Literature in Europe (OpenSIGLE) and the clinical trial registries i.e. ClinicalTrials.gov, International Standard Registered Clinical/soCial sTudy Number (ISRCTN), WHO International Clinical Trials Registry Platform (ICTRP) and the Australian New Zealand Clinical Trials Register (ANZCTR).

3.4.2 Study selection

I, as the primary researcher, screened titles of all retrieved citations. Dr. Shane Cullinan (a post-doctoral academic pharmacist and one of the publication co-authors) and I independently screened abstracts and article full-texts for eligibility according to the protocol defined inclusion and exclusion criteria. Any disagreements between us were resolved by consensus and we both agreed upon the final list of studies.

3.4.3 Inclusion and exclusion criteria

Inclusion was restricted to randomised controlled study design, i.e. randomised controlled trials (RCTs) and cluster RCTs. The control group could involve either active or inactive interventions, e.g. sham or no intervention. This study design was chosen to allow for between study comparison of intervention effectiveness in meta-analyses. Studies were included if they reported on interventions encouraging the deprescribing of existing drugs or the reduction of existing inappropriate prescribing. Only those interventions involving older patients (i.e. aged ≥65 years) or a healthcare

professional with prescribing, dispensing or administration authority were included. No restrictions were applied to language, clinical setting of the intervention, sample size, blinding procedures or other design characteristics. Interventions specifically focusing on the clinical effects of withdrawing a specific drug/drug class, e.g. opioid withdrawal effects were excluded.

3.4.4 Risk of bias assessment

Risk of bias was assessed using the Cochrane Collaboration Tool for randomised controlled studies [169] with a descriptive purpose of summarising the quality of the studies that met inclusion criteria. Studies were not excluded from data analysis because of methodological flaws if they otherwise met inclusion criteria. Incomplete outcome data were in general rated as high risk of bias if the loss of patients to follow-up was 20% or higher and rated as low risk of bias if the loss was 10% or less. Imbalance in the numbers lost to follow-up between intervention and control groups was also considered to introduce bias. Random sequence generation and allocation concealment were judged to be at low risk of bias if methods for both were described in sufficient detail to determine its adequateness. Inadequate sequence generation methods (such as date of entry) and concealment methods were judged to have high risk of bias. Blinding procedures were considered to carry a low risk of bias if the description of the procedure reflected blinding. Absence of blinding or unblinding of participants and personnel were both deemed to introduce high risk of bias. Selective outcome reporting was assessed at low risk of bias if all patient-relevant outcomes described in the methods section were fully addressed in the paper. Unclear risk of bias was judged for any study element for which there was insufficient information.

3.4.5 Data extraction strategy

Data were collected using a data extraction form (see Appendix VI) developed by me, the primary researcher and agreed with one of my supervisors, Dr. L. Sahm (L.S.). L.S. and I independently pilot tested the data extraction form on two randomly chosen studies, both of which were later included in the review. Thereafter data extraction on all studies was completed by me, the primary researcher.

3.4.6 Outcome measures

Primary outcome measures were: (i) number of total, and potentially inappropriate prescriptions, and/or drugs as defined in the individual studies according to prescribing appropriateness criteria, e.g. STOPP criteria [77], Beers' criteria [170] and local or national prescribing guidelines; (ii) proportion of participants with a reduction in number of total and potentially inappropriate prescriptions and/or drugs; (iii) and implementation of recommendations. A secondary outcome was change in Medication Appropriateness Index (MAI) score.

3.4.7 Behaviour change techniques coding

Coding of BCTs was performed independently by me, for all the included studies and three of the publication co-authors, (L.S., S. Thevelin and C.J.A. Huibers) coded a subset of studies. BCTs were identified for each intervention, using the Behaviour Change Technique Taxonomy version 1 (BCTTv1) [165]. I had completed online training in BCTTv1 prior to the coding. I created a coding manual and instructions, and these were given to the three co-authors and exercises from the online training were made available. Any queries about the coding were resolved by discussion and consensus between myself and the three co-authors. The target behaviour was the decision-making to discontinue a drug, or an inappropriate prescription. I tabulated the findings across studies by computing frequencies. The information was used to determine the BCTs used more frequently in studies that reported effectiveness of interventions to reduce number of drugs and/or improve prescribing appropriateness.

3.4.8 Statistical analysis

I, the primary researcher, calculated Odds Ratios (OR) with standard deviations (SD) for each of the reported outcomes and used RevMan version 5.3 software to statistically combine the outcome data [171]. Continuous outcomes were expressed as difference in means between groups with a 95% confidence interval (95% CI). The level of between study heterogeneity was evaluated by calculation of the I-squared and Chi-squared statistics. Where possible, stratified random effects meta-analyses were used to identify factors affecting intervention effectiveness. Subgroup analyses

were performed by risk of bias assessment, intervention setting and intervention target. If the level of reporting did not allow for inclusion of a study in one or more meta-analyses, additional information was sought from the study authors. If the information was not made available, the study was excluded from the meta-analysis.

3.5 Results

3.5.1 Literature search and review process

The database search identified 2,048 records, and grey literature yielded 175 records. After removal of duplicates and title screening, 256 abstracts were screened for eligibility and 86 of these met the inclusion criteria. Assessment of full texts resulted in 31 studies being included in this systematic review. Study selection and reasons for exclusion are illustrated **Figure 3.1.**

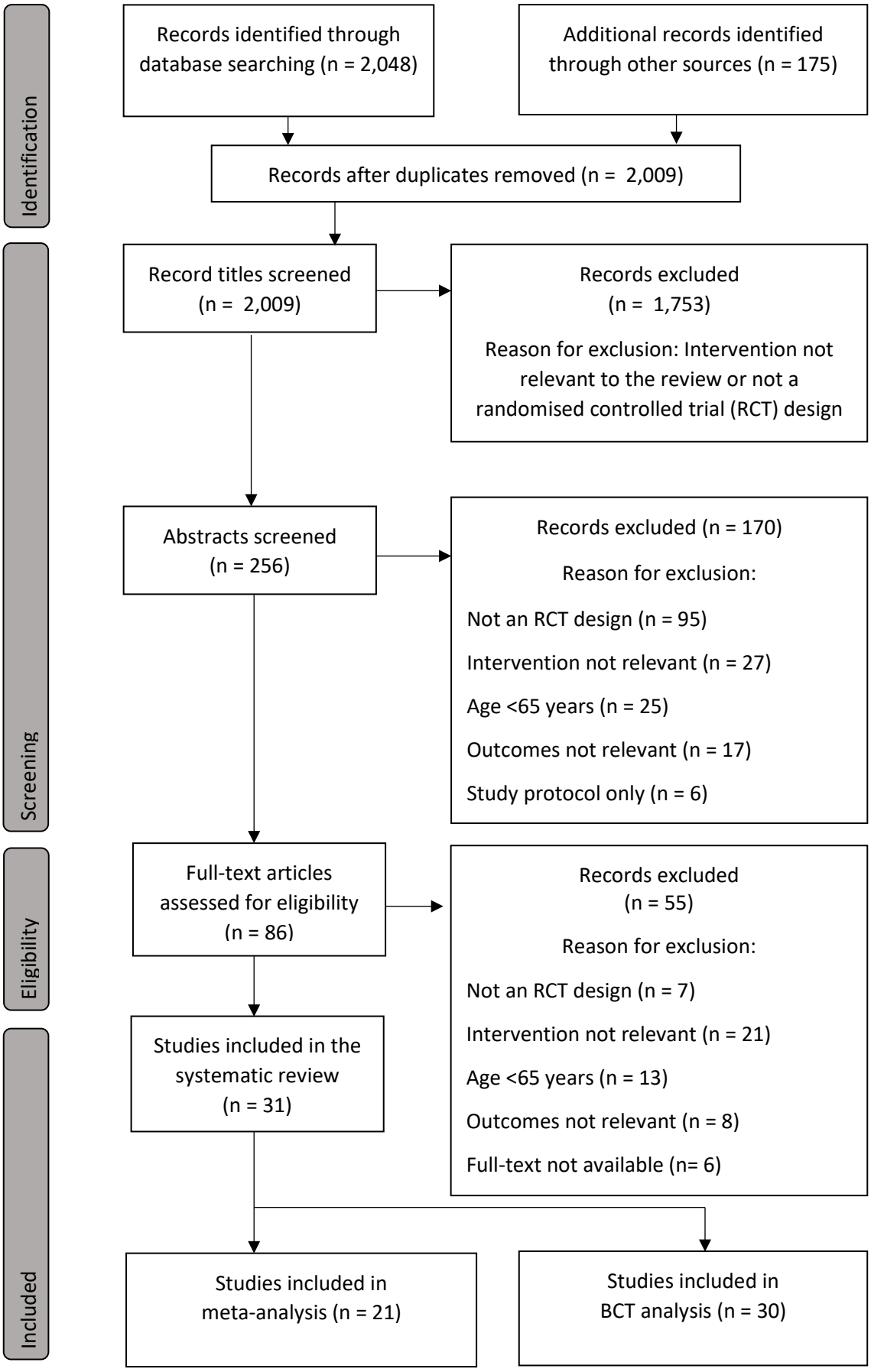

Figure 3.1 PRISMA flow chart of study selection for the systematic literature review

3.5.2 Study characteristics

Included studies were RCTs (n=26) and cluster RCTs (n=5) with a follow-up period from 30 days [172] to 13 months [173]. A total of 22,662 patients were enrolled in the studies ranging from 50 [174] to 1188 per study [144]. Detailed study characteristics are provided in **Table 3-2**. Three studies aimed primarily to reduce the number of drugs taken by patients [102, 175, 176]. Other objectives included reduced prevalence of inappropriate medications [172, 173, 177-183], improved prescribing appropriateness [41, 144, 174, 184-192], or better patient health outcomes and medicines management [185, 193-196]. Thirteen out of the 31 studies included in this review has shown evidence to support intervention effectiveness [41, 102, 145, 174, 175, 182, 185, 187, 190, 192, 194, 195, 197]. Most of the studies reporting intervention effectiveness of the key outcomes of this review delivered recommendations or feedback to the prescriber orally, often face-to-face, and many of them followed up on the recommendations/feedback given. Recommendations and feedback were given immediately after identification of a problem or at the time of prescribing using an on-demand service. For studies reporting no intervention effectiveness on the key outcomes, some of them delivered recommendations using written communication and many of the interventions did not follow up on the recommendations with the prescriber. None of the included studies reported the use of explicit theories of behaviour change as part of the interventions and no study reported the use of a systematic and theoretical approach, such as the UK Medical Research Council's complex intervention framework [198], in the intervention design. Reported educational interventions were based on the principles of constructive learning theory in one study [181] and social constructivist learning and self-efficacy theory in another study [102].

Table 3-2 Characteristics of studies included (n=31) in the systematic literature review.

Author (year)	Country Setting	No. of patients % Female	Mean age of patients (±SD), years	Intervention (I) Delivered by (D)	Target behaviour Target person(s) (P)
Allard *et al.* (2001)	Canada Community	266 67.7%	80.6 (4.5)	(I) Medication review and suggestions made and mailed to GPs. (D) Multidisciplinary team of physicians, pharmacists and nurses.	Reducing the number of potentially inappropriate prescriptions given. (P) GPs.
Bregnhøj *et al.* (2009)	Denmark Primary care physician practice	212 66.1%	76.5 (7.2)	(I) Interactive educational meeting (single intervention) and combined with individualised feedback on prescribed medication (combined intervention). (D) Clinical pharmacologist and pharmacists.	Improving prescribing appropriateness. (P) GPs.
Campins *et al.* (2017)	Spain Primary care health centres	503 58.8%	Intervention: 79.2 (±5.5) Control: 78.8 (±5.5)	(I) Medication review and recommendations provided based on the STOPP/START criteria and GP-GP algorithm (D) Clinical pharmacist	Improving prescribing appropriateness (P) Primary care physicians
Cossette *et al.* (2017)	Canada University teaching hospital	254 hospital-isations[a] 60.2%	Intervention: 81.5 (±7.7) Control: 80.5 (±7.0)	(I) Computer alerts based on geriatric explicit criteria[b] assessed for clinical relevance and recommendations formed. (D) Study pharmacist	Discontinuation of PIM and dosage decrease (P) Treating hospital physician
Crotty *et al.* (2004)	Australia Nursing home	154 59.6%	84.5 (5.0)	(I) Medication review and case conferences. (D) Multidisciplinary team of geriatrician, pharmacist, representative of the Alzheimer's Association of South Australia	Improving medication appropriateness. (P) Residential care staff and residents' GPs.
Dalleur *et al.* (2014)	Belgium Teaching hospital	146 63.0%	85.0 (5.2)	(I) Medication review and recommendations provided to discontinue medications based on the STOPP criteria. (D) Multidisciplinary team of nurses, geriatricians, dietician, occupational therapist, physiotherapist, speech therapist and psychologist	Discontinuation of PIMs (P) Hospital physicians

Author (year)	Country Setting	No. of patients % Female	Mean age of patients (±SD), years	Intervention (I) Delivered by (D)	Target behaviour Target person(s) (P)
Fick *et al.* (2004)	USA Primary care physician practice	Not specified	Not specified	(I) Decision support service comprising educational brochure, list of suggested inappropriate medications based on the STOPP criteria, and list of patients with STOPP criteria identified. (D) Research team and expert panel of physicians and pharmacists	Changing prescribing behaviour and decreasing PIM use. (P) GPs
Frankenthal *et al.* (2014)	Israel Chronic care geriatric facility	239 66.6%	82.7 (8.7)	(I) Medication review and recommendations provided based on the STOPP/START criteria. (D) Study pharmacist.	Improving clinical and economic outcomes by giving STOPP/START recommendations. (P) Chief physicians.
Fried *et al.* (2017)	USA Veterans Affairs primary care clinics	128 1.6%[c]	40.6% aged 65-70 44.5% aged 70-79 14.8% aged ≥70	(I) A computer-generated patient-specific medicines management report for the clinician and a short report for the patient. (D) Computer and research team	Improve shared decision-making about medications between patients and clinicians to improve medication regimen. (P) Clinician and patient
Gallagher *et al.* (2011)	Ireland Teaching hospital	382 53.1%	75.6 (7.3)	(I) Medication review and recommendations provided to change medications based on the STOPP/START criteria. (D) Research physician.	Improving prescribing appropriateness (P) Hospital physician and medical care team
García-Gollarte *et al.* (2014)	Spain Nursing home	1,018 73.0%	84.4 (12.7)	(I) Educational workshops, material and on-demand advice on prescriptions. (D) Nursing home physician with geriatric expertise.	Improving the quality of prescriptions (P) Nursing home physicians
Hanlon *et al.* (1996)	USA Ambulatory clinic	172 1.0%[a]	69.8 (3.8)	(I) Medication review and prescribing recommendations provided. (D) Pharmacists.	Improving prescribing appropriateness (P) GPs and patients

Author (year)	Country Setting	No. of patients % Female	Mean age of patients (±SD), years	Intervention (I) Delivered by (D)	Target behaviour Target person(s) (P)
Lenaghan *et al.* (2007)	United Kingdom Primary care physician practice	136 65.6%	84.3‡	(I) Medication review and development of action plan of agreed amendments. (D) Pharmacists.	Reducing hospital admissions and number of drug items prescribed (P) GPs and patients
Martin *et al.* (2018)	Canada Community pharmacy	489 65.8%	75 [range 66-93]	(I) Educational brochure to patients and educational material in the form on an evidence-based pharmaceutical opinion that pharmacists used to communicate recommendations. (D) Community pharmacists	Reducing inappropriate prescriptions (P) Primary care physicians and patients
Meredith *et al.* (2002)	USA Home health setting	317 74.9%	80.0 (8.0)	(I) Medication review and development of action plan to address identified problem. (D) Multidisciplinary team of physicians, nurses and pharmacists.	Improving medication use (P) Nurses and patients
Milos *et al.* (2013)	Sweden Nursing home and community	374 74.9%	87.4 (5.7)	(I) Medication review and feedback given to physician on drug-related problems. (D) Pharmacists.	Reducing the number of patients using PIMs (P) GPs
Moga *et al.* (2017)	USA University	50 70.0%	77.7 (±6.6)	(I) Interdisciplinary medication review to identify inappropriate use of anticholinergic drugs and to recommend discontinuation or substation to a safer alternative. (D) Pharmacists and physicians	Inappropriate use of anticholinergic drugs. (P) Patients
Pitkälä *et al.* (2014)	Finland Nursing home	227 71.0%	83.0 (7.2)	(I) Staff training and list of harmful medication provided to encourage nurses to bring this to the physician's attention. (D) Research team.	Improving the use of potentially harmful medications (P) Nurses

Author (year)	Country Setting	No. of patients % Female	Mean age of patients (±SD), years	Intervention (I) Delivered by (D)	Target behaviour Target person(s) (P)
Pope *et al.* (2011)	Ireland Hospital	225 62.9%	82.9[‡]	(I) Clinical assessment by a senior doctor and multidisciplinary medication review using Beer's criteria. Recommendations given to GP. (D) Consultant or senior specialist registrar and a multidisciplinary panel of consultant geriatricians, specialist registrars, hospital pharmacists and senior nurse practitioners.	Reducing the number of drugs prescribed (P) GPs
Potter *et al.* (2016)	Australia Nursing home	95 52.0%	84.0 (7.0)	(I) Medication review and cessation plan of non-beneficial medications. (D) Research team of GP and geriatrician.	Reducing the total number of medicines taken (P) GPs and patients
Richmond *et al.* (2010)	United Kingdom Primary care trusts	760 43.2%	80.4 (4.1)	(I) Pharmaceutical care including medication reviews. (D) Research team.	Improving prescribing appropriateness (P) GPs
Saltvedt *et al.* (2005)	Norway Teaching hospital	254 65.0%	82.1 (5.0)	(I) Comprehensive geriatric assessment and treatment of all illnesses. (D) Multidisciplinary team of geriatrician, nurses, residents, occupational therapists and physiotherapists.	Increasing the number of drugs withdrawn (P) Medical care team
Schmader *et al.* (2004)	USA Hospital	864 2.5%[†]	46% aged 65-73 54% aged ≥74 years	(I) Treatment in a geriatric evaluation and management unit (GEMU) in either inpatient or outpatient care or both. (D) Pharmacists and a multi-disciplinary team of geriatrician, social worker and nurse.	Improving prescribing (P) Medical care team
Spinewine *et al.* (2007)	Belgium Hospital	203 69.4%	82.2 (6.6)	(I) Pharmaceutical care including medication review and development of a therapeutic care plan with prescribing recommendations. (D) Pharmacists.	Improving prescribing appropriateness (P) Medical care team and patients

Author (year)	Country Setting	No. of patients % Female	Mean age of patients (±SD), years	Intervention (I) Delivered by (D)	Target behaviour Target person(s) (P)
Tamblyn *et al.* (2003)	Canada Primary care physician practice	12,560 62.7%	75.4 (6.3)	(I) Electronic alerts instituted in the electronic patient prescription record to identify prescribing problems. (D) Research team.	Reducing inappropriate prescribing (P) GPs
Tannenbaum *et al.* (2014)	Canada Community pharmacy	303 69.0%	75.0 (6.3)	(I) Educational booklet to empower and encourage patients to discontinue benzodiazepines. (D) Research team.	Discontinuation of benzodiazepines (P) Patients
Vinks *et al.* (2009)	The Netherlands Community pharmacy	196 74.7%	76.6 (6.5)	(I) Medication review and prescribing recommendations provided. (D) Pharmacists	Reducing the number of potential DRPs[$] and the number of drugs (P) GPs
Weber *et al.* (2008)	USA Ambulatory clinic	620 79.3%	76.9[‡]	(I) Electronic messages sent to physician via electronic medication record to give prescribing recommendations. (D) Pharmacist and geriatrician.	Reducing medication use (P) GPs
Williams *et al.* (2004)	USA Ambulatory clinic	140 57.1%	73.7 (5.9)	(I) Medication review based on MAI and prescribing recommendations provided and action plan made. (D) Pharmacists.	Simplifying medication regimens (P) Patients
Wouters *et al.* (2017)	The Netherlands Nursing homes	426 67.6%	Intervention: 83.7 (±9.5) Control: 83.2 (±8.9)	(I) Training about conducting multidisciplinary medication review (D) Research team	Discontinuation of inappropriate medication. (P) Nursing home physicians and hospital pharmacist/nursing home pharmacist
Zermansky *et al.* (2001)	United Kingdom Primary care physician practice	1188 56.0%	73.5 (6.5)	(I) Prescription review and treatment recommendations given to patients. (D) Pharmacist and physician.	Making changes to repeat prescriptions and reducing the number of medicines taken (P) Patients

[a]The randomisation was performed on hospitalisation-level rather that patient-level. This meant that a patient could be included more than once, and the 254 hospitalisations occurred in 231 patients. The baseline characteristics in the study are reported for the hospitalisations. [b]The set of criteria was based on the Beers criteria and the STOPP criteria. [c]The low proportion of females reported was explained by the nature of male patients in veterans' affairs clinics.

[†] The low percentages of females reported was explained by the nature of male patients in Veterans Affairs (VA) clinics. [‡] The SDs were not reported and could not be retrieved from the authors. [$]DRP = drug-related problem.

3.5.3 Risk of bias

Risk of bias assessment is illustrated in **Figure 3.2**. Risk of bias not pertaining to any of the defined categories were categorised as 'others' and these are described in **Table 3-3**.

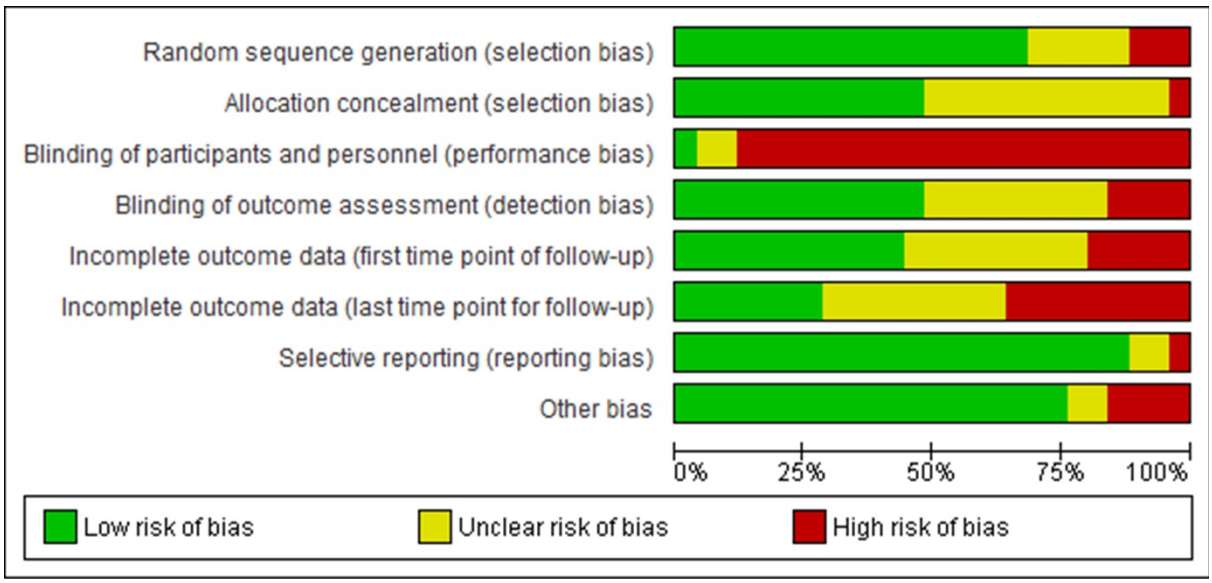

Figure 3.2 Results of risk of bias assessment

Table 3-3 Description of 'other bias' detected for the included studies.

Study	Judgement of other bias	Justification
Allard *et al.* (2001)	High risk	No information on how the study chose which physician to contact for each patient, i.e. no information of whether it was the primary prescriber or the prescriber who prescribed most of the medications. This may have had an effect on their actions on the recommendations given and their collaboration. Some of the prescribers had patients in both experimental and control group and there may have been a carry-over-effect. However, the study reported that this had no effect on the outcomes.

Study	Judgement of other bias	Justification
		No control for number of prescribers and some patients had multiple prescribers which may have had an effect on the outcomes.
Cossette *et al.* (2017)	High risk	The randomization was conducted by hospitalization; therefore, a patient could be included in the intervention and control groups during separate hospitalizations. This was the case for 10 patients.
Crotty *et al.* (2004)	Unclear risk	The study is a cluster-RCT, but the clustering was not accounted for in the data analysis. Rather than analysing the data at cluster-level, the data were analysed at patient-level by pooling the data for the intervention clusters into one group and pooling the data for the control cluster into one group (i.e. one control group and one within-facility control group). The study did not account for correlation between observations for patients in the same cluster.
Fick *et al.* (2004)	Unclear risk	During the 6-month follow-up after the end of the study, the study mentioned that: "During our study period, major changes occurred in the primary care physician network, with 78 primary care providers leaving the network, 129 joining the network….so we did not conduct a further analysis of PIM use at the provider level".
Fried *et al.* (2017)	High risk	Physicians were treating both control and intervention patients. Although, not simultaneously, this may have contaminated the control group and affected the true findings of the intervention effectiveness.
Pitkälä *et al.* (2014)	Low risk	There may have been potential contamination if some of the healthcare professionals worked in multiple wards during the study.

Study	Judgement of other bias	Justification
Pope *et al.* (2011)	High risk	Prior to admission, the suitability of each patient for admission to a continuing-care ward had been assessed by a multidisciplinary panel chaired by a consultant geriatrician. Some medication-related problems may have been solved prior to randomisation. The study commented on this. GPs in the control group had access to specialist geriatric medicine advice on request. The study did not report how often the GPs requested this and what the outcome was. This may have affected the outcomes for the control group and "hidden" the "true" effect of the intervention.
Richmond *et al.* (2010)	High risk	The study had underestimated the number of drugs prescribed to patients at the final time point used in the study. As a result, there was a significant difference in the mean number of drugs shown on prescription at the final time point compared with the number over the four previous months (difference=1.14, 95% CI 1.01, 1.27). The number of drugs affects the UK-MAI score (primary outcome), and this appeared to indicate that medication appropriateness had improved at the final follow-up time point. The study commented on this and corrected for this.
Saltvedt *et al.* (2005)	High risk	"Suitable patients were screened when there was a free bed in the specialist ward. Eligible patients who had been recently admitted to the department were preferred over those who had been there longer." This could have introduced a selection bias which could have affected the generalisability of the findings to the wider population.

Study	Judgement of other bias	Justification
Spinewine *et al.* (2007)	Low risk	Because the same physicians were caring for control and intervention patients, contamination of control patients was possible. To assess this bias, two investigators applied the outcome assessment to a random sample of 90 patients to the unit 1 year before the study, i.e. a "historical control group". This could only be done for two of three primary outcome measures.
Tamblyn *et al.* (2003)	Unclear risk	The study experienced two problems that influenced the effectiveness of the computer-system intervention, these being co-payments for prescription drugs increased when the study began and many software problems that resulted in information downloaded less often. Another potential bias was the study design using cluster-randomisation. However, the study did account for the clustering in the data analysis: "Physicians were identified as the clustering factor within which rates were examined, and an exchangeable correlation structure was used to take into account the dependence of observations for patients of the same physician." We consider no risk of bias associated with clustering and data analysis.
Tannenbaum *et al.* (2014)	Low risk	The study design was a cluster-RCT with community pharmacies as the clusters. When assessing the primary outcome (complete cessation of benzodiazepine use) the study used the participant as the unit of analysis, the community pharmacy as the cluster, an exchangeable correlation coefficient to account for clustering effects of participants within the same cluster.

Study	Judgement of other bias	Justification
Wouters *et al.* (2017)	High risk	Although the study used a cluster randomized design to prevent contamination bias, physicians from the intervention group collaborated closely with physicians from the control group. This could have increased the change that actual effects of the intervention are not detected.

3.5.4 Behaviour change techniques

All but one study [193] reported the behaviour change components underpinning the intervention and 30 of the 31 studies were included in the BCT analysis. The BCT coding is presented in **Table 3-4**. Examples of behaviours described in the included studies categorised into the BCT codes are provided in **Table 3-5**.

Table 3-4 Behaviour change techniques taxonomy version 1 (BCTTv1) applied to the included studies and the prevalence of each BCT and BCT cluster [165].

BCTTv1 cluster	All studies (n=28)	Studies reporting effect (n=13)	Weighted frequency for studies reporting effect	Studies reporting no effect (n=17)	Weighted frequency for studies reporting no effect
1. Goals and planning	19	11	24	8	13
1.1 Goal setting (behaviour)	1	1	2	0	0
1.2 Problem solving	6	3	6	3	5
1.3 Goal setting (outcome)	3	2	4	1	2
1.4 Action planning	8	4	9	4	7
1.5 Review behaviour goal(s)	1	1	2	0	0
2. Feedback and monitoring	29	10	22	19	31
2.1 Monitoring of behaviour by others without feedback	4	2	4	2	3
2.2 Feedback on behaviour	14	4	9	10	16
2.3 Self-monitoring of behaviour	3	2	4	1	2
2.4 Self-monitoring of outcome(s)	2	0	0	2	3
2.7 Feedback on outcome(s) of behaviour	6	2	4	4	7
3. Social support	12	5	11	7	12
3.1 Social support (unspecified)	10	5	11	5	8
3.2 Social support (practical)	2	0	0	2	3
4. Shaping knowledge	21	10	22	13	21
4.1 Instruction on how to perform a behaviour	21	11	24	11	18
4.3 Re-attribution	1	0	0	1	2
5. Natural consequences	11	6	13	5	8

BCTTv1 cluster	All studies (n=28)	Studies reporting effect (n=13)	Weighted frequency for studies reporting effect	Studies reporting no effect (n=17)	Weighted frequency for studies reporting no effect
5.1 Information about health consequences	9	5	11	4	7
5.2 Salience of consequences	1	1	2	0	0
5.3 Information about social and environmental consequences	1	0	0	1	2
6. Comparison of behaviour	4	2	4	2	3
6.1 Demonstration of the behaviour	3	1	2	2	3
6.3 Information about others' approval	1	1	2	0	0
7. Associations	4	0	0	4	7
7.1 Prompts/cues	4	0	0	4	7
8. Repetition and substitution	6	2	4	4	7
8.1 Behavioural practice/rehearsal	3	1	2	2	3
8.2 Behaviour substitution	3	1	2	2	3
9. Comparison of outcomes	19	7	15	9	15
9.1 Credible source	16	9	19	10	16
10. Reward and threat	1	0	0	1	2
10.4 Social reward	1	0	0	1	2
11. Regulation	1	1	2	0	0
11.1 Pharmacological support	1	1	2	0	0
12. Antecedents	4	2	4	2	3
12.1 Restructuring the physical environment	1	1	2	0	0
12.5 Adding objects to the environment	3	1	2	2	3
13. Identity	1	1	2	0	0

BCTTv1 cluster	All studies (n=28)	Studies reporting effect (n=13)	Weighted frequency for studies reporting effect	Studies reporting no effect (n=17)	Weighted frequency for studies reporting no effect
13.2 Framing/reframing	1	1	2	0	0

Table 3-5 Examples of behaviours from the included studies coded into the BCT codes and clusters.

BCT cluster	BCT code	Examples of behaviour descriptions from the included studies
Goals and planning	Action planning	"For patients in the intervention group, the pharmacist composed a list of recommended changes to medications (…) Within 2 weeks after the date of inclusion, these recommendations were discussed with the GP according to a fixed format in which the DRPs and recommendations were classified. (...) The consultation with the GP ultimately resulted in a mutually accepted list of actions for the pharmacist as well as for the GP." [199]
Shaping knowledge	Instruction on how to perform a behaviour	"Alerts were instituted to identify 159 clinically relevant prescribing problems in the elderly (…) The alerts appeared when the electronic chart was opened, when prescription record updates were downloaded, and when current health problems and prescriptions were recorded by the physician in the chart. Each alert message identified the nature of the problem and possible consequences and suggested alternative therapy in accordance with the expert consensus." [173]
Natural consequences	Information about health consequences	"Primary care physicians participated in an interactive educational meeting on the subject of polypharmacy and appropriateness of prescribing. The meeting included background information on the causes and consequences of polypharmacy, areas of concern in the treatment of the elderly and group discussions on patient cases." [184]
Comparison of behavior	Information about others' approval	"Patients were informed that their primary physician had endorsed the recommended adjustments." [197]
Comparison of outcomes	Credible source	"An experienced clinical pharmacist reviewed the drug lists and made recommendations. The pharmacist then discussed recommendations for each drug with the physician to come up with a final set of recommendations" [192]

Based on the studies reported results, 13 of the 30 studies showed an effect on the key outcomes (i) or (ii) of this systematic review when comparing the intervention group to the control group [41, 102, 145, 175, 182, 185, 187, 190, 192, 194, 195, 197]. No clear relationship was seen between the number of individual BCTs used and reported intervention effectiveness. The median number of BCTs used were similar for studies reporting effective and non-effective interventions (6 BCTs, IQR 3-8 and 5 BCTs, IQR 4-7, respectively). BCT clusters coded more frequently in studies reporting effectiveness compared to studies reporting no effectiveness were: *goals and planning; shaping knowledge; natural consequences; comparison of behaviour*; *comparison of outcomes; regulation; antecedents; and identity* (see **Figure 3.3**).

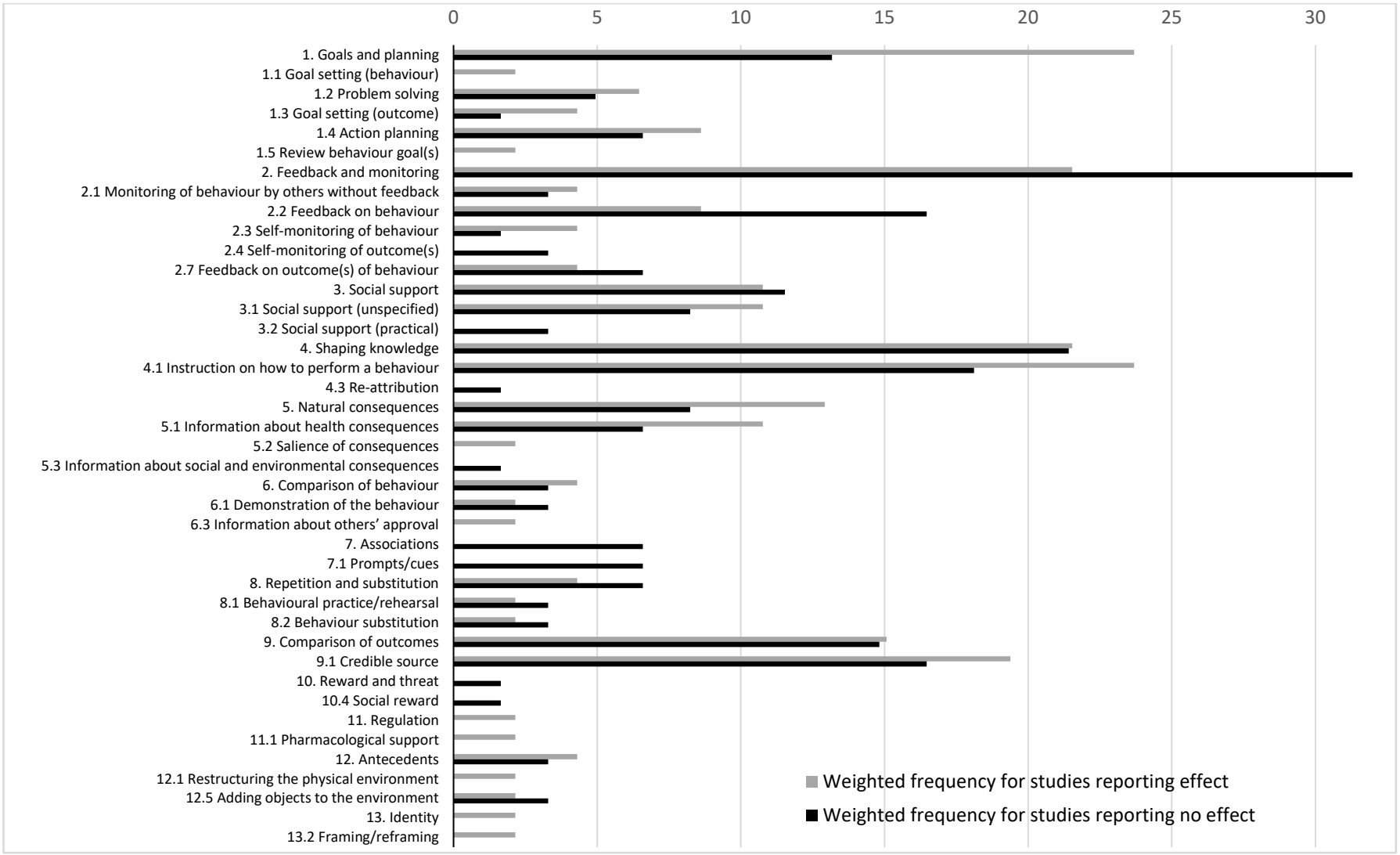

Figure 3.3 Frequency of behaviour change techniques (BCTs) coded for studies reporting intervention effectiveness on the key outcomes of this review compared to studies reporting no effectiveness of interventions. The frequencies are weighed values based on the number of studies in each group, i.e. effectiveness versus no effectiveness.

3.5.5 Intervention effectiveness

3.5.5.1 *Drug use*

Overall, the mean number of drugs post-intervention was significantly lower among intervention participants compared to the control participants in the presence of moderate between study heterogeneity (mean difference -0.96, 95% CI -1.53, -0.38, heterogeneity I^2=70% and P=0.002, **Figure 3.4**).

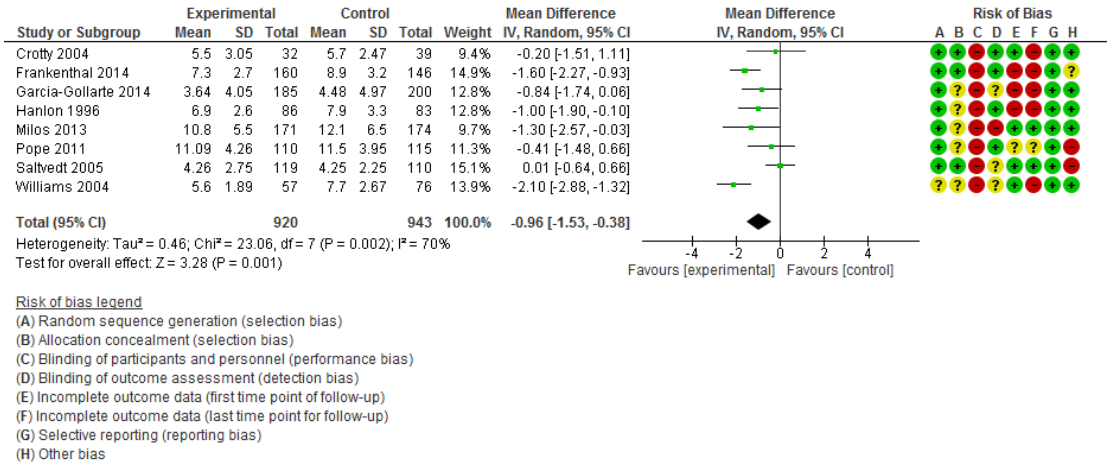

Figure 3.4 Mean number of drugs per patient post-intervention comparing experimental (intervention) group and control group.

Regarding the difference in change in the number of drugs taken per patient, deprescribing interventions lowered the number (-0.72, 95% CI -1.17, -0.27), but effects varied largely across studies (I^2=91%, P<0.001) (**Figure 3.5**). Stratified analyses by: (i) whether the intervention was patient-centred or targeting solely healthcare professionals (**Figure 3.6**), (ii) intervention setting (**Figure 3.5**) and (iii) study quality (**Figure 3.7**) showed no effect of these factors on summary estimates. In addition, the unexplained variation within subgroups remained large.

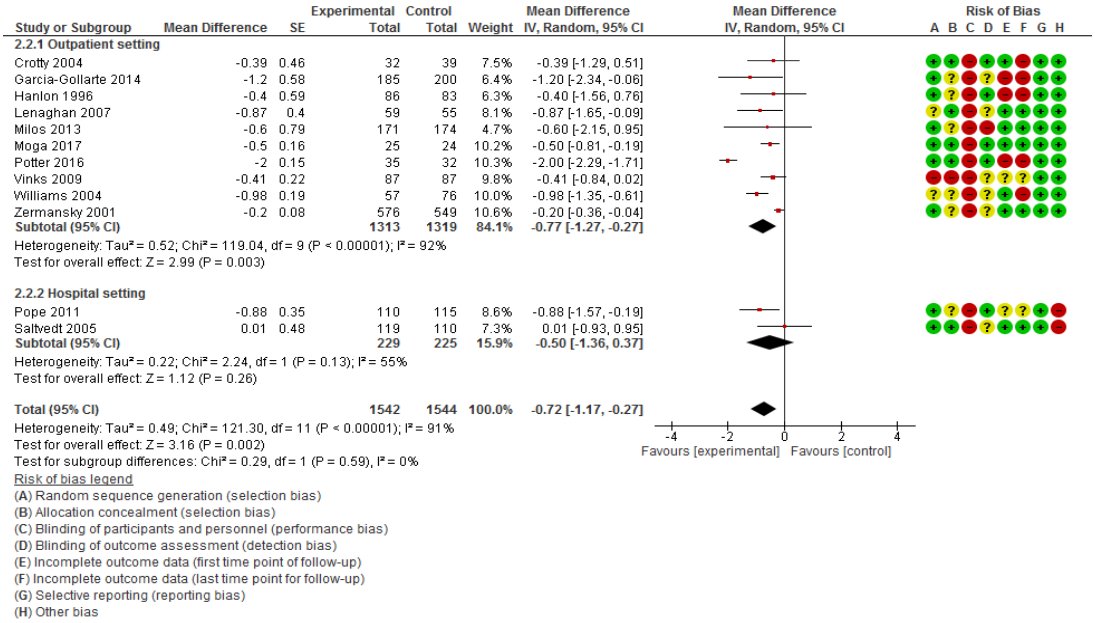

Figure 3.5 Mean difference in the change in number of drugs comparing experimental (intervention) group and control group. Subgroup analysis on intervention setting (outpatient setting versus hospital setting).

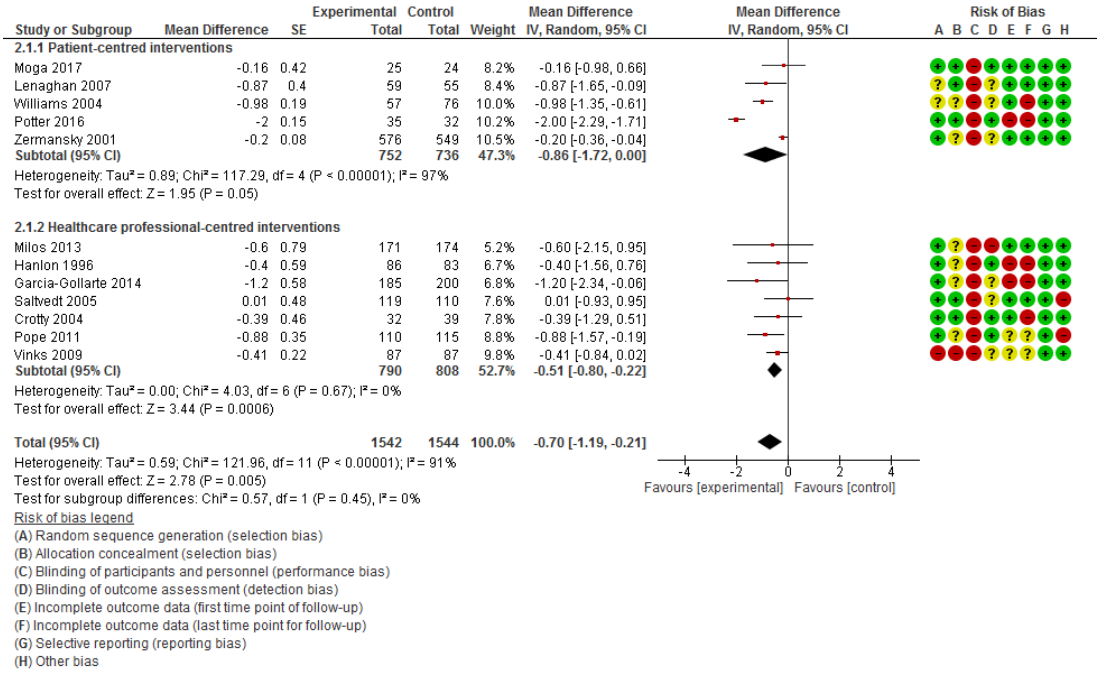

Figure 3.6 Subgroup analysis on target person (patient or healthcare professional) for mean difference in the change in number of drugs per patient.

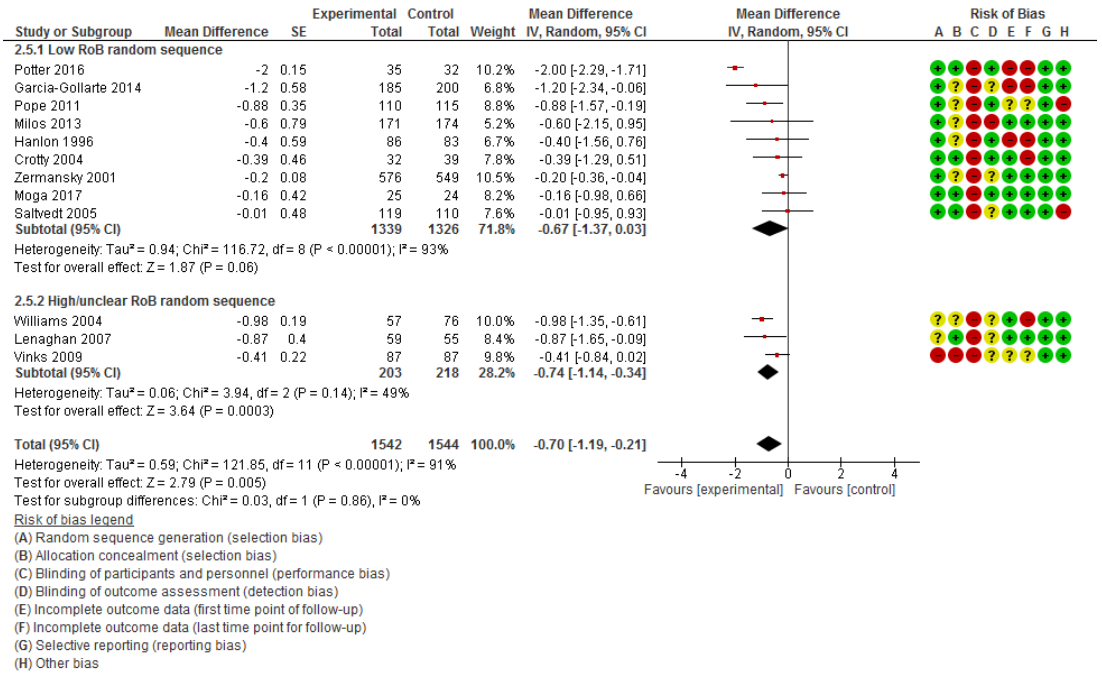

Figure 3.7 Subgroup analysis on risk of bias assessment (random sequence generation) for mean difference in the change in number of drugs per patient.

3.5.5.2 *Discontinuation of drugs*

Four of the included studies reported on the number of discontinuations of drugs/inappropriate drugs [172, 182, 183, 192]. This outcome was reported as the number of patients with a drug discontinuation post-intervention compared across three of the studies [182, 183, 192] and the findings were summarised in a meta-analysis **(Figure 3.8**). The proportion of control participants experiencing a drug discontinuation was significantly smaller than the proportion of intervention participants, but confidence intervals were wide, and a high level of heterogeneity was present. This finding is illustrated as a signi (**Figure 3.8**). The fourth study by Cossette *et al.* [172] reported a significant increase in drug cessations and dosage decreases in the intervention group compared to the control group at 48h post-alert (+30.0%) and at hospital discharge (+20.8%). However, this increase was not significant when looking at drug cessation only at hospital discharge (+10.7%, 95%CI -10.5, 31.9).

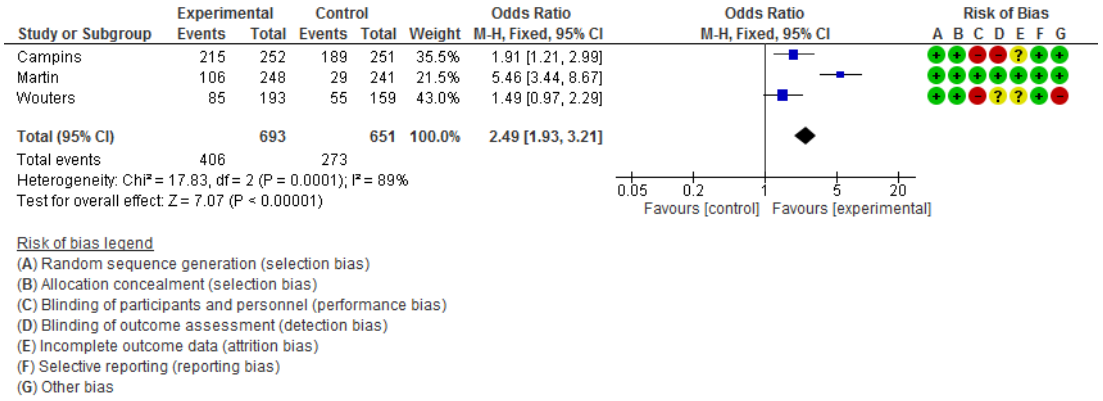

Figure 3.8 Number of participants experiencing a drug discontinuation comparing experimental (intervention) group and control group.

3.5.5.3 *Prescribing appropriateness*

Deprescribing interventions demonstrated a relatively small effect and a high level of heterogeneity on the number of inappropriate drugs per participant comparing intervention and control groups post-intervention (-0.19, 95% CI -0.40, 0.02, heterogeneity I^2=90% and P=0.07, **Figure 3.8**). The proportion of participants with at least one inappropriate drug, as defined in the individual studies, were reduced when a deprescribing intervention was applied, but confidence intervals were wide, and a high level of heterogeneity was present (**Figure 3.9**).

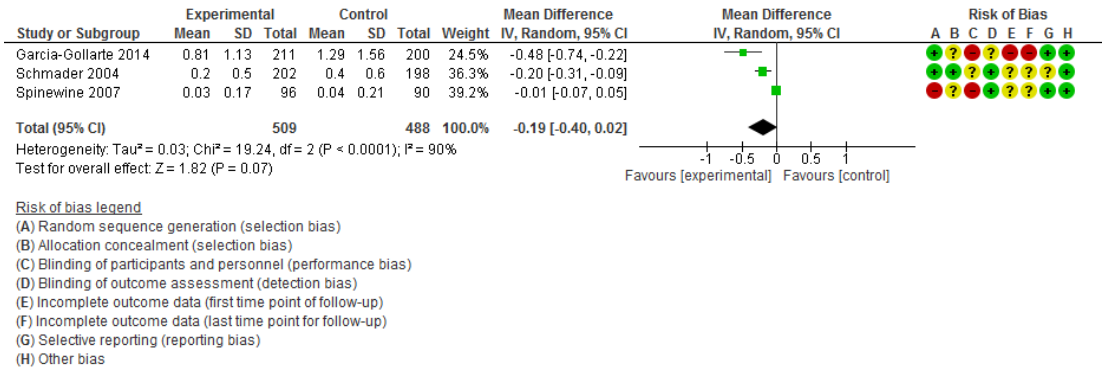

Figure 3.9 Mean difference in the number of inappropriate drugs per participant comparing experimental (intervention) group and control group.

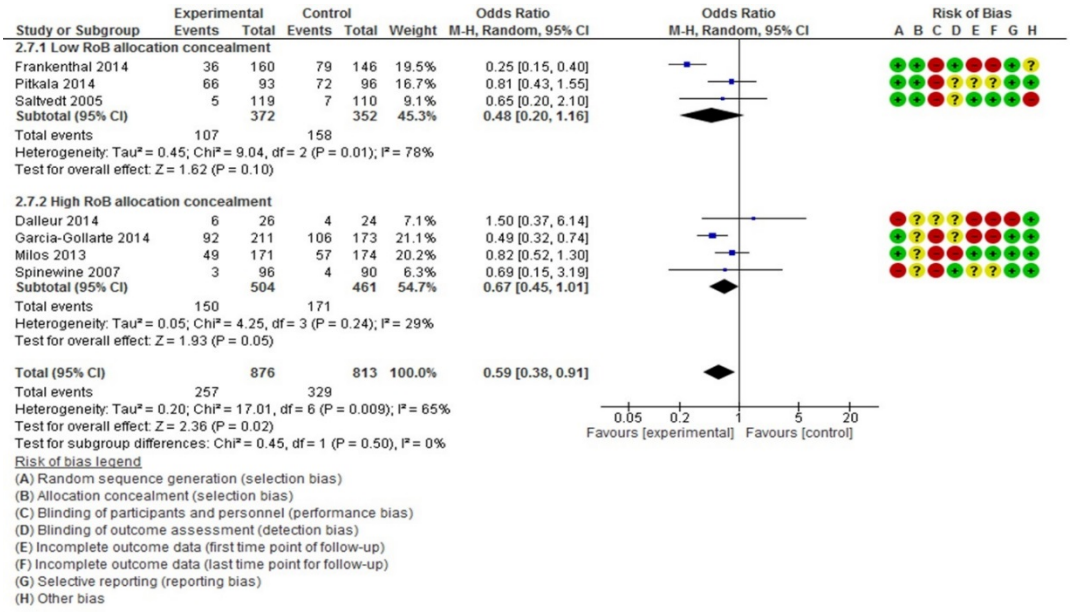

Figure 3.10 Number of participants with inappropriate drugs comparing experimental (intervention) group and control group. Subgroup analysis on risk of bias assessment (allocation concealment).

3.5.6 Implementation of recommendations

Seven studies reported implementation rates of recommendations to discontinue a medication or change a medication [179, 180, 183, 186, 192, 196, 199]. Action was taken in 55.1% of recommendations given by a pharmacist compared to only 19.8% of the nurse recommendations as part of usual pharmaceutical care by Hanlon *et al.* [186]. In the study by Vinks *et al.* [199], 27.7% of pharmacists recommendations were implemented, and action was taken in 56% of drug-related problems identified by a pharmacist in Milos *et al.* [180]. The study by Wouters *et al.* [183] reported that 97% of the interventions were implemented. The study by Campins *et al.* [192] showed that the patients' physicians accepted 80.9% of the clinical pharmacist's recommendations about PIP, while 29.7% of recommendations were implemented in Fried *et al.* [196]. A lower recommendation implementation rate of 15.4% was shown in Fick *et al.* [179] . This result was based on self-reported action taken by the physicians; only 71% of physicians reported this, which may explain the lower frequency of action observed.

3.5.7 Medication Appropriateness Index (MAI) score

Eight studies reported changes in MAI scores for participants pre- and post-interventions [41, 174, 184, 186, 188, 190, 191, 193], but only five of these studies provided sufficient data to be included in the meta-analysis (see **Figure 3.10**). Across studies, deprescribing interventions demonstrated a significant effect on reducing the MAI score (i.e. improving medication appropriateness) comparing intervention and control groups post-intervention (-5.04, 95% CI -7.40, -2.68, heterogeneity I^2=88% and P<0.0001, **Figure 3.10**). The study by Moga *et al.* [174] did not report the actual MAI-scores post-intervention but only the change in scores, and it was not possible to retrieve these values. Therefore, the results could not be included in the meta-analysis in **Figure 3.10**. However, the study showed a statistically significant reduction in MAI scores among intervention participants compared to control participants when adjusting for Clinic Dementia Rating global scores (-3.6 ±SE 1.1 versus -1.0 ±SE 0.9, P=0.04) [174].

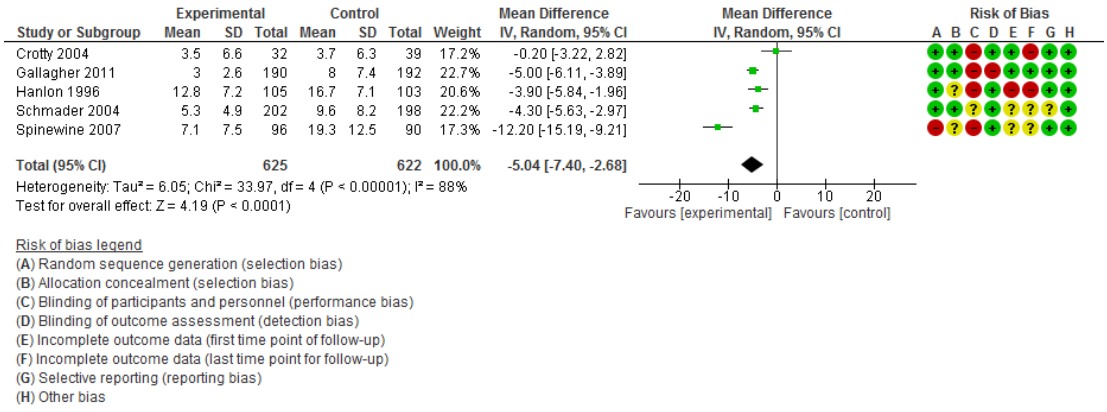

Figure 3.11 Mean difference in the change in MAI score per participant comparing experimental (intervention) group and control group.

3.6 Discussion

Effectiveness of deprescribing interventions is determined by a combination of factors. Consistent with the findings of recent reviews [71, 82], our meta-analysis showed that deprescribing interventions are effective in reducing the number of

drugs and inappropriate prescribing (reduced MAI-scores) in older people, although the evidence is heterogeneous.

Based on the findings of the BCT coding exercise, effective deprescribing interventions included (i) a goal and an action plan to solve prescribing problems, (ii) monitoring of behaviour, (iii) social support and the use of a credible source, (iv) clear instructions and guidance on implementation to the prescriber and information about health consequences of doing/not doing the behaviour. Support from colleagues and information about potential risks and benefits to the patients in the presence/absence of a behaviour change may also be effective techniques of deprescribing

Differences in the delivery of prescribing recommendations were seen in the studies reporting intervention effectiveness compared to studies reporting no effect on key outcomes of this review. Studies reporting effectiveness [41, 102, 145, 175, 185, 187, 190, 194, 195, 197] used oral and face-to-face communication to discuss and implement deprescribing recommendations consistent with the principles of educational outreach to inform clinical decision making as described by Soumerai *et al.* [200]. Investigation of the delivery of recommendations to deprescribe may provide useful information on the delivery of a successful deprescribing intervention in addition to the use of BCTs.

Pharmacist recommendations to reduce drug intake and inappropriate prescribing were frequently acted upon in some studies [180, 186], consistent with previous literature reporting benefits of pharmacist-led interventions to optimise medication use in older people [53, 201]. Other studies [179, 199] reported a lower acceptance rate of pharmacist recommendations, between 15% and 28% of recommendations implemented. Some recent research studies have demonstrated a high level of agreement between prescribers and pharmacists in the assessment of potential target medications for deprescribing [202, 203]. In contrast, other research indicates that acceptance rates for recommendations made by pharmacists are lower than the ones made by their physician colleagues [204]. The lower uptake of pharmacist recommendations despite a high level of agreement about deprescribing is noteworthy. It may indicate that challenges to deprescribing are in fact dependent on the particular ways deprescribing interventions are delivered, particularly when

there is a question of behaviour change. Based on the findings of this review, we suggest that future research should investigate the behaviours associated with the acceptance and rejection of deprescribing recommendations in order to gain a better understanding of a successful delivery of deprescribing interventions.

This is the first systematic review to identify BCTs in deprescribing interventions necessary to achieve a change in behaviours towards deprescribing. Our findings complement previous reviews on deprescribing [71, 106] by offering a broader analysis of BCTs that are effective for deprescribing.

3.6.1 Limitations and strengths

The review findings are based on a comprehensive search of the literature. The novel aspect of this systematic review is in the use of a validated taxonomy to describe intervention content that facilitates behaviour change. Limitations of this review reside mostly in the limited data available. RCTs to date are of a relatively small size (often ≤100 participants) and usually with short follow-up periods. Other limitations relate to the high-risk blinding procedures; these were needed because of the interventions in questions required blinding of the personnel whose behaviour was targeted, and this was logistically difficult. Absence of blinding procedures for outcome assessors was not considered to introduce important bias because the study outcomes, e.g. number of drugs taken, was not a very subjective measure. Random sequence generation and allocation concealment were considered highly important biases in this review because participant characteristics such as multimorbidity, age and polypharmacy could have an impact of the number of drugs taken and risk of inappropriate prescribing [55, 82, 85, 124, 152]. The meta-analysis was reliant on published or reported data, and while some studies reported outcomes that were adjusted for baseline patient characteristics others did not, which makes the direct comparison of intervention effect on specific outcomes open to question.

Similarly, and as described in a previous review [166], the BCT coding was limited to the intervention descriptions reported in the studies. Limited reporting on interventions used to encourage deprescribing could have resulted in BCTs being under-coded and others over-coded due to assumptions made about the strategies

used based on the information available. For example, it was assumed that the reporting of prescribing recommendations given to the prescriber would involve BCT codes: *instructions on how to perform a behaviour* and *feedback on behaviour*. Prescribing recommendations were a commonly used intervention in the studies, and this may have resulted in these two BCTs being over-coded. One study was also excluded from the BCT coding due to lack of information which could have potentially influenced the true findings of this review. Furthermore, it was not possible to code BCTs in the control groups due to limited reporting of the control conditions. The control conditions such as usual care in hospital settings or in outpatient settings could include BCTs with potential implications on the interpretation of the review findings. Since many interventions target multiple behaviours and outcomes, it can be difficult to explicitly link BCTs to a specific prescribing behaviour. Reporting of future behaviour change interventions would benefit from a more detailed description of the person whose behaviour is targeted for change and the intervention components implemented to change this behaviour. Reporting of this will enable future BCT analyses to better identify BCTs explicitly linked to changing the targeted behaviour. Future interventions may thus consider the use of comprehensive checklists, such as the TIDieR [205] when reporting the intervention in order to give reviewers the ability to adequately code BCTs and extensively appraise the reporting quality of such interventions [166]. This will improve the identification of relationships between BCTs used and behaviour(s) changed and inform the design of future interventions.

The main limitation of our pooled estimates is the presence of typically large between study variation and, for some of the analyses, the wide confidence intervals including trivial effects. Some may argue that a meta-analysis should not be done in the presence of substantial heterogeneity. Meta-analytical methods however allow for the exploration of sources of heterogeneity and therefore the magnitude of the summary estimates should be interpreted with caution. To minimise the level of heterogeneity due to different study designs, it was decided to limit the inclusion criteria to randomised controlled studies and cluster randomised controlled studies only. Although the direction of effect was favouring deprescribing, the magnitude of

effect was highly variable due to imprecision and risk of bias issues that lower the level of confidence in the estimates of effect.

Despite a comprehensive search of the literature, it cannot be assured that all relevant literature was identified and reviewed. This is a limitation of all literature reviews as it was in this systematic review. Inclusion and exclusion criteria applied to the screening of eligible literature may further be a limitation to the inclusion of all relevant literature. The focus of this systematic review was on healthcare professionals' views of the deprescribing process including the barriers and facilitators with deprescribing. Studies specifically focussing on the clinical effects of drug withdrawal were excluded. The clinical outcomes of drug withdrawal provide a crucial evidence-base to guide the deprescribing process and may influence deprescribing behaviours of healthcare professionals. Despite this, drug withdrawal interventions focussing specifically on clinical outcomes were excluded if they did not include the views of healthcare professionals on the deprescribing process, which was the primary focus of this review.

3.7 Conclusion

Deprescribing interventions are effective in reducing the number of drugs taken by patients and improving prescribing inappropriateness. Their success may be explained by a combination of BCTs spanning a range of different intervention functions, although this could not be shown empirically. The use of BCTs and delivery of such behaviour change interventions should be considered of importance to facilitate successful implementation of deprescribing. This systematic review contributes to the existing evidence by critically analysing the content of deprescribing interventions in terms of behaviour change, demonstrating clearly that the current evidence base is too small to derive strong conclusions on determinants of success.

4 Longitudinal patterns of potentially inappropriate prescribing in early old aged people

4.1 Chapter description

It is well-established that PIP is highly prevalent among older adults, with reported prevalence ranging from 21% to 77%, depending on the clinical setting [38, 41, 206]. PIP has been shown to be associated with an increased use of healthcare services and number of medications taken per patient. However, little is still known about the longitudinal pattern of PIP and the long-term effect on clinical outcomes.

This chapter examined the pattern of PIP over 5-year period among people in early old age (60-74 years) and provided a basis for understanding the long-term prevalence of PIP in this age group.

4.2 Publication

The work of this chapter has been published as Hansen CR, Byrne S, Cullinan S, O'Mahony D, Sahm LJ, Kearney PM. Longitudinal patterns of potentially inappropriate prescribing in early old-aged people. *European Journal of Clinical Pharmacology.* 2018;74(3):307-313. Doi: 10.1007/s00228-017-2364-6 (Appendix VII).

4.3 Introduction

Optimisation of pharmacotherapy is a core part of good medical care of older people [49, 207]. Medical treatment in older people is often challenged by age-related physiological changes affecting pharmacokinetic and pharmacodynamic responses to drugs, with higher risk of adverse drug-disease and drug-drug interactions [29, 49]. For that reason, many drugs must be used with caution in older people [49, 207]. The use of five or more daily drugs (i.e. polypharmacy) is increasing in older people and is associated with a higher risk of potentially inappropriate prescribing (PIP) for this population [115, 117]. PIP includes both the omission of a medical treatment that is clinically indicated in the patient for irrational or ageist reasons, potential prescribing omissions (PPOs) or the use of a medical treatment in which the risks outweigh the benefits through the use of potentially inappropriate medications (PIMs) [29, 37, 41].

Recent work by Cooper et al. [92] indicates high PIP prevalence in middle aged (45-64 years) people using Prescribing Optimally in Middle-aged People's Treatments (PROMPT) criteria. Using prescription databases, PIP prevalence rates among middle-aged people were found to be 21.1% and 42.9% in Northern Ireland and the Republic of Ireland, respectively [208]. The high level of PIP in middle age suggests that the well-recognised high prevalence of PIP in established old age (i.e. those aged ≥75 years) arises in late middle age/early old age [92]. However, to date, there are limited data with which to explore when in the life course the problem of PIP emerges.

PIP is well described in the older population [38, 46, 209, 210] and is shown to be associated with increasing age [29, 46] which in turn is associated with increasing multimorbidity. The acknowledged high prevalence of PIP in late life is thought to result directly from high levels of multi-morbidity and polypharmacy in this population [29, 38, 46, 194]. More information is needed on PIP in younger populations to assess potential opportunities of minimising PIP before people enter older age. Given the lack of published data on PIP in the pre-'old-old' age phase of life, we aimed to determine the longitudinal pattern of PIP in people aged between 60 and 74 years.

The central aim of the present study, therefore, was to assess the levels of PIP in early old age and to follow the trend of PPO and PIM prevalence over a 5-year interval in order to determine the longitudinal patterns of PPO and PIM prevalence.

4.4 Methods

This study involved secondary analysis of a previously described population-based cohort from a large primary-care centre in Ireland, the Mitchelstown cohort [211]. The cohort included a total of 2,047 men and women aged 50-69 years at recruitment in 2010-2011, and provided information on demographics, general health, medication use and private health insurance status. Updated information on clinical status, diagnoses and medications were obtained by researchers from annual screening of electronic patient records, and thus provided ongoing passive follow-up of participants between periods of active data collection. The follow-up screenings were scheduled every year, the first one commencing in April 2010 until April 2011, and following the patients to the end of the 5-year follow-up in October 2015. Patients were lost to active follow-up of the original cohort study [211] but this did not affect the passive follow-up data that were used in this study. I obtained detailed information on all prescribed medications from electronic patient records from enrolment in 2010-2011 until the end of 2015 [211]. The original medication data from baseline and all annual screenings were coded according to the WHO Anatomical Therapeutic Chemical (ATC) classification system [212]. Management of the original clinical data at baseline was completed and linked at patient-level to the coded medication data.

The Screening Tool to Alert doctors to Right Treatment (START) and Screening Tool for Older Persons' Prescriptions (STOPP) version 2.0 criteria [77, 213] were retrospectively applied to the medication data from baseline and annual screening of the electronic patient records in order to determine the prevalence of PPOs (START) and PIMs (STOPP) at annual time points over a prospective five-year period [77]. Participants were dichotomised according to presence or absence of any PPOs and PIMs at baseline. For a sub-analysis, the START/STOPP criteria triggered by the presence of more than one drug were removed to explore the effect of polypharmacy independent of those PPOs and PIMs triggered by drug combinations.

4.4.1 Statistics

The study population was summarised using descriptive statistics including means and standard deviations or median and interquartile range as appropriate for continuous variables, and proportions and percentages for categorical variables. Participant groups were compared using Pearson's chi-square test or Fisher's exact test for categorical variables, Mann-Whitney U test for nonparametric continuous variables, and paired t-test for normal distributed continuous variables. The proportions of patients with any PPOs or PIMs were compared for two consecutive years and for baseline and end of follow-up (year 6) using McNemar's test for paired groups [214]. Negative binomial regression models or Spearman's rank correlation model, where appropriate, were used to describe the correlation between the presence of any PPOs and any PIMs and the reported number of medicines and age for each year of follow-up. Generalised estimating equation (GEE) models with exchangeable correlations were fitted for overall PPO and PIM prevalence from baseline to follow-up, and followed by multivariate GEE analysis which adjusted for gender, age, number of medicines and number of new diagnoses over the five-year time frame to determine associations between these and PPO and PIM prevalence [215, 216]. The results are presented as both unadjusted and adjusted odds ratios (OR and aOR, respectively) with 95% confidence intervals (95% CI). Data analyses were performed using Stata software version 13 (StataCorp. College Station, TX. 2013) with a significance level of $p<0.05$.

4.5 Results

4.5.1 Baseline characteristics

From the total cohort of 2,047 patients, 978 participants (47.8%) were aged 60 to 74 years at recruitment and were eligible for inclusion in the current study. Due to incomplete data, four participants were not included in the analysis. Baseline participant characteristics are presented in **Table 4-1**. There were no significant differences in baseline characteristics between participants with PPOs and without PPOs. The proportion of people with ≥2 medications was higher for participants with PIMs compared to participants without PIMs (28% versus 19%, p=0.001); this is to be

expected, given the known association between polypharmacy and PIM occurrence [29, 38, 46, 208, 209]. Differences between participants with and without PIMs were non-significant for all other characteristics (**Table 4-1**).

4.5.2 STOPP/START

Based on data availability, 27 of 34 (79.4%) START criteria and 64 of 80 (80.0%) STOPP criteria were applied into this cohort. PPOs were detected in 304 participants (31.2%) and PIMs were identified in 347 participants (35.6%) at baseline (**Table 4.1**). Anxiety and rheumatological disorders were most often associated with PPOs, whilst hypno-sedatives (benzodiazepines and Z-drug hypnotics) and angiotensin-converting-enzyme (ACE) inhibitors were the most common drug classes accounting for PIMs (see the STOPP/START application in Appendix VIII). Three START criteria and 10 STOPP criteria are triggered by drug combinations and a subgroup analysis excluding these criteria was performed.

Table 4-1 Baseline characteristics of the total study sample (n=978) and for the study sample (n=974) dichotomized into people with and without PPOs and PIMs. Four participants had incomplete data and were excluded from the population dichotomized.

Baseline characteristics		Entire study population	With no medications (n=96, 9.9%)	With PPO (n=304, 31.2%)	Without PPOs (n=670, 68.8%)	*P* value	With PIMs (n=347, 35.6%)	Without PIMs (n=531, 54.5%)	*P* value
Population, n		978	978	974	974		974	974	
Age, years	Mean (SD)	64.8 (2.96)	64.3 (3.00)	64.7 (2.99)	64.8 (2.96)		64.9 (2.92)	64.8 (2.99)	
Age, years	Median (IQR)	64.2 (61.8-67.3)	64.2 (61.8-66.4)	64.2 (61.8-67.3)	64.2 (61.8-67.3)	0.896	65.1 (61.8-67.3)	64.2 (61.8-67.3)	0.850
60-64 years	N (%)	499 (51.0)	53 (55.2)	153 (50.3)	343 (51.2)		169 (48.7)	274 (51.6)	
70+ years	N (%)	15 (1.5)	1 (1.0)	3 (1.0)	12 (1.8)		7 (2.0)	7 (1.3)	
Gender, female	N (%)	505 (51.6)	46 (47.9)	148 (48.7)	353 (52.7)	0.247	184 (53.0)	271 (51.0)	0.564
Chronic conditions						0.200			
0	N (%)	225 (23.0)	22 (22.9)	80 (26.3)	142 (21.2)		79 (22.8)	121 (22.8)	
1	N (%)	238 (24.4)	30 (31.3)	69 (22.7)	169 (25.2)		80 (23.0)	128 (24.1)	0.931
≥2	N (%)	515 (52.8)	44 (45.8)	155 (51.0)	359 (53.6)		188 (54.2)	282 (53.1)	
Number of medications	Mean (SD)	2.1 (3.1)	0 (0)	2.4 (3.6)	2.0 (2.9)	0.144	3.2 (4.3)	1.8 (1.9)	
0	N (%)	100 (10.2)	96 (100.0)	33 (10.9)	63 (9.4)		0 (0)	0 (0)	
1	N (%)	682 (69.7)	0 (0)	200 (65.8)	482 (71.9)		250 (72.0)	432 (81.4)	<0.001*
≥2	N (%)	196 (20.0)	0 (0)	71 (23.4)	125 (18.7)		97 (28.0)	99 (18.6)	
Current smoker	N (%)	108 (11.0)	11 (11.5)	37 (12.2)	71 (10.6)	0.552	36 (10.4)	61 (11.5)	0.499
Private health insurance	N (%)	582 (59.5)	58 (59.5)	186 (61.2)	393 (58.7)	0.457	213 (61.4)	308 (58.0)	0.319
Living situation						0.379			
Living alone	N (%)	146 (14.9)	12 (12.5)	41 (13.5)	105 (15.7)		57 (16.4)	77 (14.5)	
Living with others	N (%)	638 (65.2)	67 (69.8)	203 (66.5)	435 (64.9)		218 (62.8)	353 (66.5)	0.352
Unspecified	N (%)	194 (19.8)	17 (17.7)	60 (19.7)	130 (19.4)		72 (20.7)	101 (19.0)	

*p<0.05, i.e. significant difference in the median number of medications between participants with and without PIMs.

4.5.3 PPO prevalence

The number of patients with at least one PPO increased significantly between consecutive years from baseline until year 3 of follow-up with a continuing increasing, but non-significant, trend until the end of follow-up. After 5 years, an additional 11% of participants (n=33) had at least one a PPO ($p<0.001$ **Table 4-3**). This finding shows that new patients were acquiring PPOs each year. However, the mean number of PPOs per participant did not significantly change from baseline to end of follow-up with a mean of 0.45 (SD 0.82) PPOs per participant at baseline compared to 0.42 (SD 0.49) at year 6 ($p=0.259$). This finding shows that the patients did not accrue more PPOs over time across the study population. Some of the principal PPOs identified most frequently in the study population are provided in **Table 4-2.**

Table 4-2 PPOs and PIMs identified most frequently in the study population

	Range of the number of patients in which the criterium was identified between baseline and follow-up
START criteria	
Antiplatelet therapy with a documented history of coronary, cerebral or peripheral vascular disease	28-59
Regular inhaled beta-2 agonist or antimuscarinic bronchodilator for mild to moderate asthma or COPD	31-57
Non-TCA antidepressant drug in the presence of persistent major depressive symptoms	39-53
SSRI for persistent severe anxiety that interferes with independent functioning	72-75
Disease-modifying anti-rheumatic drug with active, disabling rheumatoid disease	77-83
Vitamin D and calcium supplement in patients with known osteoporosis	36-52
Bone anti-resorptive or anabolic therapy in patients with documented osteoporosis	36-55
STOPP criteria	
Any duplicate drug class prescription	127-256
Benzodiazepines for ≥4 weeks	77-117
Acetylcholinesterase inhibitors with a known history of persistent bradycardia, hear block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate	74-80
Benzodiazepines	100-134
Hypnotic Z-drugs	71-86

Table 4-3 PPO and PIM prevalence over a five-year period (2010-2015) for the study population (n=974 for PPO and n=878 for PIM) identified by START and STOPP criteria version 2.0 and compared between each consecutive year and between baseline and five-year follow-up.

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
PPO, n (%)	304 (31.2)	338 (34.7)	362 (37.2)	385 (39.5)	398 (40.9)	412 (42.3)	411 (42.2)
Difference, % (95% CI)	-	3.5 (1.9; 5.1)	2.5 (0.9; 4.0)	2.4 (0.8; 3.9)	1.3 (-0.1; 2.8)	1.4 (0.0[a]; 2.9)	-0.1 (-1.2; 1.0)
P value	-	<0.001*	0.001*	0.002*	0.052	0.035*	0.845
PIM, n (%)	347 (39.5)	392 (44.5)	459 (52.1)	458 (52.0)	451 (51.2)	444 (50.4)	402 (45.6)
Difference (95% CI)	-	4.8 (2.9; 6.6)	7.6 (5.4; 9.9)	-0.1 (-2.9; 2.6)	-0.8 (-3.5;19.2)	-0.8 (-3.4; 1.8)	-4.8 (-6.8; -2.7)
P value	-	<0.001*	<0.001*	0.933	0.550	0.525	<0.001
Comparing baseline and year 6. PPO Difference, % (95% CI)						11.0 (8.7; 13.3), *P*<0.001	
Comparing baseline and year 6. PIM Difference, % (95% CI)						5.9 (3.9; 7.9), *P* <0.001	

*p<0.05, i.e. statistically significant. [a]the confidence interval was 0.003; 0.029, and did not included zero explaining the slightly significant value of P.

Unadjusted odds ratio (OR) showed a significant increase in the PPO prevalence comparing 5-year follow-up to baseline (OR 1.08, 95% CI 1.07; 1.09, **Table 4-4**). The multivariate GEE model showed that number of medicines and number of new diagnoses were significantly associated with change in PPO prevalence and the change in prevalence comparing follow-up to baseline was not significant after adjusting for these variables. The multivariate analysis showed no significant association of age and gender with change in PPO prevalence (**Table 4-4**).

Table 4-4 Univariate and multivariate GEE models for PPO and PIM prevalence showing the changes in the proportion of patients with a PPO or PIM during the study period and the association with the potential covariates; gender, age and number of medicines. Study population n=974 for PPO and n=878 for PIM, excluding n=96 with no medications at baseline.

	Any PPO	Any PIM
Unadjusted odds ratio (95% CI)		
Follow-up vs. baseline	1.082* (1.071; 1.093)	1.042* (1.029; 1.055)
Adjusted odds ratio (95% CI)		
Follow-up (vs. baseline)	1.037 (0.995; 1.080)	1.005 (0.963; 1.047)
Age (per year older)	1.033 (0.992; 1.075)	1.023 (0.984; 1.065)
Gender (female vs male)	0.813 (0.639; 1.033)	0.909 (0.717; 1.151)
Number of medicines (per higher number)	1.021* (1.011; 1.030)	1.103* (1.084; 1.123)
Number of new diagnoses[a] (per higher number)	1.054* (1.043; 1.065)	1.016* (1.022; 1.030)

*p<0.05, i.e. statistically significant. [a]new diagnoses refer to the diagnosed conditions after baseline data collection.

A positive but non-significant correlation was found between the number of PPOs and older age for all years of follow-up (**Table 4-5**).

Table 4-5 Correlation between older age and the number of PPOs and PIMs.

Correlation coefficient (*P*-value)	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
PPO and older age	-0.001 (0.978)	0.019 (0.561)	0.030 (0.359)	0.057 (0.077)	0.047 (0.142)	0.050 (0.118)	0.057 (0.074)
PIM and older age	0.036 (0.284)	0.085 (0.012)	0.063 (0.063)	0.070 (0.038)	0.054 (0.109)	0.050 (0.142)	0.068 (0.045)

The number of PPOs and number of medicines were positively correlated for all years with the exceptions of baseline and year 4 of follow-up **Table 4-6**).

Table 4-6 Correlation between number of medicines and new diagnoses and number of PPOs and PIMs for the study population (n=974 for PPOs and n=878 for PIMs)

Correlation coefficient (95% CI)	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
PPO and no. of medicines	0.073 (-0.015; 0.161)	0.323* (0.168; 0.479)	0.337* (0.175; 0.500)	0.302* (0.141; 0.462)	0.128 (-0.030; 0.286)	0.165* (0.008; 0.321)	0.163* (0.006; 0.319)
PPO and no. new diagnoses[a]	-	0.531* (0.234; 0.791)	0.341* (0.109; 0.574)	0.305* (0.017; 0.592)	0.526* (0.225; 0.826)	0.432* (0.141; 0.723)	0.629* (0.309; 0.948)
PIM and no. of medicines	0.186* (0.144; 0.228)	0.601* (0.456; 0.745)	0.684* (0.529; 0.840)	0.734* (0.580; 0.888)	0.621* (0.468; 0.774)	0.650* (0.499; 0.801)	0.632* (0.482; 0.781)
PIM and no. of new diagnoses	-	-0.043 (-0.337; 0.251)	-0.068 (-0.302; 0.167)	-0.074 (-0.364; 0.215)	0.143 (-0.168; 0.453)	0.181 (-0.119; 0.481)	0.013 (-0.321; 0.347)

When excluding the START criteria triggered by drug combinations (e.g. prescribing bisphosphonates and vitamin D and calcium, in patients taking long-term systemic corticosteroid therapy) a higher number of medicines and new diagnoses were still significantly associated with the change in PPO prevalence in the multivariate GEE analysis (aOR 0.99, 95% CI 0.98; 0.99 and aOR 1.06, 95% CI 1.05; 1.07, respectively). The number of PPOs was not positively correlated with number of medicines after excluding the criteria triggered by drug combinations **Table 4-7**.

Table 4-7 Correlation between number of medicines and number of PPOs and PIMs - excluding STOPP/START criteria triggered combination of drugs:

Correlation coefficient (95% CI)	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
PPO and no. of medicines (n=974)	0.003 (-0.066; 0.072)	0.007 (-0.065; 0.079)	-0.011 (-0.078; 0.056)	-0.033 (-0.093; 0.026)	-0.065 (-0.122; -0.009)	-0.065 (-0.116; -0.013)	-0.049 (-0.100; 0.002)
PIM and no. of medicines (n=878)	0.263* (0.221; 0.305)	0.239* (0.205; 0.273)	0.237* (0.201; 0.273)	0.213* (0.181; 0.246)	0.225* (0.192; 0.258)	0.220* (0.186; 0.255)	0.221* (0.187; 0.255)

4.5.4 PIM prevalence

Prevalence of PIMs (described as the proportion of people with at least one PIM) increased significantly between consecutive years from baseline to year 2 of follow-up and decreased slightly thereafter ending with a significant decrease between year 5 and year 6 (**Table 4-3**). Despite this, the overall PIM prevalence from baseline to end of follow-up increased significantly from 39.5% of participants receiving one or more PIMs at baseline to 45.6% at end of follow-up. The unadjusted GEE model showed a significant increase in the PIM prevalence comparing follow-up to baseline (OR 1.04, 95% CI 1.03, 1.06, p<0.001; **Table 4-4**). This finding shows that new patients were acquiring PIMs each year. The mean number of PIMs per participant did, however, decrease significantly from 0.82 (SD 1.53) at baseline to 0.45 (SD 0.5) at end of follow-up (p<0.001). This finding points towards a subset of the population accumulating PIMs rather than an increase in the mean number of PIMs across the whole population. Some of the principal PIMs identified in this study population are provided in **Table 4-2.**

Adjusted odds ratios showed that higher numbers of medicines and higher numbers of new diagnoses were positively and significantly associated with change in PIM prevalence (aOR 1.10; 95% CI 1.08; 1.12 and aOR 1.02, 95% CI 1.00; 1.03, respectively), consistent with the published literature. No significant association was found between PIM prevalence and age or gender (**Table 4-4**). The regression models showed a significant positive correlation between number of daily medications and the number of PIMs prescribed at baseline during all years of follow-up (**Table 4-6**). There was also a positive correlation between older age and the number of PIMs

(**Table 4-5**). The odds of receiving any PIM was affected by the number of new diagnoses but there was no significant correlation between the number of PIMs and number of diagnoses (**Table 4-6**).

Excluding the STOPP criteria triggered by drug combinations both a higher number of daily medications and new diagnoses were still significantly associated with the change in PIM prevalence in the multivariate GEE analysis (aOR 1.07, 95% CI 1.06; 1.08 and aOR 1.02, 95% CI 1.01; 1.03, respectively). A positive correlation between the number of PIMs and number of medications was still shown for all years of follow-up when excluding the STOPP criteria triggered by drug combinations (e.g. STOPP C5 criterion i.e. to discontinue Aspirin in combination with, vitamin K antagonist, or direct thrombin inhibitor or, factor Xa inhibitors, in patients with chronic atrial fibrillation), see **Table 4-7**.

4.6 Discussion

This study illustrates that inappropriate prescribing is present even in early old aged community-dwelling people. This prescribing challenge comprises both prescribing omissions and use of inappropriate medications to similar degrees. It is also a persistent problem with a tendency to increase over time as people progress to more advanced old age.

Our findings showed that over time the number of people with a PPO increases significantly, and that the odds of receiving a PPO increases with higher number of medicines and new diagnoses independent of PPOs triggered by drug combinations. These findings are similar to those of Moriarty *et al.* [46] that showed an increasing trend in PPO prevalence in people aged ≥65 years significantly associated with age, higher number of medications and higher number of chronic conditions. The associations between higher number of medications with PPO prevalence found in Moriarty *et al.* [46] and the current study may indicate that older people experience side effects from their medications resulting in new diagnoses that generates a higher number of PPOs. Similarly, a continuing prevalence of underuse (PPOs) and misuse (PIMs) in multimorbid older people results in poorer

health outcomes. A recent study by Wauter *et al.,* [217] has shown that in community dwelling persons aged ≥80 years every additional PPO significantly increases the rate of hospitalisation (by 26%) and mortality (by 36%).

In early old aged people, our findings showed that the odds of receiving a PIM increased slightly but significantly over time (OR 1.04, 95% CI 1.03, 1.06), a finding similar to that in an Irish older person population studied by Moriarty *et al.* [46] with an odds ratio of PIM prescription of 1.08 (95% CI 1.03, 1.13). Polypharmacy was found to be significantly associated with a higher risk of PIMs in our study, a finding that is well documented in the literature [29, 38, 46, 208, 209], and was also shown to be independent of PIMs triggered by drug combinations. In addition, our findings showed a significant impact of the number of new diagnoses on PIM prevalence. Although PIM prevalence increased, the mean number of PIMs per patient decreased over time. This finding points towards that a subset of this cohort that was accumulating PIMs rather than an increase in mean number of PIMs across the whole cohort. A preliminary characterisation of this subset of participants showed a similar mean age compared to the entire study population (65.0 versus 64.8 years) and a similar gender distribution (48.3% male versus 51.6% female). This subset of patients was taking a higher number of medicines at baseline compared to the entire population (9.2 versus 2.1) and a third of the subset suffered from hypertension (33.3%), a quarter (26.7%) suffered from low back pain and nearly a fifth (18.3%) had osteoarthritis at baseline. This is an area of research that needs further enquiry in order to identify factors that heighten the risk of community dwelling older people acquiring PIMs. Future studies should examine in more detail how clustering of patients based on their number of PIMs occurs.

Our data did not show a significant association between change in either PPO or PIM prevalence and age in this early old aged cohort (mean age 64.8 years (SD 3.0). In contrast, Moriarty *et al.* [46] found that advancing age was significantly associated with both increasing PPO and PIM prevalence in people aged ≥65 years (mean age 74.8 years, SD 6.2 years). These contrasting findings suggest that in early old aged patients, age in itself may not have the same influence on PPO or PIM prevalence as it does in patients after the age of 70 years. It has also been observed that in the 'old old' population (i.e. those aged over 85 years), age alone may no

longer have such a significant impact on PPO and PIM prevalence, as was recently found by Wahab *et al.* [29].

The present study findings indicate that PPOs and PIMs, which are recognised to be highly prevalent in the older population aged 75-84 years [218] and 'old old' population aged ≥85 years [29, 208], are also present in early old age. Our data indicate that both PPO prevalence and PIM prevalence gradually increases over a five-year period as people progress from early old age towards more advanced old age.

This study was not designed to determine the association between prevalence of PPOs/PIMs and clinical outcomes. However, a trial conducted in hospitalised older patients in Ireland has demonstrated that improving prescribing appropriateness reduces the prevalence of falls and all-cause mortality [41]. In addition, the trial showed a reduction in the risk of drug-drug interactions, drug-disease interactions and under prescribing when improving prescribing appropriateness. Preventing a lack of prescribing of appropriate medications may thus prevent disease deterioration and accompanying diseases, e.g. a controlled and well-medicated blood glucose level in diabetic patients may result in better clinical outcomes and lower risk of diabetes-related morbidities [41]. Another Irish study in an older community dwelling population (aged ≥70 years) showed an association between the prevalence of PIP and ADEs. Patients with ≥2 PIMs were twice as likely to experience an ADE [49]. In the study, antithrombotic agents, aspirin and warfarin in particular, were the drugs most frequently associated with a higher prevalence of ADEs, and 59% of patients in the cohort reported bruising, bleeding, indigestion or heartburn. Analgesics, psychoanaleptics and psycholeptics were frequently associated with ADEs such as dizziness, unsteadiness on feet and constipation [49]. Considering the results of these two previous studies, reducing the prevalence of PIMs and PPOs may result in improved clinical outcomes for the older patients.

Although it is known that a substantially high prevalence of PIP has a negative impact on medication management and adherence in older patients, this is an area that has received little attention. Non-adherence to medication increases the likelihood of ADEs and drug-related hospital admissions caused by overuse, underuse or misuse of prescribed medication [49, 217]. Medication non-adherence is known

to be associated with a higher number of daily medicines, such that there is an estimated increase of 16% non-adherence for each additional daily medication taken [219]. Improving medication adherence by preventing PIP could therefore play an important role in reducing the need for healthcare services among older adults and improve the overall quality of their pharmacotherapy. In the elderly multi-morbid hospitalised population, STOPP/START criteria have been shown to significantly improve prescribing appropriateness [41] and to minimise adverse drug reactions (ADRs) [220]. It is likely (although not yet proven) that routine application of STOPP/START criteria in late middle-aged/early old aged patients in the primary care setting would significantly improve the medication appropriateness, medication adherence and reduce the incidence of both ADRs and ADEs in this cohort also.

Routine application of the STOPP/START criteria to medication data requires a thorough therapeutic and pharmacological understanding and knowledge of the patient's clinical status. Additionally, individual patient preferences, and level of medication adherence is important to know when applying the STOPP/START criteria in practice. Reviewing a patient's medication can thus require the consultation of several information sources (e.g. hospital discharge letters, prescribed medications, pharmacy-dispensed medications, use of over-the-counter (OTC) medications, herbal medicines, and patient interviews) and adds to the workload of applying STOPP/START criteria in practice. Currently in Ireland, the GP oversees the patient's overall medical treatment. As described in Chapters 2, 6 and 7, GPs in Ireland already have a considerable workload and welcome support from pharmacists. Supporting the application of STOPP/START in primary care, the community pharmacist may be useful in gathering the information needed, e.g. conducting patient interviews and looking at medicines dispensed, and OTC medicines used. Combined with their pharmacological knowledge, community pharmacists may provide a useful support to the GP in the application of STOPP/START criteria to improve prescribing appropriateness. Future studies should focus on the community pharmacist-GP collaboration in applying STOPP/START criteria with the aim to reduce the prevalence of PIP in primary care.

4.6.1 Strengths and limitations

The present study is the first, to my knowledge, to report the pattern of PIM and PPO prescribing over a five-year period in early old aged people (60-74 years). The use of longitudinal data describing prescription medication in this study provides important information on long-term patterns of PIP. However, the study was not without limitations. The STOPP criteria have been developed for people aged ≥65 years and the applicability of the criteria to a younger population is questionable. However, the study population all entered the age group of ≥65 years at end of follow-up and thus in scope for the STOPP criteria population. It was therefore deemed appropriate to apply the criteria to the study population aged ≥60 years at recruitment. The study was also limited with regards to the available clinical information when applying the STOPP/START criteria. Information on treatment failures, improvement or worsening of symptoms was not available and laboratory values were only available at baseline. Consequently, it was assumed that the laboratory values were still valid during the years of follow-up and not all STOPP/START criteria could be applied due to the lack of clinical information. Additionally, some criteria may have been over triggered due to a lack of detail for diagnoses such as anxiety. Prolonged use of benzodiazepines (more than four weeks) may be appropriate among patients with severe mental illnesses or personality disorders. Equally, omission of medical treatment of mild forms of anxiety would not necessarily reflect an omission of treatment since some of these patients may have been treated appropriately using non-pharmacological approaches e.g. cognitive behavioural therapy, not recorded in this study. Another limitation of the current dataset is that it lacks any information on medication adherence and individual preferences. Data on medication use obtained from electronic patient records do not provide any evidence that the patients are taking the medication or taking the medication as prescribed. This information would have been useful in ensuring that the actual medication use was analysed. The data analysed were also not reporting individual patient preferences in terms of medical treatment or other non-medical therapies. Finally, patients who had died during the follow-up were not excluded from the data analysis. Although only 16 participants (1.6%) died during the years of follow-up this could impact the results and is a limitation of the study. Nevertheless, the data indicate that PIP in early old age very

likely contributes significantly to the high prevalence of PIP in more advanced old age. Based on the similarities of the study findings with comparable studies [38, 46, 217], the study findings are considered to be relevant to other European countries.

4.7 Conclusion

In conclusion, this is the first study to examine the longitudinal pattern of PIP among people in early old age in the primary care setting. The data show that approximately one in three persons aged 60 to 74 years living independently in the community has one or more PIMs or PPOs and that over a 5-year follow-up interval, PPO prevalence rises significantly to over 40% whilst PIM prevalence exceeds 45%. Polypharmacy and multimorbidity have a significant impact on the odds of receiving PPOs and PIMs independent of those triggered by drug combinations. These findings alongside the data emerging from recent clinical trials [41, 220] that describe the positive impact of STOPP/START criteria as an intervention support the use of STOPP/START criteria in the routine review of medication lists of patients in early old age (60-74 years) in the prevention of PIP among older people in primary care.

5 Application of STOPP criteria version 2.0 - potential cost reductions in an Irish primary care cohort

5.1 Chapter description

In Chapter 4, a high and increasing prevalence of PIP was demonstrated among early-old aged people (aged ≥60 years). The published literature has suggested negative patient-related outcomes of PIP with an increasing use of healthcare services. PIP has been described as a burden to the healthcare system, clinically as well as economically. However, little research has focused on the potential associated cost reductions by applying explicit guidelines to reduce PIP. Therefore, this study was conducted to identify potential financial benefits of applying the STOPP criteria in a primary care cohort. The results of this study will add to the thesis discussion of the potential benefits of deprescribing in primary care settings.

This study was a secondary analysis of data collected from a primary care cohort as part of a previously published study [211]. I did not contribute to the data collection, but the data were made available for my analysis in this chapter. I applied the STOPP/START criteria version 2 and calculated the associated drugs costs when analysing this data.

5.2 Introduction

Older people (defined as 65 years and older) frequently live with multiple comorbidities requiring complex pharmacotherapy regimens [158, 221]. As a result, the multimorbid, older patient often bears the burden of polypharmacy; commonly defined as the daily use of five or more medicines [158, 221]. If implemented correctly, polypharmacy may be both appropriate and necessary. Nonetheless, polypharmacy is associated with increased risk of adverse drug events (ADEs), falls, and drug-drug interactions [20, 222]. Achieving optimal polypharmacy in multi-morbid older people is challenging and potentially inappropriate prescribing (PIP) is a frequent and well-described phenomenon in this patient population [27, 34, 38, 44, 49, 153, 158, 207, 210, 223]. Exposure to PIP is associated with poorer patient outcomes and presents a clinical burden worldwide [24, 49, 50, 224-230].

Several explicit tools for identification of PIP exist including the STOPP/START explicit criteria [77]. Applying STOPP/START in the Irish healthcare setting has demonstrated a PIP prevalence of 42% amongst older people (aged ≥70 years) is associated with increased ADEs, poorer health outcomes and higher rates of visits to hospital emergency departments [49]. These higher rates of PIP, and associated healthcare services utilisation present an economic burden to the healthcare system as well as a clinical one [228]. Among the older people in the study (aged ≥70 years), 36% experienced PIP equivalent to healthcare expenditure of €45 million, comprising 9% of the total pharmaceutical expenditure for this age group [228].

In addition to increased healthcare services utilisation, prescribing of potentially inappropriate medicines (PIMs), a significant part of PIP, may also give rise to unnecessary drug expenditures to both patients and the healthcare system. In Ireland, PIMs have been identified in 36% of those aged 70 years and older in 2010 [37], and later in 2015, 65% of Irish people aged 65 years and older received at least one PIM [46]. Looking specifically at the PIP of proton pump inhibitors (PPIs), it seems that a prescribing culture of adding on medicines exists rather than discontinuing them. The total expenditure of PPIs reimbursed in Ireland has increased significantly from €7 million in 1995 to €95 million in 2009 i.e. almost a 14-fold increase. Switching a patient's PPI to a less expensive generic PPI or reducing it to a maintenance dose after 12 weeks have been shown to result in a 46% reduction in the cost of PPIs and

may also have positive impact on patient health outcomes and pill burden [231]. These high rates of inappropriate medicine use, not just for PPIs, may thus point to a need to discontinue PIMs to reduce costs.

Despite the existing evidence of the PIP and PIM prevalence among older Irish people and the associated health expenditures, the evidence is limited on the trends in PIMs and medication costs over time. Therefore, this study aimed to estimate the prevalence of PIMs and associated costs in an older patient population (aged ≥65 years) over a three-year period from 2015 to 2018 in a primary care setting. The findings of this study will inform the discussion of the potential cost reductions of applying the STOPP criteria to identify and reduce PIMs as a strategy to reduce overall PIP in primary care.

5.3 Methods

5.3.1 Study population

This study was a secondary analysis of a population-based cohort from a large primary care centre in southern Ireland described in detailed elsewhere [211]. In summary, the Mitchelstown cohort study was part of the original Cork and Kerry Diabetes and Heart Disease Study undertaken in 1998. The Cork and Kerry Diabetes and Heart Disease Study was conducted in two phases, and as part of phase II, the new Mitchelstown cohort was recruited. The Mitchelstown cohort was recruited from a single large primary care health centre, the 'Livinghealth Clinic' in Mitchelstown, county Cork. The Mitchelstown cohort study included collection of qualitative and quantitative data in an effort to describe the current health status in Ireland, and to assesses individual determinants, behavioural factors and social circumstances on health. Recruitment of the Mitchelstown cohort was undertaken from 2010 to 2011. Patients were randomly selected from all registered patients aged 50-69 years attending the Livinghealth Clinic in Mitchelstown. In total, 3,807 potentially eligible participants were identified from the practice registry, and after exclusion of duplicates, deaths and ineligibles, 3,051 were invited to participate in the study. An invitation letter signed by a GP in the practice was sent out to all 3,051 participants with a reply slip. Reminder letters were sent to non-responders after 4

weeks. Of the 3,051 invited, 2,047 completed the baseline assessment (response rate: 67%). As the cohort was embedded in the single large primary care health centre with electronic patient records, it was possible to access measurements undertaken at routine GP and / or nurse visits. These data provided ongoing passive follow-up of participants between waves of active follow-up. Annual rescreens of the practice electronic records extracted information on vital status, number of GP visits, new diagnoses, specialist referrals and medications [211]. During the eight years of follow-up; 45 people had died when year 6 of follow-up was started. The previous study (Chapter 4) reported on the study population aged ≥60 years at recruitment in 2010-2011 and the prevalence of PIP from baseline to year 5 of follow-up, i.e. from April 2010 to October 2015. This present study follows on from the previous work (Chapter 4) by looking at the same study population and the level of PIP from April 2015 to January 2018 (i.e. follow-up years 6, 7 and 8) and the associated costs. This population aged ≥60 years at recruitment was chosen as these participants would all have entered old age defined as ≥65 years at end of follow-up.

5.3.2 Medication data

Detailed information on all prescribed medications was obtained from electronic patient records. The medications were coded using the WHO - Anatomical Therapeutic Chemical (ATC) Classification System [212] which is a seven-digit code. This hierarchal ATC system divides medicines into different groups according to the organ, or system upon which they act and/or, their therapeutic and chemical characteristics. These codes were then used in data analysis [232]. Unlike the data used in the previous study (Chapter 4), information on the brand name of the medication prescribed, dose and frequency of dosing, was available for the follow-up data used in this study.

5.3.3 PIP prevalence

STOPP version 2.0 criteria [77] were retrospectively applied to the medication data from the annual follow-up screenings between 2015 and 2018 in order to determine the prevalence of PIMs at annual time points over a prospective three-year period.

When applying the STOPP criteria to the dataset, a number of assumptions were made. Despite very comprehensive information on current diagnoses and prescribed medications (including dosage, frequency and brand name), information was lacking on up-to-date laboratory values, medications tried before recruitment and persistence in symptoms/provoking disease factors throughout the study period. These assumptions were made in agreement between one researcher and a hospital physician who were both familiar with the STOPP criteria. The hospital physician was a specialist Registrar in geriatric medicine who was experienced in applying the STOPP criteria to geriatric patients. Examples of assumptions made were:

- For STOPP criteria considering the estimated Glomerular Filtration Rate (eGFR), it was assumed that if the criteria were relevant with regards to baseline eGFR value that it was then reasonable to trigger the criteria again during follow-up, e.g. direct thrombin inhibitors or metformin if eGFR <30 ml/min/1.73m^2.
- The STOPP criterion for long-term aspirin at doses greater than 160 mg per day was assumed triggered if aspirin was prescribed at doses greater than 160 mg for two consecutive years of follow-up.
- The STOPP criterion for loop diuretic prescribed as first-line treatment for hypertension was assumed triggered if (i) the patient did not have any other indication for loop diuretic (heart failure, valvular heart disease, chronic kidney disease or liver cirrhosis/failure) and (ii) the only possible indication was hypertension, and (iii) no other antihypertensives were prescribed.

5.3.4 Costs analysis

The net ingredient cost (NIC) was calculated in Euro (€) for each medication identified as potentially inappropriate by the STOPP criteria. The NICs were retrieved from the July/August 2018 issue of the Monthly Index of Medical Specialties (MIMS) Ireland [233]. These NIC data were the prices to wholesalers of medicines and provided for medicines reimbursed on the Irish General Medical Scheme (GMS), the High-Tech scheme and hospital-only products. The GMS provides free primary care, including

GP and hospital services and medicines for eligible patients. The patients pay a prescription levy of €2.00 per prescription item, up to a maximum of of €20.00 per month. The High-Tech scheme facilitates the supply of certain medicines which were previously supplied primarily in the hospital setting [234]. The NICs enable the prescriber to compare the cost of proprietary medicines but do not bear any relation to the retail costs of drugs, nor to the cost of drugs obtained on private prescriptions. The NIC of the brand prescribed was used in the present study. If the brand name was not provided or that brand was no longer available at the time of the data analysis, the cost of the cheapest available generic was used. The NIC was then calculated for the supply as stated in the medication information and based on the dosing frequency specified on the prescription. If information of the dosing frequency was missing a dosing frequency of maintenance dose for the specific drug was used. Most prescriptions were for a one-month supply i.e. 30 days. The cost of a drug for a month supply was either for 28 days or 30 days depending on the pack size available for the drug. The NIC was then used to estimate the cost implications of STOPP medications. The pricing represents the NIC alone and does not account for associated dispensing fees. Costs were adjusted for claimants receiving the same medications for more than one criterion. For amitriptyline, the cost of this drug was not available from the Irish MIMS. Amitriptyline (10 mg) is prescribed on a named-patient basis in Ireland, whereas Amitriptyline 25 mg is the licensed dose in Ireland. The prices for Amitriptyline 10 mg and 25 mg were retrieved from an Irish Pharmacy database based upon invoice price.

5.3.5 Statistical analysis

The study population was summarised using descriptive statistics including means and standard deviations (SDs) for continuous variables, and proportions and percentages for categorical variables. The prevalence of PIMs identified by the STOPP criteria was calculated as a proportion of the eligible study population. The prevalence of PIMs between consecutive follow-up years was compared using McNemar's test for paired groups [214]. Logistic regression models were used to describe the association between age, sex, number of daily prescription medicines,

new diagnoses and the odds of receiving PIMs. Data analyses were performed using Stata® software version 14 (StataCorp. College Station, TX. 2013). Statistical significance was assumed with a p-value of < 0.05.

5.4 Results

From the original cohort, a total of 978 participants (47.8%) were aged 60 to 74 years at recruitment in 2010-2011. Similar to Chapter 4, four participants had incomplete data and were excluded from the data analysis. At baseline, there was an almost equal distribution of gender in the study population, with 505 female (51.6%) participants. The mean age of participants was 64 years (SD ±2.99) at baseline. Characteristics of the participants at all years' follow-up between 2010 and 2018 are presented in **Table 5-1**. During follow-up from year 1 to year 8, a total of 45 participants had died and these were censored from the data analysis as they died in this study.

Table 5-1 Cumulative data on the study characteristics and prevalence of STOPP criteria applied to the study population aged 60-74 years at recruitment (baseline) in 2010/2011 (n=978).

Year of follow-up	Number of prescribed drugs Mean (±SD)	Polypharmacy (≥5 ATC daily drugs) N (%)	New diagnoses per year Mean (±SD)	Participants with ≥1 PIM N (%)	PIM per person* Mean (±SD)
Baseline (n=974)	5.2 (4.39)	466 (47.8)	N/A	347 (35.6)	2.1 (1.83)
Year 1 (n=974)	6.42 (5.59)	548 (56.4)	0.3 (0.64)	393 (40.5)	2.4 (1.96)
Year 2 (n=974)	8.2 (7.53)	625 (64.4)	2.2 (4.23)	463 (47.7)	2.5 (2.06)
Year 3 (n=974)	8.4 (7.50)	614 (63.5)	2.1 (4.72)	460 (47.6)	2.7 (2.33)
Year 4 (n=974)	8.1 (7.17)	609 (63.1)	2.1 (4.24)	452 (46.8)	2.8 (2.54)
Year 5 (n=974)	8.1 (7.32)	600 (62.6)	1.8 (3.50)	391 (40.8)	2.6 (2.57)
Year 6 (n=954)	6.51 (5.17)	498 (52.2)	1.6 (3.29)	485 (50.8)	3.0 (2.85)
Year 7 (n=941)	6.32 (4.16)	475 (50.5)	1.9 (3.47)	446 (47.4)	2.8 (2.52)
Year 8 (n=928)	5.32 (4.12)	463 (49.9)	1.4 (2.67)	482 (51.9)	3.0 (2.79)

*For people with ≥1 PIM criteria applied to their data.

5.4.1 STOPP criteria

STOPP criteria version 2.0 consists of 80 criteria divided into 13 categories by physiological system [77]. Of the 80 STOPP criteria, a total of 74 criteria (92.5%) were applied to the data for the present study population for the follow-up years 6 to 8. The STOPP criteria applied to the year 0 to year 5 are presented in the previous study (Chapter 4). Due to lack of clinical information ten criteria could not be applied to the data set (see **Table 5-2**). The STOPP criteria were applied and the frequency of each criterion in the study population is presented in **Table 5-3**.

Table 5-2 STOPP criteria version 2 not applied to the dataset due to insufficient information

STOPP criteria not applied to the data
A1 - Any drug prescribed without an evidence-based clinical indication.
A2 - Any drug prescribed beyond the recommended duration, where treatment duration is well defined.
B4 - Beta blocker with symptomatic bradycardia (< 50/min), type II heart block or complete heart block (risk of profound hypotension, asystole).
B11 - ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia.
C3 - Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding) (high risk of bleeding).
D7 - Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications (risk of anticholinergic toxicity),
H3 - Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief)
H4 - Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis (risk of systemic corticosteroid side-effects).
H6 - Long-term NSAID or colchicine for prevention of relapses of gout where there is no contraindication to a xanthine-oxidase inhibitor e.g. allopurinol, febuxostat (xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).
L1 - Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first line therapy for mild pain (WHO analgesic ladder not observed).

Table 5-3 Frequency and cost of STOPP criteria applied to the study population for year 6 to year 8 of follow-up sorted by the criterion with the highest cost.

	Total times the criterion was applied			Total cost of criterion (€)		
STOPP Criteria	Year 6 n=954	Year 7 n=941	Year 8 n=928	Year 6 n=954	Year 7 n=941	Year 8 n=928
D10: Neuroleptics as hypnotics	42	40	37	1061.12	973.54	970.75
K2: Neuroleptic drugs	54	51	47	1061.12	968.63	945.84
L3: Long-acting opioids without short-acting opioids for break-through pain	26	21	18	849.61	753.77	716.07
L2: Use of regular opioids without concomitant laxative	26	59	43	478.81	694.07	659.37
H2: NSAID with hypertension or heart failure	42	44	47	389.91	404.41	435.91
D11: Acetylcholinesterase inhibitors with a known history of persistent bradycardia etc.	81	79	79	341.29	321.78	322.26
A3_SSRI: duplicate SSRI therapy	44	42	42	323.74	311.36	311.36
M1: Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties	14	14	14	251.82	251.82	251.82
A3_ Benzodiazepine: duplicate benzodiazepine therapy	40	36	36	238.44	234.2	234.2
K1: Benzodiazepines	143	122	118	248.20	211.49	204.37
K4: Hypnotic Z-drugs	85	81	79	252.46	237.06	232.05
F2: PPI at full therapeutic dosage for > 8 weeks	16	20	20	221.23	278.56	278.56
D5: Benzodiazepines for ≥ 4 weeks	106	122	118	208.92	210.67	203.39

	Total times the criterion was applied			Total cost of criterion (€)		
A3_ACE inhibitor: duplicate ACE-inhibitor therapy	25	25	25	181.78	181.78	181.78
C9: Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus	8	8	8	137.26	137.26	137.26
H7: COX-2 selective NSAIDs with concurrent cardiovascular disease	7	8	11	132.3	118.13	165.38
J3: Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes	44	47	50	129.16	143.52	154.69
F3: Drugs likely to cause constipation	6	9	6	90.67	142.15	90.67
C8: Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors for > 6 months	5	5	5	71.48	71.48	71.48
A3_NSAID: duplicate NSAID therapy	9	9	8	70.48	70.48	70.48
A3_Beta blocker: duplicate beta-blocker therapy	19	18	18	58.95	54.5	54.5
J5: Oestrogens without progestogen in patients with intact uterus	10	9	9	60.72	54.35	54.35
D6: Antipsychotics in those with parkinsonism or Lewy Body Disease	4	4	5	49	49	56.52
B6: Loop diuretic as first-line treatment for hypertension	22	25	27	49.49	59.13	57.25
H8: NSAID with concurrent corticosteroids without PPI prophylaxis	7	7	7	44.41	44.41	44.41
B12: Aldosterone antagonists with concurrent potassium-conserving drugs	8	8	8	43.4	43.4	43.4
C10: NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination	6	6	6	38.05	38.05	38.05

	Total times the criterion was applied			Total cost of criterion (€)		
D8: Anticholinergics/antimuscarinics in patients with delirium or dementia	2	2	2	34.06	34.06	34.06
D12: Phenothiazines as first-line treatment	13	12	12	31.33	31.33	31.33
H9: Oral bisphosphonates in patients with a history of upper gastrointestinal disease	4	5	5	26.69	31.36	31.36
A3_Loop diuretic: duplicate loop diuretic therapy	11	11	11	13.58	13.58	13.58
B9: Loop diuretic for treatment of hypertension with concurrent urinary incontinence	5	6	6	12.43	14.28	14.28
H1: NSAID with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist	1	1	1	10.39	10.39	10.39
H5: Corticosteroids for osteoarthritis	8	8	1	9.9	41.85	2.97
F4: Oral elemental iron doses greater than 200 mg daily	2	2	0	8.12	8.12	0
B3: Beta-blocker in combination with verapamil or diltiazem	3	3	3	7.38	7.38	7.38
K3: Vasodilator drugs with persistent postural hypotension	1	2	2	7.37	13.22	13.22
D9: Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia	1	1	2	5.81	5.81	13.33
B7: Loop diuretic for dependent ankle oedema	2	3	3	3.7	6.18	6.18
D2: Initiation of tricyclic antidepressants as first-line antidepressant treatment	3	3	3	2.49	2.49	2.49
C5: Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation	2	4	4	1.9	3.8	3.8

	Total times the criterion was applied			Total cost of criterion (€)		
G4: Benzodiazepines with acute or chronic respiratory failure	1	3	3	1.54	3.34	3.34
C4: Aspirin plus clopidogrel as secondary stroke prevention	1	1	1	0.95	0.95	0.95
D3: Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects with a history of prostatism or previous urinary retention	1	1	1	0.74	0.74	0.74
B1: Digoxin for heart failure with preserved systolic ventricular function	1	1	1	0.471	0.471	0.471
B2: Verapamil or diltiazem with NYHA Class III or IV heart failure	0	0	0	0	0	0
B5: Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	0	0	0	0	0	0
B8: Thiazide diuretic with current significant hypokalaemia, hyponatraemia hypercalcaemia or with a history of gout	0	0	0	0	0	0
B10: Centrally-acting antihypertensives	0	0	0	0	0	0
B13: Phosphodiesterase type-5 inhibitors in severe heart failure	0	0	0	0	0	0
C1: Long-term aspirin at doses greater than 160mg per day	0	0	0	0	0	0
C2: Aspirin with a past history of peptic ulcer disease without concomitant PPI	0	0	0	0	0	0
C6: Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease without a clear indication for anticoagulant therapy	0	0	0	0	0	0
C7: Ticlopidine in any circumstances	0	0	0	0	0	0

	Total times the criterion was applied			Total cost of criterion (€)		
C11: NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis	0	0	0	0	0	0
D1: Tricyclic antidepressants with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention	0	0	0	0	0	0
D4: Selective serotonin re-uptake inhibitors (SSRIs) with current or recent significant hyponatraemia	0	0	0	0	0	0
D13: Levodopa or dopamine agonists for benign essential tremor	0	0	0	0	0	0
D14: First-generation antihistamines	0	0	0	0	0	0
E1: Digoxin at a long-term dose greater than 125μg/day if eGFR < 30 ml/min/1.73m2	0	0	0	0	0	0
E2: Direct thrombin inhibitors (e.g. dabigatran) if eGFR < 30 ml/min/1.73m2	0	0	0	0	0	0
E3: Factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m2	0	0	0	0	0	0
E4: NSAID's if eGFR < 50 ml/min/1.73m2	0	0	0	0	0	0
E5: Colchicine if eGFR < 10 ml/min/1.73m2	0	0	0	0	0	0
E6: Metformin if eGFR < 30 ml/min/1.73m2	0	0	0	0	0	0
F1: Prochlorperazine or metoclopramide with Parkinsonism	0	0	0	0	0	0
G1: Theophylline as monotherapy for COPD	0	0	0	0	0	0
G2: Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD	0	0	0	0	0	0

	Total times the criterion was applied			Total cost of criterion (€)		
G3: Anti-muscarinic bronchodilators with a history of narrow angle glaucoma or bladder outflow obstruction	0	0	0	0	0	0
I1: Antimuscarinic drugs for overactive bladder syndrome with concurrent dementia or chronic cognitive impairment or narrow-angle glaucoma, or chronic prostatism	0	0	0	0	0	0
I2: Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope	0	0	0	0	0	0
J1: Sulphonylureas with a long duration of action with type 2 diabetes mellitus	0	0	0	0	0	0
J2: Thiazolidenediones in patients with documented heart failure	0	0	0	0	0	0
J4: Oestrogens with a history of breast cancer or venous thromboembolism	0	0	0	0	0	0
J6: Androgens in the absence of primary or secondary hypogonadism	0	0	0	0	0	0
A3 total: combination of all A3 criteria	687	645	645	-	-	-

5.4.2 PIP prevalence for year 6 to year 8 of follow-up

Between 46% and 52% of the participants received one or more PIMs, and the mean number of PIMs per participant varied between 2.8 and 3.0 (±SD 2.52 to 2.85), respectively (**Table 5-1**). The McNemar's tests showed that the proportion of people with at least one PIM significantly decreased between years 6 and 7 of follow-up (from 50.8% to 47.4%, difference in proportions -0.05, 95% CI -0.07; -0.03, McNemar's Chi^2=28.10, p<0.001), but then significantly increased from years 7 to 8 of follow-up (from 47.4% to 51.9%, difference in proportions 0.05, 95% CI 0.03; 0.07, McNemar's Chi^2=42.32, p<0.001). When comparing year 6 to year 8 of follow-up the difference in the prevalence of STOPP PIMs was not statistically significant (difference in proportions -0.003, 95% CI -0.02; 0.01, McNemar's Chi^2=0.26, p=0.612).

A higher number of prescription medicines was statistically significantly associated with higher odds of receiving a PIM for all three years of follow-up (**Table 5-4**). At year 6 and 8, participants with a higher number of medicines were more than twice as likely to receive a PIM compared to people with a lower number of medicines. No significant associations between age, sex, life status and the odds of being prescribed a PIM were shown for all three years of follow-up (**Table 5-4**). Number of new diagnoses was significantly associated with the odds of any PIM for year 6 of follow-up but non-significant for year 7 and 8 (**Table 5-4**).

Table 5-4 Adjusted odds ratio (aOR) for the association between the presence of a PIM and age, gender, number of drugs, new diagnoses and life-status (n=978).

	Adjusted odds ratio (95% CI)			
	Age (per year older)	**Gender (male vs female)**	**Number of drugs prescribed (per higher number)**	**Number of new diagnoses (per higher number)**
Year 6 (n=954)	0.98 (0.92;1.04) p=0.457	0.84 (0.58;1.20) p=0.336	2.01 (1.84;2.20) p<0.001	1.02 (1.00;1.03) p=0.036
Year 7 (n=941)	0.99 (0.93;1.04) p=0.641	0.96 (0.69;1.34) p=0.812	1.71 (1.60;1.84) p<0.001	1.01 (1.00;1.02) p=0.063
Year 8 (n=928)	0.98 (0.93;1.05) p=0.600	0.86 (0.60;1.25) p=0.431	2.10 (1.91;2.31) p<0.001	1.01 (1.00;1.02) p=0.085

A significant and positive correlation was shown for the number of prescribed drugs and the number of PIMs for all years of follow-up (**Table 5-5**).

Table 5-5 Correlation between the number of PIMs and the number of ATC-coded drugs.

	Number of STOPP criteria and number of drugs		
Correlation Coefficient (CC)	**CC**	**95% CI**	**p**
Year 6 (n=954)	0.184	(0.169;0.200)	<0.001
Year 7 (n=941)	0.233	(0.212;0.253)	<0.001
Year 8 (n=928)	0.235	(0.217;0.253)	<0.001

5.4.3 Cost

The total NIC of the PIMs was €87,152.04 per annum at year 6 and increased to €86,112.48 per annum at year 8 of follow-up. The mean cost of PIM per participant per year was €179.64 in year 6; to the mean PIM cost was €178.68 in year 8 of follow-up. **Table 5-6** summarises the estimated costs of PIM.

Table 5-6 Estimated NIC of the PIMs.

Cost*	Year 6 (n=954)	Year 7 (n=941)	Year 8 (n=928)
Cost of all PIMs per month	€7262.67	€7288.35	€7176.04
Cost of all PIMs per year	€87,152.04	€87,460.20	€86,112.48
Cost of PIMs per person per month (participants with ≥1 PIMs)	€14.97	€16.72	€14.89
Cost of PIM per person, per year (participants with ≥1 PIMs)	€179.64	€200.64	€178.68

*All cost estimates in this table are adjusted for the same drug triggering more than one criterion.

5.5 Discussion

This study demonstrated that approximately half of an older community-based population (46%-52%) in southern Ireland were receiving at least one PIM according to the STOPP criteria.

A decrease in the number of participants with ≥1 PIM was seen between year 6 and 7. This could be explained by the number of participants who died between year 6 and 7; 13 participants died of which 11 had ≥1 PIM in year 6. The prevalence of PIM did however increase in year 8 back to a similar level as for year 6. This increase may be related to the higher number of new diagnoses in year 7 compared to both year 6 and year 8. It is likely that a higher number of new diagnoses in year 7 resulted in new medicines prescribed to treat the new diagnoses and these may have been appropriately prescribed in year 7. In year 8, these new medicines could have been identified as inappropriate due to the duration of the medicine now having exceeded the level of appropriateness or that the new diagnoses in year 7 was no longer present in year 8, making the use of the prescribed medicines inappropriate. Finally, the proportion of people with ≥1 PIM between year 6 to year 8 of follow-up is varying with -3% to +4% and some of this variation may also be explained by prescriber variation and year to year variation in prescribing patterns.

A higher number of medicines significantly increased the odds of PIMs according to STOPP criteria. This adds to the evidence of the association between polypharmacy and PIP shown previously (Chapter 4) and described elsewhere in the

literature [37, 38, 208, 209]. This association persisted despite a reduction in the mean number of prescribed drugs for year 6 to 8 of follow-up compared to the previous five years of follow-up reported in Chapter 4. This change in the number of prescribed drugs is to some extent explained by the exclusion of participants who had died during follow-up from the study analysis in this study, while these were not excluded in Chapter 4, which was a limitation of Chapter 4. However, this only partly explains the difference in the mean number of drugs prescribed. The Mitchelstown study was conducted from 2010 to 2018. During that time, inappropriate prescribing, stopping unnecessary drug use and excessive prescribing of drugs has gained more attention. This was seen in Chapter 2 and 3 with the high number of citations retrieved when searching for literature on deprescribing, inappropriate prescribing and polypharmacy management. In chapter 6 and 7, community pharmacists and GPs also describe an awareness of the issues around PIP and the need for deprescribing showing that these areas are also gaining more attention in the Irish primary care setting. Hence, it is likely that this increased focus could have affected prescribing behaviours of the prescribers and patients in the Mitchelstown study resulting in a lower number of drugs prescribed in the latter years of follow-up. However, the findings of this study still show a high prevalence of PIMs among older people that does not attenuate over a three-year period. The associated cost of PIM use is high and may be a useful opportunity for cost reduction by applying STOPP criteria proactively to identify and discontinue PIMs in community dwelling older people.

The total NIC per participant per annum found in our study was lower than the one found in the previous published Irish study by Cahir *et al*. [37] (€178.68-€200.64 versus €318). Explanations of this difference may be found in the study population. The population in Cahir *et al.* [37] was older compared to our study. Cahir *et al.* [37] included only people aged 70 years and older with 62% of participants aged ≥75 years and showed that PIM was significantly more likely in people aged ≥75 years than the younger participants. Our study included people aged 60-74 years at the time of recruitment such that the oldest participant would be 82 years old at the end of follow-up. As shown in previous studies, the so-called '*old old*' population, often defined as 85 years and older usually have more medications than their '*young old*' counterparts aged 65 to 84 years. Since it is recognised, and also shown by our

results, that the prevalence of PIP is significantly and positively associated with higher numbers of medicines, this may explain the difference in cost of PIP. Even though our findings suggest lower costs of PIM compared to the data published by Cahir *et al.* a decade previously [37], our findings highlight the fact that we may have reached a plateau, and that we are not reducing PIM prevalence and costs, beyond this point.

Benzodiazepines, hypnotic Z-drugs and acetylcholinesterase inhibitors were among the most commonly drug classes associated with the PIMs identified in this study. These drug classes are known to be associated with ADEs such as falls, hip fractures, confusion and impaired cognitive function [235-237]. Reducing the prevalence of these drugs when prescribed inappropriately will reduce prescribing budgets as shown in this study but may also reduce indirect costs of healthcare services utilisations associated with the adverse outcomes of these drugs. Unnecessary drug class duplication was another common cause of the PIMs identified. Duplicate therapy of drugs added unnecessary medicines expenses as shown in this study and is an important source for reducing prescribing costs in older people. Additionally, duplicate drug therapy may increase the risk of adverse patient outcomes and adds to the pill burden in polypharmacy patients already taking a high number of medicines daily.

5.5.1 Strengths and Limitations

The strength of this study is in the detailed information of prescribed medication over a period of years from 2015 to 2018. When applying STOPP criteria, the comprehensive history of the patient's conditions and medication use strengthens the application.

The study had some limitations including the use of STOPP criteria on a population aged ≥60 years at recruitment. The STOPP criteria have been developed for people aged ≥65 years and the applicability of the criteria to a younger population is questionable. However, the study population all entered the age group of ≥65 years at end of follow-up and thus in scope for the STOPP criteria population. It was therefore deemed appropriate to apply the criteria to the study population aged ≥60 years at recruitment. Another limitation was the use of the explicit STOPP criteria on

a dataset without being able to contact patients, their carer, or prescribers, directly, to check the clinical relevance of the PIP identified. This also means that in some instances, medicines defined as inappropriate in this study may in fact be appropriate, once the full clinical picture emerges. As with any other study applying explicit PIP criteria to a database, it is important to stress that the medicines are identified as '*potentially inappropriate'*, and as distinct from '*definitely inappropriate*'. When considering the appropriateness of a patient's pharmacotherapy, both the prescriber and the patient should agree whether a medication is actually inappropriate and not merely potentially inappropriate but reasonable to continue considering all circumstances.

Another limitation was the identification of drug class duplication. Drug class duplication could be appropriate in some patients for which a strength of a medication was needed that was not commercially available. Drug duplication could also be appropriate for patients in which the dosage regimen prescribed was different doses at different time points, e.g. 10 mg in the morning and 20 mg in the evening.

The information on the duration of treatment was not available from the dataset and the medications prescribed were a 'snapshot' of a single month's prescriptions during each year of follow-up. Thus, when applying STOPP criteria, for which the duration of treatment is crucial, e.g. PPIs at full therapeutic dose for 8 weeks or more, it was assumed that the patient had been taken the medication for one year, if the medication was prescribed over two consecutive years. Another limitation was the lack of up to date laboratory values such as the sodium levels, so that the use of a drug that has previously caused hyponatraemia may not be clinically relevant anymore if the patient's serum sodium concentration has reached the normal range at the time of assessment for PIMs. Medication data were obtained from the patient's electronic records and were data on medication prescribed. For that reason, this study was limited in that it was not possible to identify if the patients were dispensed the medication prescribed, whether a cheaper brand was dispensed or if the patients were actually taking the medication as prescribed. When stopping some inappropriate medicines, there may be a need for initiating another to relieve

withdrawal symptoms. Also, it could be necessary to switch the patient to another drug class rather than discontinuing drug treatment completely. This was not accounted for in this study and could have influenced the actual cost reductions of applying STOPP criteria to medication data in primary care.

The pharmacist's dispensing fee and the cost of a healthcare professional reviewing and communicating the identified PIMs was not included in the cost estimates and both of these may be important further sources of cost if PIMs were to be identified and prevented regularly in the primary care setting. Finally, this study did not consider potential prescribing omissions (PPOs). As shown in Chapter 4, the prevalence of PPOs rose significantly in the same study population over a 5-year follow-up period and was present in over 40% of people at end of follow-up. Failure to prescribe appropriate medicines for disease prevention and symptom relief could have a substantial impact on clinical outcomes, such as disease progression in the older population with a need for more monitoring, hospitalisations etc. Reducing the prevalence of PPOs may thus have important financial implications in terms of reducing the healthcare services utilisation. Additionally, stopping inappropriate medicines could in some instances warrant the starting of appropriate medicines and this would have affected the true cost reductions of identifying and eliminating PIMs in this study. As such, the START list to identify PPOs has been created to be used in tandem with the STOPP criteria to give a more complete assessment of the PIP in older people. The findings from Chapter 4 indicate that PPOs of essential medicines in older people are at least as prevalent as the prescribing of PIMs which should be avoided in older people. It is thus a weakness of this study not to consider PPOs and the potential cost reductions of reducing the prevalence of PPOs. Acknowledging these study limitations, this study still provided useful insights into PIM prevalence in recent years in an Irish older population and associated costs.

5.5.2 Implications for future practice

Although there are clear cut potential savings from PIM curtailment amongst community-dwelling older people, the high and persistent PIM prevalence points towards a need for new strategies to reduce PIM prevalence in practice.

Interventions are needed to target primary care where a large proportion of prescribing takes place as well as continuation and transcribing of prescriptions from hospitals and specialists [228]. For multimorbid community-dwelling patients with polypharmacy and in high risk of receiving PIMs, it is likely that they will visit the community pharmacy on a monthly basis to collect their prescription medications. Community pharmacists will thus dispense prescriptions monthly and review these prescriptions upon each dispensing. This could provide an opportunity for community pharmacists to identify PIMs during medicines dispensing and advising the GP to discontinue/review these. However, the identification of PIMs requires an assessment of the patient's medicine and clinical history. Today, no system exists in Ireland, in which patient information is shared with the community pharmacies. Future interventions aiming to reduce PIMs in primary care should focus the attention towards sharing information to enable community pharmacists to identify PIMs and advising GPs to reduce/review these. This could be an important way of preventing long-term iatrogenic harm in a setting which is built to maintain long-term treatment and relationships with the patients. However, involving community pharmacists in the reduction of PIMs in primary care raises the question of a potential conflict of interest for the pharmacy business owner. If community pharmacists are asked to identify PIMs, with a goal to reduce the number of PIPs dispensed, it reduces the dispensing fees for the pharmacy and may cause a loss of earnings to the pharmacy. Intervention designers needs to address this potential conflict of interest if interventions to reduce PIMs are to be implemented in practice.

5.6 Conclusion

This study estimated a high prevalence of PIMs (46% - 52%) and associated costs (€86,112.48 - €87,460.20) in older people between 2015 and 2018. The findings reveal a high and unchanging prevalence of PIMs in recent years despite the increasing focus on PIMs in the literature and existing PIMs guidelines based on explicit measures of PIP. Benzodiazepines, hypnotic Z-drugs, ACE-inhibitors were common causes of the identified PIMs and reducing the number of these drugs when

prescribed inappropriately may, in addition to reduction in prescribing budgets, also reduce the risk of adverse effects associated with these drug classes.

6 Qualitative analysis of community pharmacists' opinions on their involvement in reducing potentially inappropriate prescribing

6.1 Chapter description

From the previous chapters, pharmacist support in deprescribing is a suggested strategy to reduce PIP. However, several barriers to pharmacist participation in deprescribing exist as viewed by other healthcare professionals. Given the lack of published qualitative research exploring the views of community pharmacists on their role in reducing PIP, the aim was to carry out a qualitative study to add to the literature as well as guiding the next research for this thesis.

6.2 Publication

The work of this chapter has been published as: Hansen CR, Byrne S, O'Mahony D, Kearney PM, Sahm LJ. Qualitative analysis of community pharmacists' opinions on their involvement in reducing potentially inappropriate prescribing. *European Journal of Clinical Pharmacology.* 2018; 75(2):265-274. Doi: 10.1007/s00228-018-2578-2 (Appendix IX)

6.3 Introduction

Older multi-morbid people are at substantial risk of having potentially inappropriate prescribing (PIP) [41, 77]. The risk of PIP increases as people grow older and is strongly associated with the higher number of daily medicines used to treat multi-morbid illness [46, 238, 239]. Patient safety is at risk when older people are exposed to PIP because of the associated ADEs and drug-related hospitalisations directly or indirectly related to PIP [206, 240]. Previous studies indicate a high prevalence of PIP among independently living older people in the primary care setting in Ireland, with reported prevalence estimates of 21% - 57% [46, 49, 153, 238]. Similar prevalence estimates have been described in Northern Ireland (34%) [38] and in other European countries, e.g. Spain (38% - 46%) [241] and the Netherlands (35% - 85%) [239]. No intervention has so far succeeded in reducing the substantial PIP prevalence in primary care despite the existence of explicit criteria to identify PIP being available for over 10 years, as well as the evidence that when heeded and acted upon, they are effective in reducing PIP in hospitalised, older patients [41, 239, 242]. The two most commonly cited sets of PIP criteria in the published literature are Beers' criteria [87-91] and Screening Tool of Older People's Prescriptions (STOPP)/Screening Tool to Alert to Right Treatment (START) criteria [77]. There are currently published four randomised clinical trials showing the clinical efficacy of applying STOPP/START criteria to reduce PIP [41, 178], falls incidence and overall medication cost [194], as well as incidence of ADRs [242] in the hospital and nursing home settings.

Detailed assessment of new and repeat prescriptions and formal structured medication review are recognised ways of identifying PIP. Medication review is a broad term covering several interventions carried out by prescribers themselves or by other practitioners providing advice to prescribers (e.g. pharmacists) with the overall aim of improving the quality, safety and appropriateness of use of medicines [243]. Studies in primary care settings have demonstrated a significant positive effect of pharmacist-led medication reviews on prescribing appropriateness in older people, either measured by an improvement in the MAI scores, a prevalence of drug-related problems or a reduction in the number of PIMs [53, 199, 244]. Despite variations in study setup, these interventions all showed the positive outcomes of medications reviews being conducted by pharmacists followed by recommendations

given by the pharmacists to the prescribing physician. Recommendations given varied between the interventions and included: (1) recommendations to stop a medication; (2) highlighting inappropriate prescribing; (3) suggesting changes to the dosing or dosing interval; (4) recommending changing to an alternative medication etc. Systems for providing feedback to the prescribing physician varied in the studies from (i) face-to-face discussions, (ii) written feedback and (iii) telephone conversations. Despite these study variations, the current studies point towards pharmacist-led medications reviews followed by feedback to the prescribing physician as a strategy to reduce PIP [57, 180, 186, 188, 199, 245]. Considering the findings of these previous studies, pharmacists are in a favourable position to identify and help reduce PIP through conducting medication reviews and providing feedback to the prescriber. However, prevalence data of PIP among community-dwelling older people indicate that pharmacists are not undertaking the potentially important role of identifiers of PIP with a connected remit of PIP prevention [246-248].

An important question to ask is whether community pharmacists are equipped to take on this role in terms of their current knowledge, resources needed to conduct medication reviews in practice and the clinical information available to them to make clinically relevant recommendations. Hence, when designing an intervention to change traditional working practice, it is fundamental to understand the processes, barriers and facilitators (e.g. resources, knowledge and available information) underlying the behaviour in relation to the particular work practice in question such as the barriers and facilitators [249, 250]. In this study, the pharmacists' behaviours in reducing PIP were expected to change, and it was deemed essential to understand the barriers and facilitators for the involvement of community pharmacists in reducing PIP. The Theoretical Domains Framework (TDF) was originally developed by Michie *et al.* [251] with 12 domains and later updated to 14 domains by Cane *et al.* [252]. The TDF considers a wide range of possible theoretical explanations for the relevant behaviours [249, 253, 254] and has been widely used in health research to define behaviours and to identify barriers and facilitators to those behaviours . The 12 domain TDF [251] has been widely used in health research to define behaviours and to identify barriers and facilitators to that behaviour [249, 254, 255]. In this study, the 14 domain TDF was employed to identify

barriers and facilitators of pharmacist involvement in reducing PIP. The 14 domain TDF has previously been used to explore a similar topic: the utilisation of a screening tool in medicines use reviews (MURs) by community pharmacists [256]; and was deemed appropriate to investigate their involvement in reducing PIP.

Whilst large randomised controlled trials have examined various ways to assess the interventions targeted at prevention of PIP in hospital care settings [41, 83, 84], little research has been carried out in primary care. To date, the views of the community pharmacists on reducing PIP have received little attention [256]. Therefore, this study aimed to explore the views of community pharmacists on their potential involvement in reducing PIP, and to determine the perceived barriers and facilitators to the implementation of PIP reduction in community pharmacy practice.

6.4 Methods

6.4.1 Compliance with Ethical Standards

Ethical approval for this study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals prior to recruitment (Appendix X). Written informed consent was obtained from all participants included in the study.

6.4.2 Sampling

Community pharmacists working in the vicinity of Cork City and its surrounding hinterland were recruited using convenience sampling based on a sampling matrix. The convenience sampling method was chosen due to time constraints of the study and to increase the likelihood of respondents. Hence, a close geographic proximity allowed the researcher to conduct face-to-face interviews with participants at suitable location. Currently working in community practice was the only inclusion criterion, and there were no exclusion criteria.

A sampling matrix was designed to ensure variation of important participant characteristics in the study population. The design of the matrix was informed by the experience and knowledge of me, the primary researcher, two PhD supervisors and co-authors of the publication (S. Byrne and L.J. Sahm) and a panel of pharmacists with

backgrounds in both academia and community pharmacy practice. The final matrix design was approved by me and the four PhD supervisors and co-authors of the publicaton. Matrix parameters chosen were: (i) experience working with nursing home residents (either from working in a nursing home or from working in a pharmacy serving nursing homes), (ii) years of experience working as a community pharmacist (<3 years, ≥3 years and ≥10 years), and (iii) number of pharmacists working simultaneously in the pharmacy. A cut-off of 3 years of community experience was chosen as a matrix parameter because community pharmacists in Ireland after a 3-year period can choose to take up employment subsequently as Supervising / Superintendent Pharmacists[1]. Being a supporting or supervising pharmacist was considered to influence the level of confidence and knowledge regarding PIP. A threshold of 10 years or more experience was then agreed by the researchers and the expert panel because seniority of ≥10 years was likely to influence their opinions and answers. Experience of working in a nursing home was considered to have an influence on the pharmacists' answers relating to medication reviews as these are commonly undertaken by pharmacists in Irish nursing homes. The number of registered community pharmacists on duty in the pharmacy at any one time was believed to have an impact on their perceived capability to perform medication reviews compared to those pharmacies with a single community pharmacist on duty and was included as a matrix parameter. Although not matrix parameters, the areas in which the pharmacists worked i.e. urban or rural setting as well as local community affluence or disadvantage were considered when recruiting participants. Areas with social affluence or disadvantage were identified from the deprivation index viewer (available from www.pobal.ie) [257]. See the sampling matrix in **Table 6-1**.

[1] The Supervising/Superintendent pharmacists is the person responsible for the day-to-day management and operation of the pharmacy and must have a minimum of three years' post-registration experience (http://www.thepsi.ie/gns/Pharmacy_Practice/practice-guidance/Guidance_for_pharmacists/Guidance_for_Supervising_Pharmacists.aspx)

Table 6-1 Sampling matrix used for the recruitment of community pharmacist

X: pharmacy with 1 licensed pharmacist on duty **O: pharmacy with 2 licensed pharmacists on duty**	**<3 years of experience**	**3-9 years of experience**	**≥10 years of experience**
Nursing home experience	X O	X O	X O
No nursing home experience	X O	X O	X O
Sum	**4**	**4**	**4**
			Total 12 interviews at a minimum

Pharmacies located in Cork City and County were identified. An initial list of pharmacies was created considering: (i) the characteristics of the area in which the pharmacy was located (i.e. urban, rural, disadvantage or affluent), and (ii) if the pharmacy was an independent pharmacy individual or a chain pharmacy (i.e. pharmacies owned by the same pharmacy chain were initially avoided). The pharmacies were contacted by telephone. I, the primary researcher introduced the study to the pharmacist on duty and asked if he/she would consider taking part in the study. Written information about the study was offered (by email) prior to the interview. An agreed interview date, time and location were then arranged. During the interview, pharmacists were asked about (i) their numbers of years practising in community pharmacy, (ii) experience of working in a nursing home, and (iii) number of pharmacists on duty daily to ensure that all matrix parameters were fulfilled at the end of recruitment. In addition, a '*snowballing'* sampling method was used to recruit pharmacists, whereby a community pharmacist interviewed identified other community pharmacists who would fulfil certain matrix parameters.

6.4.3 Interview topic guide

The interview topic guide (see Appendix XI) was designed to explore the 14 domains of the TDF framework [251, 252] whilst also allowing the participants to freely share their opinions. Using the TDF to design the topic guide is a helpful way of formulating questions that would enable the identification of the relevant behaviour and the

barriers and facilitators to that behaviour. The use of a TDF-formulated topic guide has also been shown to effectively elicit responses from the interviewees that they would not otherwise report [250]. The topic guide was refined by consensus among all researchers and with an expert panel of experienced pharmacists with backgrounds in academia and community pharmacy practice. The topic guide was pilot tested in two community pharmacists. During the study it was refined on an iterative basis after each interview was transcribed to allow for emerging themes to be explored in subsequent interviews. Interviews were conducted until the point of thematic saturation as described by Francis *et al.* [258] was achieved. The interviews were introduced with some general questions regarding their awareness and beliefs about PIP and medication reviews. Participant demographic details were also collected including gender, age, number of years of experience in community pharmacy. Participants were shown the recently developed deprescribing algorithms and asked to give their opinion about the content, layout and usefulness in their daily practice [80, 96-98]. These deprescribing algorithms have been developed to create decision-support tools for deprescribing. The algorithms and accompanied guidelines provide a rationale for evidence-based deprescribing and the steps of a safe deprescribing process for health care professionals and patients. At the time of the study, deprescribing algorithms were available for four drug classes: proton pump inhibitors (PPIs), antipsychotics, antihyperglycemics and benzodiazepine receptor agonists [80, 96-98]. Since the study, another deprescribing algorithm has been published for cholinesterase inhibitors and memantine [99].

6.4.4 Data collection

Semi-structured interviews with pharmacists working in community pharmacies in Ireland were conducted by me, the primary researcher. This type of interview was chosen as it encourages interviewees to share the views and opinions that were important to him/her at that time [259]. Interviews were all conducted face-to-face at the pharmacist's place of work but telephone interviews were also offered. At the time of the interviews the participant received an information letter and gave their written consent. Interviews were audio-recorded and transcribed verbatim.

6.4.5 Qualitative data analysis

Transcripts were anonymised and transferred to QSR NVivo® Version 11 software. In line with framework analysis, a familiarisation process took place whereby I, as the primary researcher, repeatedly listened to the interview audio-recordings and read the interview transcripts. From the transcribing and familiarisation process the primary researcher attained an overview of specific beliefs within the data [260]. Following this step, excerpts from the interview transcripts were coded into one or more of the 14 TDF domains. Three randomly selected transcripts were coded by a PhD supervisor (L.J. Sahm) to ensure validity and reliability of the data analysis. Disagreement in coding between the two researchers was resolved through discussion and consensus. Domains for which transcript excerpts were encoded were summarised. Supporting excerpts were attached to each domain summary. The two researchers then determined the domains of relevance for PIP reduction using a similar approach to previous studies [249, 256]. A domain was deemed relevant if excerpts were coded frequently or if the participants emphasised the significant impact of barriers and/or facilitators within a domain on their involvement in reducing PIP.

6.5 Results

A total of 21 community pharmacists were approached of whom 18 agreed to participate in the study; one pharmacist declined to participate, and two others were unavailable at the time of the study. Interviews were conducted in the 3-month period from June to August 2017. The interviews had an average duration of 19 minutes (SD$\pm$6.00 minutes) and took place at the pharmacy in which the participant worked. Data saturation was reached after 15 interviews with no new themes emerging from conducting an additional three interviews, i.e. a total of 18 interviews. Characteristics of the participants are described in **Table 6-2**.

Table 6-2 Characteristics of interview participants (N = 18)

Characteristics	Value
Pharmacists working in urban areas, N (%)	15 (83%)
Pharmacists working in rural areas, N (%)	3 (17%)
Areas categorised as affluent[a], N (%)	5 (83%)
Areas categorised as deprived[a], N(%)	13 (17%)
Gender, females, N (%)	12 (67%)
Age, years, median (IQR)	30 years (27-35 years)
Years of experience, median (IQR)	6 years (IQR 3-8 years)
Pharmacists graduated before 2010, N (%)	7 (39%)
Pharmacists working in a pharmacy with only one licensed pharmacist on duty, N (%)	8 (44%)
Pharmacists with nursing home experience, N(%)	8 (44%)

[a]data obtained from pobal [257].

Community pharmacists were familiar with the term '*inappropriate prescribing'* and defined this as: (i) any medication prescribed that has the potential to cause harm, side-effects or drug interactions; (ii) overprescribing or prescribing without a documented indication; (iii) prescribing a medicine to relieve side-effects of another medicine that the patient is taking; (iv) prescribing any medication for longer than indicated; and (v) prescribing a medicine not suitable for older people. A few pharmacists mentioned explicit STOPP/START criteria [77, 213] to identify PIP but the majority referred to treatment guidelines such as those produced by the NICE [261] [261] no pharmacist used an explicit set of criteria to identify PIP in their routine work. The pharmacists perceived the presented deprescribing algorithms [80, 96-98] to give a good overview and to be user-friendly. However, some pharmacists also believed that the information on the algorithms was well-known among pharmacists and did not believe algorithms to have significant influence on their involvement in reducing PIP.

Pharmacists described medication reviews as the systematic process of reviewing patients' medications and identifying drug-related problems. No pharmacist had experience of doing medication reviews in the community pharmacy

setting in Ireland, but some had experience from educational sessions or from working in hospitals or nursing homes. No pharmacist interviewed was carrying out medication reviews for older patients as part of their current routine practice.

6.5.1 Qualitative analysis themes

Transcript excerpts were most frequently coded into five domains: (i) *beliefs about capabilities, (ii) environmental context and resources, (iii) knowledge, (iv) social influences and (v) social professional role and identity*. The two domains of *memory, attention and decision processes* and *reinforcement* were less frequently coded. However, those participants who made comments coded into these domains attached significant importance to the factors identified. The interview data coded into these seven domains are summarised below with illustrative quotations. The remaining TDF domains were coded infrequently and three of them; *beliefs about consequences, emotion, goals* and *skills* were not coded at all.

6.5.1.1 *Beliefs about capabilities*

Pharmacists perceived themselves as appropriate healthcare providers to identify PIP. Competencies were attributed to: being trained to do it; being good at identifying PIP; having a good relationship with patients due to the nature of patients visiting their pharmacy more often than their General Practitioner (GP); and looking at older patients' prescription drugs with a fresh perspective.

Beliefs about capabilities were affected by a pharmacist's level of confidence and this subsequently influenced the likelihood of the pharmacist communicating any recommendations to the GP. One pharmacist's self-perceived duty as a pharmacist gave her the confidence to act when an instance of PIP was identified.

> *"I'd be fairly confident. I'd be kind of, just thinking in my own head: 'Look, I have a duty of care' and if the doctors are a little bit annoyed with me, I'll take that."* [Pharmacist 17, female, support pharmacist, 6 years of experience].

Another, younger pharmacist (1.5 years of experience) described how her lack of confidence restrained her from actively giving her input despite her beliefs about her role:

> *"I wouldn't go down the route and ring up a doctor and saying: 'You shouldn't be on this'. The patient has been on this for longer than two weeks, you shouldn't be giving this anymore'. I just don't. That is probably my role to some extent, but I wouldn't like going down that route of complaining to another healthcare professional about what they are doing, so."* [Pharmacist 6, female, support pharmacist, 1.5 years of experience]

6.5.1.2 *Environmental context and resources*

Being busy with serving many patients and doing administrative work were believed to restrict time to do medication reviews and to have follow-up contact with prescribers to discuss potential changes. Pharmacists described a need to prioritise their time and focus on more immediately unsafe issues, such as major drug-drug interactions, rather than reviewing medication lists for PIP, which was felt to have more medium or long-term implications for the patient. Protected time to review medications facilitated by extra pharmacist staff was a suggested solution.

> *"Well it's just, I guess, everybody's busy. Things maybe aren't reviewed as often as they should be (…). So, you know, it doesn't, it it just flies by and you know, you've got a number of other reasons, which are far more immediate in terms of inappropriate prescribing, that you need to look out for. So, you know, those are the ones that you're going to go for, the ones that are immediately unsafe, I guess."* [Pharmacist 2, male, supervising pharmacist, 6 years of experience]

Another challenge was a perceived lack of communication between pharmacists and GPs, and this was thought to lead to confusion about medication changes and to impede the implementation of these changes. Pharmacists described being unsure where the responsibility for stopping PIP resides:

"*I think communication is a huge issue because (…) if something [prescription] comes out from the hospital, the GP might not want to stop it. You know the hospital's intention might have been 'let's go on this for 6 weeks'. But then the GP puts it on the repeat and then it comes to the pharmacist and I'm looking at it and they've been on it for two months. I'm not going to ring the GP after two months and say 'oh, it's probably inappropriate for you to stop this now'. It's kind of like who actually [should tackle instances of PIP], and where does the buck stop. Who should say 'this is where it stops' or 'this is where it starts' or."* [Pharmacist 16, female, support pharmacist, 1 year of experience]

Suggested improvements included more direct lines of communication and willingness to collaborate from all parties:

"But the channels need to be a bit more open. Sometimes they're very closed and if they were a bit more open and a bit more receptive to what our role as like a professional could be. Which I think some, some of them aren't, then I think it would help a lot (…) It would need to have the agreement of the GP and everybody working in unison instead of you going: 'oh, we're gonna stop this, 'cause this is', and they're not adhering that to stop that (…) So, definitely need to be structured. Needs to be all parties working together and definitely somebody on either site communicating to go: 'look we're going to meet with the doctor' and better to do it face-to-face than over the phone I feel because you don't really get a grasp of what's going on over the phone." [Pharmacist 9, male, support pharmacist, 3.5 years of experience]

Geographic proximity and face-to-face interaction were believed to be key facilitators of a good collaborative relationship:

"Well, we are lucky here because we're in a primary care centre, so I have a direct line. If I was waiting for a secretary to pass on a message to the GP to

get back to me. A lot of the time that becomes difficult. So, the majority of my prescriptions would be coming from the GPs upstairs and we have a very good rapport which makes it much easier." [Pharmacist 15, female, supervising pharmacist, 7 years of experience]

Other challenges pertained to a lack of patient information, e.g. diagnosis or indication for a drug. Receiving hospital discharge letters and gaining access to a centralised clinical record system for sharing patient information between pharmacists and GPs were suggested improvements.

6.5.1.3 *Knowledge*

Pharmacists believed their pharmacology/therapeutics knowledge to be sufficient to identify PIP but stressed the need for continuing professional education to bring their knowledge in line with new medications and most up-to-date guidelines. Interdisciplinary training was suggested as one way to meet these educational needs whilst simultaneously improving collaboration between pharmacists and GPs:

"I think interdisciplinary training would be very good (…) let them [GPs] understand how we [pharmacists] work and the position that we are in, because we [GPs and pharmacists] often don't understand our jobs and they can explain. I mean we [pharmacists] go to visit the GP for our own thing. So, we kind of have a little bit more of an understanding [of the GP's work]. But they [GPs] may never come to a pharmacy and they may not know how we operate." [Pharmacist 6, female, supervising pharmacist, 5 years of experience

Guidelines were considered to be valuable information sources partly because of their generally easy application to daily practice and partly for the evidence-base guidance to pharmacists' recommendations. However, some pharmacists criticised guidelines for limitations such as describing how to identify PIP without specific guidance on how to manage it:

"It is useful [deprescribing algorithms] but at the same time I feel like it's something that we all already know (…) I don't think it's the spotting is the big problem. It's what do you do when you do spot it? So, it's the training of what are we actually supposed to do. So, I suppose you do spot it but I don't necessarily know what you're supposed to do with it." [Pharmacist 16, female, support pharmacist, 1 year of experience]

6.5.1.4 *Social influences*

Patient demands and their relative interest in medication were noted to strongly influence the changing or discontinuation of medication. Some patients were described as demanding treatment and not being content to adjust their medication due to fear of change or loyalty to the doctors' prescription orders. Pharmacists also noted however that their regular contact with patients put them in a position to influence the patients' behaviours.

"I sometimes, depending on the doctor, encourage the patient to go back and ask. If you just say to the doctor, eh to the patient: 'maybe say to the doctor could you check your levels'. So, like you say it in a nice way, so they don't go like: 'well the pharmacist said'. But you know that they kind of think themselves and maybe they should be questioning it. You're kind of empowering them a bit." [Pharmacist 5, female, supervising pharmacist, 8 years of experience]

6.5.1.5 *Social professional role and identity*

Pharmacists described their current role as including: (a) informing patients about their medication; (b) maintaining patient safety perspective over financial benefits for the pharmacy; and (c) being familiar with patients' particular medication needs.

"I kind of think that sometimes you're the last portal between you know the doctor and the patient. So, it's your, I suppose, responsibility is to identify anything that's inappropriate but then make sure as well at the patient site that they can use it, take or use their product as best that they can to get the most benefit out of it (…) So, I'd like to see patients more informed and more as you say kind of independent in their own health care. But that's kind of our job too to try and encourage that." [Pharmacist 12, female, support pharmacist, 6 years of experience]

Pharmacists agreed that they had a role in PIP prevention but were divided regarding the extent to which they should intervene when PIP is detected. A clear description of the pharmacist's role in reducing PIP and an acceptance of this role among healthcare professionals was suggested as a way in which to increase the involvement of pharmacists:

"The overall responsibility I think is a two-way thing. I think it's between the GP and pharmacy, and I don't think either holds the overall responsibility." [Pharmacist 13, male, supervising pharmacist, 3 years of experience]

"We should be doing more but we're doing less [medication reviews and preventing PIP]. Whether that's business or whether that's some people are, not being lazy, but shying away from it because they're being afraid that they're out of touch. Older pharmacists. I'm not sure, but definitely there's this un-realisation of what our role should be in that for sure." [Pharmacist 9, male, support pharmacist, 3.5 years of experience]

6.5.1.6 *Memory, attention and decision process*

Raising awareness of PIP among pharmacists, doctors and patients was thought to enhance PIP reduction. Suggested initiatives were awareness/information

campaigns run by health authorities for patients and/or healthcare providers. The purpose of these campaigns should be to inform patients and GPs about particularly problematic drug classes and raise awareness:

> "*Well those IPU [Irish Pharmacy Union] and HSE [Health Services Executive] campaigns about generic medications for example, have been very successful. I think a similar campaign along the lines of 'do you need everything you're taking?'. Or encouraging patients to go to their doctor. I think, to a certain extent, the prescription levy did this very well. Where people went to their doctor and asked: 'do I really need to be taking all this?'"* [Pharmacist 10, male support pharmacist, 4.5 years of experience]

6.5.1.7 *Reinforcement*

State reimbursement, or professional acknowledgement, for doing medication reviews were both considered to be motivating factors to do medication reviews. However, concerns were raised about the quality of Government-funded mandatory medication reviews and how incentives might shift focus away from patient benefits to financial and personal benefits instead:

> *"I suppose it's [PIP] a bit under the radar in a lot of my daily work because you're not incentivised to look for it"* [Pharmacist 2, male, supervising pharmacist, 6 years of experience]

> *"But I think if you try and force people to do it [medication reviews] for even for like a financial thing. Reimbursement or anything like this, it's just going to come to like the same thing as we do with say the HSE claims or something. Say, you're doing it for the wrong reasons and even in that case you mightn't do it properly."* [Pharmacist 7, female, support pharmacist, 1.5 years of experience]

6.6 Discussion

This study used a theoretical approach to explore the views of community pharmacists on their involvement in reducing PIP in older people and their perceived barriers and facilitators to this. Despite beliefs about capability and responsibility for reducing PIP, structured medication reviews and recommendations about stopping medications do not form a routine part of daily practice for community pharmacists in Ireland. It is clear from this study that for some pharmacists there was a sense of conflict in what they knew to be the identifiable instances of PIP and what they actually did to reduce PIP.

Pharmacists expressed uncertainties about the extent of what their role in reducing PIP should be. They described a reluctance to work outside of their current defined role and to challenge prescribing decisions taken by GPs, such as recommending drug discontinuation. The consequences of uncertainty about the pharmacist's role in patient care, such as reducing PIP, have also been described in the literature [247, 262]. In the study by Patterson *et al.* [262], the varying and inconsistent description of pharmacists' responsibilities in a primary care team was considered to hinder collaboration between pharmacists and other healthcare professionals. They referred to how some fellow healthcare professionals felt that pharmacists do not adequately handle their responsibilities and described a likely relationship between this belief and a general lack of awareness of the role of the pharmacist [262]. Schindel *et al.* [247] described how a lack of consistency in the community pharmacy service influences patients' expectations in that they may be informed variably about pharmacist services.

When asked specifically about stopping medications, pharmacists in this study described uncertainty of where final responsibility for PIP avoidance lies. In a recent review (see Chapter 2), this same theme caused confusion for GPs and also differing opinions among GPs regarding pharmacist support. Extending the role of the pharmacist to include direct patient care may therefore require a clear description of the roles and responsibilities to be undertaken by pharmacists to be communicated to all stakeholders.

The study findings suggest a need for a shared goal of medicines optimisation, and that by having more interdisciplinarity within the training of conducting medication reviews, this could be achieved. Consistent with the findings, the study by Patterson *et al.* [262] from the US described that collaboration between pharmacists and GPs was challenged by (i) a lack of understanding of each other's professional role in combination with (ii) the busy professional practice environment and (iii) the absence of a shared patient information platform. To date, there is no centralised system in which patient information is shared between community pharmacies and GP practices in the Republic of Ireland. It would be reasonable to suggest that having access to diagnoses and co-morbidities would increase the clinical relevance of pharmacist recommendations and improve communications with other healthcare providers. Sharing patient clinical data was suggested to be one fundamentally important way to improve communication and collaboration between community pharmacists and GPs. This was also suggested in the study conducted in the US by Bergman *et al.* [246] as a means of improving satisfaction among some GPs with pharmacist recommendations, which were often criticised for lacking consideration of patient context. Keller *et al.* [248] also showed how shared patient information enhanced the communication between pharmacists and physicians and increased mutual professional trust between them.

Pharmacists in the present study welcomed more education and guidelines for reducing PIP. These guidelines should ideally: (i) give instructions on the steps following the identification of a PIP; (ii) be up-to-date; and (iii) be used by all, including prescribers. To date, guidelines on stopping PIMs in older people have been criticised for being too disease-specific and not addressing the steps of stopping and/or changing a medication identified as inappropriate [124, 125, 263]. There is a need to design guidelines that meet the needs of healthcare professionals in busy medical and pharmacy clinical practice in terms of content, instructions and relevance. Beers' criteria and STOPP/START criteria as well as the recently developed deprescribing guidelines and algorithms by Farrell *et al.* [80, 96], Bjerre *et al.* [97] Pottie *et al.* [98], Reeve *et al.* [99] and the newly developed STOPP Frail criteria [93] may meet these requirements for application in routine clinical practice. However, a recent study by Cardwell *et al.* [256] has highlighted a number of barriers to the

utilisation of screening tools by community pharmacists in routine practice, those barriers being similar to those identified in the present study. Future investigation on the application of deprescribing guidelines in primary care setting is thus warranted and may provide useful insights into the implementation of more deprescribing to reduce PIP in primary care.

Whilst some studies to date have shown a positive impact of pharmacist involvement in reducing PIP in primary care [53], more research is needed into the effective implementation of such interventions. The majority of barriers and facilitators identified in this study fall under the TDF domains of: *environment; knowledge;* and *social professional role and social influences.* The design of future interventions should target these domains. The findings suggest that future research should focus on the creation of guidelines that suit the primary care setting as well as investigating new strategies to improve the collaboration and communication between healthcare professionals both across and within care settings. Policy makers and the educational sector, such as universities and postgraduate training bodies, could support the work of community pharmacists in preventing PIP by offering continuous training and encouraging interprofessional education, whilst also researching new ways of making more patient-specific information available to the pharmacist.

6.6.1 Strengths and limitations

A strength of this study is its use of a robust theoretical framework to analyse the interview data. Using the TDF ensures that a large variety of factors on behaviour are considered compared to a more restricting set of factors being explored when using individual theories of behaviour change [256]. The use of the TDF also allows the mapping of findings to theory and is a useful way of identifying mediators of change. Although the use of a pre-specified framework to develop the interview topic guide and to analyse the data can prevent the emergence of non-predefined themes of relevance, nevertheless the TDF has been applied successfully in previous studies to describe topics similar to this study [249, 254-256].

The purpose of using the TDF in this study was to identify the domains important to PIP as viewed by community pharmacists, and this was done by allowing

all domains to be explored in the interviews while narrowing the focus to the most relevant domains as viewed by the community pharmacists interviewed during the study and to report these. During the interviews, the topic guide was updated to target emerging themes from subsequent interviews. This resulted in the removal and addition of interview questions which led to the exclusion of some domains whilst adding more questions relating to other domains to investigate those in-depth. This iterative update of the interview topic guide was done based on the themes assigned high importance to the topic from the interviewees while leaving out domains that were not important to the interviewees. This explains why interview excerpts were less frequently coded into some domains compared to others. It is, however, important to note that the domains not reported in the result section are relevant to PIP although not identified as the most important domains in this study. Some domains, e.g. *optimism* and *emotion*, were either not coded or less frequently coded and these individual domains were not identified as highly relevant to PIP and thus not reported in the study. However, some of the findings relating to these low frequency domains may still be important to PIP and have, to some extent, been covered in other domain descriptions reported in the study. As an example, the domain *emotion*, was described by some interviewees, who described a fear of upsetting the doctors as a barrier to contacting them about PIP. However, this fear was mainly described as a result of the pharmacist's level of confidence and the domain *beliefs about capabilities* was more frequently coded.

This study was not without limitations. The sample size of 18, although acceptable for qualitative research, is relatively small. The nature of qualitative analysis is subjective and despite the use of a sampling matrix to recruit participants, the findings of this study, as with any qualitative research, are not generalisable to all community pharmacists. Additionally, the convenience sampling methods has its limitations in relation to the generalisability of the study population and the self-selected study population may have introduced a degree of self-selection biases.

Despite the limitations of this study and the differences in healthcare practices, the findings of this study are still likely to be relevant to healthcare providers in other countries. The collaboration between the community pharmacists and the GPs is an important area of improvement in PIP. Specific areas in the

collaboration to be targeted may be different considering the current collaboration between community pharmacists and GPs in a given country. However, as highlighted in study, agreeing on clear definitions of what the role of the community pharmacist should be in reducing PIP is an important starting point to encourage the pharmacists to extent their role and to improve their collaboration with the GP. Another target area, not specific to Ireland, is the insufficiency of available guidelines to guide PIP reduction. There is a need to ensure that guidelines are up-to-date, are used by all healthcare professionals, are relevant and give the instructions needed. Hence this study has identified key areas in PIP to be targeted, and although specific to Ireland, the key areas, if considered in the country-specific setting, are relevant to other countries.

6.7 Conclusion

Community pharmacists are aware of PIP in older people and its related problems. They believe to fulfil a duty of care by ensuring rational use of medication in patients and they welcome an extension to their role to include reducing PIP. But today the role of the pharmacist in reducing PIP is neither a role that is well-defined, implemented in community practice in Ireland nor a role known to healthcare professionals and patients.

Community pharmacists are trained and have sufficient knowledge to identify PIP but are lacking the resources, such as time and financial resources, to prioritize the reduction of PIP in their daily work over more immediate issues. Conducting medication reviews as a basis for PIP identification and clinically relevant recommendations should include information of current medication use, patient preferences (e.g. medication compliance issues) and clinical patient data. Dispensed medication and conducting patient interviews are sources of information available to the community pharmacists today which puts them in an ideal position to identify PIP. However, clinical patient data is lacking and compromises the clinical relevance of pharmacists' recommendations to reduce PIP. This is a barrier to the collaboration between community pharmacists and GPs.

This study provides useful insights into the target domains for overcoming barriers of pharmacist involvement in reducing PIP in primary care and may prove

useful in the design of future pharmacist-led interventions to reduce PIP. Although exclusive to Irish community pharmacists, the findings may be of use in the expansion of the role of the community pharmacist in other countries with similar pharmacist practices.

7 The role of the community pharmacist in deprescribing - views of community pharmacists and general practitioners

7.1 Chapter description

One barrier to deprescribing identified in Chapter 2 and 6 was the lack of clear descriptions of the role of the prescriber and the community pharmacist in deprescribing. In this chapter, the current and the potential role of the community pharmacist in deprescribing was explored by examining the views of GPs and community pharmacists.

7.2 Introduction

In Ireland, the role of the community pharmacist is still mainly one of safeguarding rational use of medicines by dispensing the right medicine, to the right patient, at the right time. Decision making in relation to patients' pharmaceutical care is still firmly within the remit of GPs [126, 264]. However, when one looks outside of Ireland, one sees in countries like Canada, the United States of America (USA), Australia and the United Kingdom (UK) the expansion of the role of the pharmacist in community care settings [60, 247, 265, 266]. In these countries, community pharmacists have greater involvement in the provision of patient care services, specifically in support of medicines management. Examples include the Medication Therapy Management (MTM) services in the USA, the Home Medicine Review (HMR) in Australia and the Medicines Use Reviews (MURs) in the UK [60, 62]. Community pharmacies in Ireland, as in other countries, provide easily accessible sources of information and advice to patients in the primary care settings [267]. The inclusion of pharmacists as patient care providers in the primary care settings has thus been suggested as a mean of overcoming the increasingly complex medicines management needs of our older population [266].

Pharmacist-led medicine management in community settings has shown to significantly reduce the rates of medication-related problems (MRPs), potentially inappropriate prescribing (PIP) and related costs [60, 264]. Furniss *et al.* conducted an RCT in 14 nursing homes in England and showed that pharmacist-led medication reviews decreased the number of medicines and associated costs [268]. Other studies have also demonstrated positive outcomes of pharmacist-led medication reviews by showing significant differences in the change in the number of medications [269], reduction in the number of prescribed and administered drugs, reductions in prescribing costs and number of falls when comparing intervention groups to control groups [269, 270]. Published reviews of the literature have also highlighted that pharmacist-led interventions appear to produce the desired effect on inappropriate prescribing [51-53, 201]. In the review by Castelino *et al.* [51], two of the included studies showed a significant effect of the pharmacist-led intervention on inappropriate prescribing demonstrated by lower MAI-scores in the intervention group. Three out of five studies included in the review by O'Riordan *et al.* [53] also

showed a reduction in the MAI score, and one study reported a reduction in newly dispensed PIMs for intervention group participants. These reviews highlight and support the important role that pharmacists play in improving the quality of medication use in the elderly. In line with this, the systematic review conducted and reported in Chapter 3, also summarized these positive effects of pharmacist involvement on number of drugs and prescribing appropriateness. Included studies in this review demonstrated that collaboration with pharmacists reduced the mean number of drugs prescribed , reduced the number of unnecessary drugs, MAI scores, number of inappropriate drugs when comparing intervention groups to control groups [190, 192, 197].

Considering these proven benefits, it is feasible to imagine provision of services to support deprescribing by community pharmacists in Ireland. However, such new arrangements are likely to require new strategies to empower the community pharmacist whilst simultaneously, being mindful of the risk of disenfranchising the GP [264].

Consensus exists that collaboration between GPs and community pharmacists is crucial to medicines management, and several models have been developed [271-275]. These different models [271-275] have described the key concepts of collaboration. These include communication, skills, trust, interdependency, perceptions and expectations about each other, interest in collaboration, and role definition. The models suggest that it is necessary to describe the current collaborative setting in order to establish a collaborative working relationship. Describing the current situation includes an understanding of the perceptions GPs and community pharmacists have of each other, of their individual skills and expectations in the job, and their interest in collaborative working practices [276].

Research examining the perceptions of community pharmacists and GPs of pharmacists' roles in the era of new initiatives to collaboration with the aim of reducing PIP has been minimal. From qualitative interviews with community pharmacists in Ireland (Chapter 6), it was clear that they did not believe that they have a major role in PIP reduction in practice. This was despite a belief that reducing

PIP was a role that the pharmacist was trained to undertake. The interview study showed role ambiguity and lack of clear direction regarding the pharmacist's contribution to patient care in community practice (Chapter 6).

Before integrating the community pharmacist in patient care and adding deprescribing to their role, there is a need to explore the views of GPs and community pharmacists on their respective roles in deprescribing and to identify the barriers and facilitators to more pharmacist involvement in deprescribing. This study is the first to use a qualitative study design aiming to explore the views of community pharmacists and GPs on the role of the community pharmacist in deprescribing. This study aims to provide insights into how the community pharmacist role is perceived and elucidate differences in the views of GPs and community pharmacists on their involvement in deprescribing. These findings may be useful to other professionals and policy makers wanting to integrate community pharmacists into deprescribing management in primary care settings. The findings of this study will contribute to the ongoing expansion of the role of community pharmacists in Ireland and in other jurisdictions.

7.3 Methods

7.3.1 Study design

A qualitative study design was chosen to explore the views of community pharmacists and GPs on current practices of deprescribing, and the future developments of new practices with increased pharmacist involvement. In pharmacy practice research, qualitative methods are often used to identify, improve and develop current practices and are a useful way of understanding existing practices and beliefs [277].

7.3.2 Ethical compliance

Ethical approval was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals prior to recruitment of study participants (Appendix XII). For interviews conducted face-to-face written consent was obtained prior to the

interview. For interviews conducted over the telephone an oral consent was given by the participant before the interview and a written, informed consent was obtained after the interview by email.

7.3.3 Recruitment

Participants eligible for inclusion in this study were community pharmacists and GPs working in the greater Cork region, in southern Ireland. Participants were recruited using a convenience sampling strategy from September to December 2018. Convenience sampling relies on data collection from a population who are readily available to participate in a study [259]. This recruitment strategy was chosen due to time constraints and the need to increase the likelihood of respondents. Community pharmacies and GP practices located in the greater Cork region were identified from a map. An initial list of pharmacies and GP practices was created based on considerations to the location (i.e. located in an urban, rural, affluent or disadvantaged area). Community pharmacies previously included in the study described in Chapter 6 were not contacted. The community pharmacy and primary care practices were contacted by telephone, and the study was presented to the pharmacist/practice receptionist. Follow-up phone calls as appropriate were made. All community pharmacists and GPs who agreed to participate were included in the study as no exclusion criteria were specified to allow for a sufficiently high number of participants in the study. A mutually convenient interview date, time and interview type (face-to-face or telephone interview) was arranged with each study participant.

Since the purpose of qualitative research is often, as in this study, to identify patterns pointing to similarities of views and opinions of participants, a minimum number of participants was required in order to ensure that all relevant patterns would be found. Recruitment was continued until data saturation occurred, i.e. until no new themes appear [277]. Data saturation was considered individually for interviews with community pharmacists and GPs. This decision was made because the two groups had different professional backgrounds and would be expected to have different views on the topic. In order to be able to present both the views of community pharmacists and GPs, it was therefore deemed important to reach data

saturation within each group of participants. A large within-group homogeneity was believed to exist in that the participants in each group were practising under the same legislation, in the same geographical area, and were therefore likely to have the same perspectives on geriatric pharmacotherapy/polypharmacy. The research question was believed to be very specific in that it related to one process, i.e. deprescribing in a specific population, i.e. older people and with the involvement of one profession, i.e. the community pharmacist. Based on these beliefs, I, the primary researcher, decided to aim for 10 interviews with community pharmacists and 10 interviews with GPs. Using the approach described by Francis *et al.* [258], three additional interviews in each participant group were conducted until no new themes emerged. If no new information arose from the last three interviews compared to the preceding 10, this indicated that data saturation had been reached. If new themes emerged in the latter interviews, an additional three interviews would be conducted and compared to the previous 13 interviews. This process would continue in this manner until data saturation was reached.

7.3.4 Interviews

Semi-structured interviews with community pharmacists and GPs were conducted by me, the primary researcher. This type of interview allows the interviewer and interviewee to diverge from the questions as well as the order and weight of these, so as to elaborate on some perspectives in greater detail or to pursue new ideas [277, 278]. This type of interview allows the interviewer and interviewee to diverge from the questions as well as the order and weight of these, so as to elaborate on some perspectives in greater detail or to pursue new ideas [277, 278].

Based on the findings of the previous qualitative study [126] the interview topic guide was designed and was introduced with questions about the interviewee's understanding and familiarisation with deprescribing (a copy of the topic guide is available in Appendix XIII). If a participant was not familiar with the term '*deprescribing'*, this term was explained to them by me, the interviewer. This was done to make sure that all participants fully understood the research topic. The topic guide was developed by the primary researcher and the four supervisors of this PhD study and designed to be used for both GPs and community pharmacists. The topic

guide was then piloted with a community pharmacist with a background in academia to ensure that I was familiar with the questions. This community pharmacist was a PhD candidate known to me, the primary researcher. The community pharmacist had experience with conducting qualitative interviews with healthcare professionals himself and had the knowledge to provide useful input into how the primary researcher conducted the interview and the topic guide questions. The topic guide was further refined on an iterative basis during the study to allow emerging themes to be explored more in subsequent interviews. Minor changes to the topic guide were undertaken by me, the primary researcher but more extensive amendments were approved by all four supervisors of the PhD study before the topic guide was finalised. Interviews were audio-recorded with consent from the participants and transcribed verbatim by me, the primary researcher. Transcripts were offered to be returned to participants for their review. This allowed the participants to remove or revise some of their answers. However, only one participant wanted to review the transcript and made no revisions.

7.3.5 Qualitative data analysis

Transcripts were anonymised and transferred to the QSR NVivo® Version 12 software. The interview transcript data were analysed by me, the primary researcher, using a thematic content analysis (CA) approach described by Braun and Clarke [279]. Thematic CA is a useful approach for describing the salient issues for a group of respondents, in this study the challenges of deprescribing in primary care and community pharmacist involvement. The thematic CA helps reducing the complexity of participants' answers by looking for patterns or 'themes' in the data [279, 280]. Themes are recurrent concepts that summarise the views and beliefs raised by the participants [280]. The findings from interviews with GPs and community pharmacists were pooled and thematic CA was applied using the common steps, including:

1) familiarisation with the data from listening to the audio recording, transcribing and reading of the transcripts,

2) identification of codes to create a list of codes,

3) recoding of transcripts according to the list of codes,

4) organisation of codes into themes pertinent to the research topic [280].

The audio recordings were all transcribed and initially coded by the primary researcher who created a list of initial codes. Four interviews were independently coded by one of the supervisors of the PhD study (L.J. Sahm) to evaluate the accuracy of the coding by me, the primary researcher, and to agree on the final coding system. To compare the level of agreement between the primary researcher and L.J. Sahm, the kappa coefficient was estimated [281]. The codes were then organised into themes by the primary researcher. All four supervisors of this PhD study read four interview transcripts to assess whether the themes captured the interview content.

7.4 Results

A total of 26 interviews were conducted with GPs and community pharmacists. In both groups of participants, data saturation was reached after 10 interviews with no new themes emerging in the subsequent three interviews. Characteristics of participants and interviews are provided in **Table 7-1**.

Table 7-1 Characteristics of study participants and interviews (n=26)

Characteristic	GPs (n=13)	Community pharmacists (n=13)	Total (n=26)
Response rate (%)	31%	75%	45%
Gender, female (%)	8 (62%)	9 (69%)	17 (65%)
Age (years), mean (SD)	47 years (11.2)	34 years (7.9)	40 years (11.5)
Experience, mean (SD)	16 years (13.0)	9 years (7.1)	13 years (11.0)
Face-to-face interviews, N (%)	3 (23%)	12 (92%)	15 (58%)
Telephone interviews, N (%)	10 (77%)	1 (8%)	11 (42%)
Length of interview, mean (SD)	16:55mins. (4.61)	20:32 mins. (7.30)	18:43mins. (6.26)

Among the participants (both GPs and community pharmacists) there were large differences in how familiar they were with the term deprescribing. Ten participants (three community pharmacists and seven GPs) were aware of the term "deprescribing" and could give a clear description of it. Four participants (three community pharmacists and one GP) were partially familiar with the term and could describe it to some extent, while six participants (five pharmacists and one GP) were not familiar with the term and this was then explained to them. All participants believed deprescribing had important patient benefits including better medication adherence, fewer side effects, improved quality of life, and lower risk of drug-drug interactions as potential benefits.

7.4.1 Inter-rater reliability

A mean kappa score of 0.841 (SD $\pm$ 0.040, Range: 0.800-0.896) was obtained which demonstrated a high level of agreement between coders before the coding system was finalised. After the comparison of coding, the two coders discussed the disagreements in coding to reach consensus of the final coding system. Furthermore, all researchers agreed that the themes generated were representative of the content of the interviews.

7.4.2 Thematic content analysis

Five themes emerged from the thematic CA:

(i) the GPs' role in deprescribing - is there room for a community pharmacist?

(ii) working relationship,

(iii) the role of the community pharmacist in deprescribing,

(iv) patients' interaction with the healthcare system and

(v) environmental factors.

Summary descriptions of each theme are provided below with supporting quotations.

7.4.2.1 *Theme 1: The GPs' role in deprescribing - is there room for a community pharmacist?*

GPs described their role as keeping a holistic view of a multi-morbid patient's medical treatment seen by multiple prescribers. GPs described their responsibilities in deprescribing to be as follows: (i) to initiate the process, (ii) to review a patient's medication for appropriateness, (iii) to assess the risks and benefits of treatment and (iv) to eliminate the risk of side effects and drug interactions. These responsibilities were believed by some GPs to be part of the routine review of a patient's medicines while others felt that they were not sufficiently involved in deprescribing:

> *"Well every time you're doing a repeat prescription to be reviewing the medication and the need for them and the indication for them. Making sure that things don't interact and that things are being monitored probably. So, yeah I suppose we have a massive responsibility in deprescribing."* [Participant 15, GP, female, 1 years of experience]

Community pharmacists described a similar centrality of the GP's role and similar responsibilities such as regular review of medicines when initiating and renewing prescriptions. Despite the centrality of the GP's role in deprescribing, a reluctance to deprescribe by GPs was described by community pharmacists and GPs. Factors associated with this reluctance were (i) a professional courtesy not to interfere with prescribing decisions made by prescriber colleagues and (ii) a concern about the consequences and responsibilities for stopping a medicine:

> *"I suppose a lot can be started in the hospital setting and GPs are reluctant to stop anything unless the Consultant will give them a 'go ahead' and a lot of the time patients can be on waiting lists for Consultants. So, it [deprescribing] doesn't necessarily happen an awful lot then (…) I think there's a certain amount of worry there that if there's any issues down the line and they [GPs] take the responsibility for stopping something, that it could be a problem then"* [Participant 11, Pharmacist, male, 9 years of experience]

Even though the GPs believed they had a key role in deprescribing, they welcomed the idea of having support from community pharmacists. Community pharmacists were perceived as helpful information sources and the advice from a community pharmacist was valued and welcomed by all the GPs interviewed. Nonetheless, there was a realisation that maybe not all GPs would be open to this:

> *"But to be able to say: 'look, I [the pharmacist] was going through this patient's script (sic) and I just wanted to bring it to your [GP] attention that ah, due to age, they no longer benefit from statin'. Something like that I think would be great. But you know again I think it should be very gently because I know doctors can get really rankling if they feel that pharmacists are telling them what to do."* [Participant 18, GP, female, 8 years of experience].

Working together with community pharmacists on deprescribing was perceived to be a good way of ensuring continuity of care when both parties would agree on the patient's treatment plan:

> *"When we put prescription prompts, I suppose we're hoping that the pharmacist will also be picking up on these things, and kind of repeating the message to the patient (…) I think sometimes it would be good to close the loop of communication because I think patients do sometimes assume that we're all in very intimate communication about everything, but we don't actually know what the patient is saying to the pharmacist about something always, and we don't know what the pharmacist is saying to the patient either"* [Participant 14, GP, female, 4 years of experience]

A mutual openness and appreciation of pharmacist involvement in deprescribing to the one described by the GPs was not experienced by the community pharmacists. Prescriber- and age-dependent motivation to involve the community pharmacist was considered to be a factor in the lack of openness among GPs. Younger GPs were perceived to be motivated to collaborate with community pharmacists whereas older and more experienced GPs were described as being inclined to continue their usual practice of prescribing. Even for the more receptive GPs, community pharmacists were unsure if their advice would be accepted as they observed no action was taken after advice was given. In other instances, the community pharmacists were unsure if a specific piece of advice was acted upon, due to the passage of time between advice being given and a change to the prescription:

> *"They [GPs] wouldn't be great at taking on the advice. But you know they are pleasant enough to deal with (…) maybe about the benzos and stuff they mightn't be [great at taking on the advice], but you never know because it could be in a few months or something they might decide to reduce them down. So, we don't know."* [Participant 10, Pharmacist, female, 9 months of experience]

The perceived lack of openness from some GPs resulted in the community pharmacists selectively choosing to interact with the more welcoming GPs and avoiding those GPs less inclined to interact with them. Additionally, community pharmacists described how they would consider the seriousness of the effects of an inappropriate medicine before suggesting changing it to less welcoming GPs:

> *"I suppose sometimes you kind of know which GPs may not be so receptive, and which then, unfortunately, makes you less likely to approach them, because you know sometimes it just makes life very difficult. I mean, obviously if you see something completely inappropriate, you contact about that. But sometimes with, if it's just suggestions, not so much."* [Participant 6, Pharmacist, female, 9 years of experience]

Community pharmacists also acknowledged that due to the lack of clinical data some of their advice was limited in terms of its clinical relevance. Consequently, the community pharmacists had a lower expectation of GPs to accept their advice but nonetheless hoped to be heard:

> *"But even when I do raise an issue, I'm well aware that, look it may not be possible to do that, it may not even be advisable to do it. There might be a very good reason why the patient is on something that I'm not aware of. So, I would expect to be heard out alright, but I wouldn't necessarily expect that it would lead to an actual deprescribing or lead to action as such."* [Participant 12, Pharmacist, male, 7 years of experience].

7.4.2.2 *Theme 2: Working relationship*

GPs and community pharmacists commonly interacted but primarily on the initiative of the pharmacist. Typical interactions were to: correct prescribing errors and drug interactions, clarify prescription discrepancies, request prescriptions, or substitute medications due to short supply. These corrective actions of immediate problems

were more common interactions between GPs and community pharmacists in contrast to the more strategic preventative actions i.e. deprescribing to avoid adverse outcomes from long-term medicine use:

> *"Now we interact with the community pharmacist every day actually. On a daily basis (…) Deprescribing? Probably not as often as other things I would say. Not that frequently would be the answer to that question (…) the commonest discussion with pharmacists would be probably errors in our prescribing, actually. Incorrect dosage, a computer error on prescriptions. Query on dosage, query on amount. You know, unavailability of drugs is the commonest things at the moment."* [Participant 13, GP, male, 24 years of experience]

By being the person who highlighted errors to GPs, community pharmacists described how they believed that this negatively affected their relationship because they perceived that GPs would feel that the community pharmacists were targeting their prescribing practices in a destructive manner:

> *"I think the issue is that the only point of contact we have with them really is when we're ringing them up and it seems like we're criticising their practice or giving out to them. So, you can kind of feel why they don't take too kindly to you ringing up and being like 'oh no that's wrong'"* [Participant 2, Pharmacist, female, 10 months of experience]

From the GPs' point of view, the working relationship with the community pharmacists was perceived to be good but hindered at times by some community pharmacists dispensing full month's supplies of medicines, in the absence of a prescription. This may happen on occasion due to an emergency, however some GPs felt that this was a method by which they were obliged to provide a prescription after the medication had been dispensed and without the GP's review of the medicines:

"Some of them are issuing repeat prescriptions to patients on a non-emergency basis with the full prescription reissued without the patient being reviewed, and we are being asked to send them a prescription, post-dispensing. They find that very convenient some of the elder patients, but I don't know if they are getting the follow-up care that they need or not. So that can be a bit antagonistic for us." [Participant 14, GP, female, 4 years of experience]

Good lines of communication were perceived to be important in building a strong collaborative relationship. Some community pharmacists described how this was challenged by having second-hand communication either with General Practice receptionist who acted as gatekeeper for the GP or with the patient who acted as an intermediary.

"I think there is a bit of a barrier there to the communication between us and the doctors. And then a lot of the time we're interacting with the secretary who then is interacting with the doctor and then things get all muddled up. And you know there's like no straight answers (…) So, it's all second-handed information you're getting back as well. And then like I suppose the enthusiasm isn't really there to be proposing this like optimal practice." [Participant 2, Pharmacist, female, 10 months of experience]

Other community pharmacists described that communicating deprescribing recommendations to GPs was most successfully done when communicating through the patient, i.e. advising the patient to go to their GP and to suggest deprescribing of certain drugs:

"I find that myself that my most effective means of making recommendations can be directly to the patient who takes then the information to the doctor. It's listened to them because there has to be listened to them." [Participant 16, Pharmacist, male, 15 years of experience]

Other suggested improvements to building collaborative relationships between GPs and community pharmacists in deprescribing were to: (i) introduce clearer definitions of the roles of the GP and the community pharmacist in deprescribing, (ii) and to encourage knowledge-sharing as an integrated part of their interaction:

"I think it's to get more agreement between pharmacists and GPs and their representative body in terms of what services are going to be provided and the roles. What's expected of the role of the GP and the role of the pharmacist. Like that has to be very clear on it." [Participant 9, GP, female, 17 years of experience]

"Like we might see from just studying in college that maybe like, x medication shouldn't be prescribed to a certain patient group but they [GPs] might be like 'oh I have loads of experience in prescribing it'. So, even if you got an explanation as to why it probably would help expand everybody's understanding. And so, like I could look at that then and you know I could also come back to them with my research on it after being told that or something." [Participant 2, Pharmacist, female, 10 months of experience]

7.4.2.3 *Theme 3: The role of the community pharmacist in deprescribing*

GPs and community pharmacists described the general role of the community pharmacists as a safety net for detecting prescribing errors and that community pharmacists should act as gatekeepers of dispensed medicines and to highlight any medication non-adherence.

"*I suppose the most common thing would be a pharmacy query about an error in a script (…) it might be naming errors or a dosing error or clarification on that (…) So, you know, if we adjust the dose and it's not clear that have changed the dose on the prescription or it's not clear where the change has come from then we might get a call [from the community pharmacist] for clarification on that. They are probably the most common. After that there might be a call about concerns about a patient and their medication. So, if the patient isn't collecting the medication or if they come into the pharmacy and they look very confused about their medication."* [Participant 14, GP, female, 4 years of experience]

Some participants (both GPs and community pharmacists) described a potential role for the community pharmacist to initiate the deprescribing conversation with selected patients and to reinforce and support deprescribing decisions made by GPs in cases where patients were uncertain or opposed to deprescribing of certain drugs. However, collaboration and communication, such as prescription prompts, between the GP and the community pharmacist is warranted and enables the pharmacist to understand the GP's reasons for prescribing changes and, to reinforce them:

"I suppose reinforcing their message and having their back. Because you will frequently get, if the GP does try and lower certain medications or stop them, the patient will come in and immediately begin complaining about the GP who has stopped or lowered their medication. In that case you're doing the GP no favours at all if you side with the patient and it's very important that you reinforce the message as to why the dose is lowered." [Participant 12, Pharmacist, male, 7 years of experience].

"When we [GPs] put prescription prompts, I suppose we are hoping that the pharmacist will also be picking up on these things and you know kind of repeating the message to the patient." [Participant 14, GP, female, 4 years of experience]

Community pharmacists believed that if they had a good relationship with patients,

these patients would share information with the community pharmacist that they might not share with GPs, e.g. personal circumstances and reasons for not taking their medicines. Community pharmacists' regular contact with patients when collecting their medicine was also believed to put the community pharmacist in a favourable position to identify lack of medication adherence.

> *I suppose we're, whereas the GP might only see a prescription, as I said once every 6 months or say once every maybe twice a year or once a year, we are seeing it every month. You know, we are going through that prescription every month. So, we do see it a lot more often. We see the patient probably a lot more often (…) So, you know, if something is left on the prescription when it shouldn't be, it would be, I'm sure, beneficial for the GP for at least for us to be highlighting it to them."* [Participant 11, Pharmacist, male, 9 years of experience]

This information about medication adherence was appreciated by GPs:

> *"But I suppose say it for a lot, for some of my geriatric patients, you know, if there was an issue with compliance or if you know that they were coming back in requesting medication before it was due. Often things like that would be flagged by the pharmacists that we would deal with, which is very helpful."* [Participant 9, GP, female, 17 years of experience]

Looking at expanding the role of the community pharmacist to include prescribing and deprescribing, the views among participants were divided. Some community pharmacists believed that authorisation for prescribing and deprescribing should be granted to them whereas other pharmacists and GPs believed that community pharmacists should not have a role to discontinue medicines but to recommend and advise it:

"I mean, ideally I would like to see pharmacists prescribe (…) I think that the whole prescribing competency is key to this 'cause to me deprescribing is gonna be invested in the same people with prescribing competency." [Participant 1, Pharmacist, male, 15 years of experience]

"I wouldn't necessarily agree with pharmacists prescribing (…) I don't, because we're not prescribers. We're not GPs. And I think it's really important not to confuse the two roles, because I'm not a GP. You know, I'm a pharmacist." [Participant 6, Pharmacist, female, 9 years of experience]

"If pharmacists have a good relationship with the GP as we have with our pharmacists downstairs here then they can advise us that maybe it's not such a good idea for these tablets to be prescribed" [Participant 13, GP, male, 24 years of experience]

Other suggestions to expand the role of the community pharmacist in deprescribing were to extend the responsibility for medicines review to community pharmacists and extending more services from General Practice to the pharmacy, such as monitoring of blood glucose and blood pressure as well as services similar to influenza vaccination which is currently routinely administered by some community pharmacists in Ireland. A perceived outcome of transferring more services to the pharmacy was improved credibility of the community pharmacist role for both patients and GPs:

"Can you imagine how the role would change if we were to do medication reviews? (…) Now, I have to say when the pharmacy takes on a new role, whether it's diabetes, cholesterol, INR, flu shot, the respect that's shown is second to none. I have experienced such." [Participant 17, Pharmacist, female, 2 years of experience]

7.4.2.4 *Theme 4: Patients' interaction with the healthcare system*

The success of deprescribing a medicine was believed to be linked to a patients' perceptions of medicines and their willingness to stop them. Patients' acceptance of deprescribing recommendations was believed to be influenced by either a lack of awareness about the risks associated with long-term use of certain medicines and the level of awareness about their medicines from online information sources. Pharmacist involvement in deprescribing was dependent upon the relationship between community pharmacists and patients. Patients who were loyal to one pharmacy usually had a good relationship with the community pharmacist. The community pharmacist would know their history in detail and the patients would have greater confidence in their pharmacist's recommendations and thereby would be more responsive to them:

> *"Patients listen to pharmacists quite well but they tend to shop around and go to different pharmacies, different times. So, yeah it would depend on the patient's relationship with the pharmacist. But if they have a good relationship, yes, they certainly will listen to their advice."* [Participant 4, GP, male, 5 years of experience]

Participants also highlighted the importance of good GP-patient relationships to enhance patients' willingness to stop certain medicines. In general, there was a sense of patients selectively sharing their personal information with GPs and community pharmacists depending on the relationship they had with them. This reinforced the crucial importance of a close collaboration between GPs and community pharmacists in deprescribing:

> *"And like on a day-to-day basis you find out different things that, they don't think, they don't find important. Like you know if they sat down with the doctor they'll be like: 'Oh, I would never say that to the doctor. That's a waste of the doctor's time'. But it's so important to them and it's so important to*

their care. So, I think the, the pharmacist is definitely very important in terms of that." [Participant 21, Pharmacist, female, 3 years of experience]

"*I suppose, you know, information about the patient's usage of the medication. If there's feedback from the patient that they [community pharmacists] are getting that we might not be getting then that would be helpful."* [Participant 14, GP, female, 4 years of experience]

7.4.2.5 *Theme 5: Environmental factors*

When asking the participants about the challenges to community pharmacist involvement in deprescribing, many external factors were mentioned. Time was the most frequent factor mentioned. With limited time available to deprescribe, prioritisation of the more critical issues over the more preventive actions; such as deprescribing of medicines, was a perceived necessity. Linked to a lack of time available for deprescribing for both community pharmacists and GPs was the lack of enough staff and the absence of financial incentives for deprescribing:

"I would love to see us getting paid for patient medication review (…) Because if you were getting paid for it you would have more time and you would be able to hire a second pharmacist too, and to actually spend the time with the patient because you wouldn't be under the same pressure." [Participant 23, Pharmacist, female, 16 years of experience]

Interdisciplinary training and shared guidelines between community pharmacists and GPs were suggested ways of improving the collaboration between GPs and community pharmacists in deprescribing:

"If there was training that brought pharmacists and GPs together, even on a small scale. Like the local pharmacy and the local GP within an area, they could establish a protocol of like, you know, in a certain case when a pharmacist can intervene and obviously within certain things they can't, and

they just refer on. Because it works with other things. Like over-the-counter medications, and I know it's not the same idea but. There's a protocol and if you follow the protocol it usually is safe." [Participant 21, Pharmacist, female, 3 years of experience]

Another suggested way of giving community pharmacists a greater role in deprescribing was to make deprescribing a mandatory official role of the community pharmacist and the GP by inserting descriptions of the respective roles in deprescribing into their contracts. In addition to making deprescribing a formal part of the role of the community pharmacist, structuring the deprescribing process was also highlighted as a way of enhancing the role of the community pharmacist in deprescribing. Current deprescribing practice was considered opportunistic rather than systematic. Lack of time, staff and funding were believed to lower the likelihood of successful deprescribing particularly when no agreed formal structure for deprescribing was in place:

"Well it would definitely help if there was a procedure in place that GPs and pharmacists could both buy into, that both were aware of and that would allow you if identified to say 'okay, I've identified an issue here, the next step is communicate with the GP or whatever'. And if the GP was also aware of this process it would help." [Participant 12, Pharmacist, male, 7 years of experience]

Finally, there was an expressed need to raise awareness of deprescribing and the role of the community pharmacist among patients. Awareness campaigns, information leaflets and educational sessions were suggested initiatives to raise awareness for and patients, preferably supported by State agencies and GP and pharmacist unions:

"I think again, even if the HSE did a leaflet, you know 'can you take less medicine?' or something. So, that the concept is out in the community that

you might not need all of the tablets that you're taking" [Participant 18, GP, female, 8 years of experience]

7.5 Discussion

This study is the first, that I am aware of, to explore the views of GPs and community pharmacists on the role of the community pharmacist in deprescribing and the barriers and facilitators to this role. From the analysis, these views were grouped into five identifiable themes that likely influence the success of deprescribing i.e. (i) the GPs' role in deprescribing - is there room for the community pharmacist? (ii) working relationship, (iii) the role of the community pharmacist in deprescribing, (iv) patients' interaction with the healthcare system, (v) environmental factors. The findings of this study provide useful insights enabling a better understanding of the barriers and facilitators to increased community pharmacist involvement in deprescribing. These findings will also help inform what the role of the community pharmacist could be in deprescribing.

An interesting finding of this study was that community pharmacists and GPs had very different perspectives on the current involvement of community pharmacists in deprescribing. Whilst GPs described frequent interactions with pharmacists, some community pharmacists described difficulties with getting past the General Practice receptionist to speak directly with GPs, such that the relationship lacked direct interaction. Conversely, GPs described good interactions with community pharmacists about immediate issues in medicines management, such as changing a drug due to an adverse interaction. Importantly, community pharmacists wanted more interaction about long-term preventive actions including deprescribing. A Canadian study has described that expectations and appreciation of each other's role in a team approach to medicines management will be affected by experiences of doctors and pharmacists working together in a team [247]. In our study, the main interaction between community pharmacists and GPs was when community pharmacists contacted GPs to propose corrections to immediate issues of their prescribing practice. With this being the main interaction, a sense of community pharmacists being primarily critical of GPs' prescribing practices was

evident, and this rather negative interaction may thus be a hindrance to developing collaboration on deprescribing. However, examining the positive experiences, there was a sense of the community pharmacist providing a safety-net to the GPs, capturing prescribing errors in older patients at the point of dispensing medication. If seen in this positive light, the community pharmacist's role in deprescribing may be perceived positively and increase pharmacist involvement in deprescribing.

Expanding the role of the community pharmacists will inevitably result in overlapping roles with the GP, which may in turn cause confusion about the responsibilities, creating a risk of interprofessional tension [247, 282]. As expressed by the GPs of the present study, community pharmacists working outside their scope and routine dispensing of monthly supplies of medicine on a non-emergency basis were felt to antagonise the GP's role in deprescribing. By giving the community pharmacists a more advisory role in deprescribing, some GPs felt that the professional role boundaries are being impinged upon. The process of accepting new responsibilities within a professional role, such as deprescribing, involves understanding and acceptance of the previous roles that are relevant to the new role [247]. In this study, GPs considered the community pharmacist a valued source of information regarding drug interactions and patient medication non-adherence such that this a likely role for them with a wider deprescribing remit. From a survey in the USA, primary care physicians believed collaboration with pharmacists would improve medication adherence in older patients. This belief was the most significant predictor of physician attitude to collaboration with pharmacists [265]. Similarly, this belief could be shaping the attitudes among GPs to the role of the community pharmacist in deprescribing.

Community pharmacists themselves described their regular patient contact and patients' loyalty to their local pharmacy as major advantages for community pharmacists' involvement in medication adherence, and something that could be drawn upon for the benefit of older patients. Although GPs did not report a firm belief in the loyalty of patients to one pharmacy, most community pharmacists did. A public survey in England in 2012 supports this belief held by pharmacists, and showed that patients who regularly take medicines and use the pharmacy services had a preference for using the same pharmacy where the pharmacist and the other

pharmacy staff know them well [283]. In Ireland, a similar situation exists due to the system of reimbursement. Patients under the Drugs Payment Scheme (DPS) are advised to use the same pharmacy in a month to avoid paying more than the maximum €134 a month. The pharmacy will keep a record of the total amount paid by the patient in one calendar month and stop charging the patients once they reach the €134 mark [234, 284]. Similarly, patients under the GMS scheme may benefit from using the same pharmacy in one month to avoid paying more than the monthly prescription levy cap of €20 [234]. Frequent consumers of medicines under the Irish medicine schemes may thus be more loyal to one pharmacy than perceived by the GPs interviewed in this study.

In an era of expanding the role of the community pharmacist, there may also be a need to redefine the role of the pharmacy. In many UK rural communities, community pharmacists already act as primary care providers due to the fact that local GPs are overworked and have limited time, similar to the findings of the present study [247]. In such circumstances, patients seek healthcare services in the pharmacy because they have fewer options to find them elsewhere [247]. Devolving patient care more to the community pharmacy warrants consideration of the role of the community pharmacy. If the vision for the pharmacy is to provide quick medication supply to customers while they shop for other errands, then moving towards more availability and longer opening hours may be the way forward. Changing the role of the pharmacy from a shop to a healthcare centre may also change the expectations of patients. That is, some older people see themselves as patients and others as customers when going to the pharmacy, which in turn may affect their views of the community pharmacist as a shopkeeper or healthcare professional [247].

Finally, the present study described a need to promote the role of the community pharmacist more among older patients. GPs advocating the pharmacy service to their patients may be one way of promoting the community pharmacist's role in deprescribing. In a UK survey, the promotional method judged most effective was direct recommendations by GPs [283]. Previous experiences with the community pharmacist can positively influence older patients' expectations of community pharmacists and may increase their frequency of pharmacist consultation. Establishing consistency in the pharmacy services has been described to be

important in shaping patients' expectations [247]. The present study findings indicate that there is a need to define the role of the community pharmacists, and to define the future services to be undertaken by community pharmacies such as deprescribing. If the roles and services provided in community pharmacies are well defined, then it is likely that patients will change their expectations and start using the pharmacies more for patient care issues.

7.5.1 Future implications

In proposing the expansion of the role of the community pharmacist in deprescribing for older people, first there is a need for a clear definition of deprescribing and for RCTs with demonstrable evidence that deprescribing works and that pharmacist involvement is effective in facilitating the deprescribing process. Secondly, there is a need to match pharmacists' competencies to this supportive new role in deprescribing. Interdisciplinary training and shared guidelines as suggested in this study, might provide a useful way of teaching new competencies to community pharmacists while simultaneously improving collaborative relationships with GPs. Today, various tools exist to facilitate appropriate prescribing and optimization of medication use, such as, but not limited to, the STOPP/START [77], the STOPPFrail [93] and the deprescribing algorithms [80, 96-99]. Educators in clinical pharmacy and medicine should consider action in the development of the respective curricula in the area of collaborative deprescribing in primary care settings and in the incorporation of the existing tools to guide both prescribing and deprescribing. In addition, State- and union-led initiatives are needed to define clearly and precisely the role of the community pharmacist in deprescribing for older people. There is also a need for the State and the unions representing community pharmacists and GPs to mediate and agree the collaboration between community pharmacists and GPs in their overlapping roles in deprescribing and to jointly agree and negotiate the resources needed to facilitate this initiative.

7.5.2 Limitations

As with other types of qualitative research, the views of those represented in our study may not necessarily concur with those of other GPs and community pharmacists elsewhere in Ireland. A nationwide study might identify regional differences in community pharmacists' and GPs' views of community pharmacist involvement in deprescribing, as well as different descriptions of the role of the pharmacist in deprescribing for older people. Using convenience sampling to recruit participants facilitated the sampling but can potentially introduce selection bias. The GPs and community pharmacists participating in the study could potentially have a more positive attitude towards changing practices in relating to deprescribing which may have influenced their answers to questions. Those who have an interest in this topic, of changing current practice of community pharmacists to be more involved in deprescribing, may also be reflected in the difference in response rates for community pharmacists and GPs (75% and 31%, respectively). Community pharmacists may have had a greater interest in discussing the topic as it relates to their profession. However, the difference in response rates may also be linked to the different work structure of the two professions. The GPs had to find a time slot during their working day to complete the interview and most of them used a consultation slot or their lunch break. Although the community pharmacist has also a busy working day, most of the pharmacists could find a time during the day or week that was usually quiet in the workplace. In addition, most of the pharmacists interviewed were working together with other pharmacists, pharmacist technician(s), or pharmacy staff, who could stand-in while the pharmacist was doing the interview. To ensure that all participants were familiar with the term 'deprescribing', each interviewee was asked if they knew the term and asked to give a description of the meaning of the term at the beginning of the interview. Dependant on how familiar the interviewee was with the term, I, the interviewer then gave more detailed information of what the term entails or gave a complete description of the term. This was done to ensure that all interviewees had a similar understanding of deprescribing. However, as there is no standardised approach to deprescribing, between-interviewee differences in the understanding of what deprescribing entails could have existed which may have influenced their answers to the questions. The

profession of me, primary researcher (clinical pharmacist), could also in theory, introduce a professional bias. For participating community pharmacists this may have caused them to give answers that may have been more critical of the GPs' work practices, whereas the GPs may have been more positive towards community pharmacist involvement.

Interviews were conducted either face-to-face or via telephone. Although there could be an expectation of low complexity and comprehensiveness of answers via telephone, evidence suggests that there is little difference in the content and quality of answers to leading questions obtained in person or via telephone [285]. By offering both telephone and face-to-face interviews to the participants, more participants were able to participate. The telephone interviews particularly suited the GPs, many of whom had difficulties finding a suitable time for these interviews during their busy working day. Consequently, most interviews (10 out of 13) with GPs were conducted via telephone whereas all but one interview with community pharmacists were conducted face-to-face. This difference in interview method between GPs and community pharmacists may have resulted in an imbalance of the comprehensiveness of the interviews, and the interviews with GPs were on average shorter than the ones with the community pharmacists (16:55 mins. compared to 20:32 mins.)

7.6 Conclusion

In conclusion, community pharmacists expressed a need for more interaction with GPs on deprescribing in older people, while GPs were pleased with their current interactions with community pharmacists. Expanding the role of the community pharmacist in deprescribing needs clear definitions of the roles and responsibilities as well as clear communication of these to both GPs and patients. Community pharmacists are perceived as excellent sources of prescription medication information and are consequently considered to have a potentially important role in deprescribing if a properly structured collaborative relationship is established between GPs, community pharmacists and patients. Structuring the deprescribing process and teaching collaboration were useful ways of facilitating the new role in

deprescribing. Loyalty among older patients to pharmacies and regular contact with these pharmacies are factors to exploit more in centralising the role of the community pharmacist in older patient care. Although exclusive to Irish community settings, the findings of this study may be of use in the other countries seeking to expand the role of the community pharmacist from drug supplier to patient carer in the area of medication review.

8 Discussion

This thesis identified the challenges and potential benefits of deprescribing in an Irish primary care setting and investigated the potential role of the community pharmacist in deprescribing. This chapter will be an interpretation and discussion of the key findings presented in the individual study chapters. To start, this chapter will summarise key findings of each individual study chapter and interpret them to describe implications of the research to practice. At the end, the chapter will provide recommendations for future work and conclusive remarks.

8.1 Summary of findings

Beginning this doctoral work in 2015, deprescribing was a relatively new term and unexploited in the Irish setting. Therefore, the first objective of this thesis was to review the existing qualitative and quantitative literature on deprescribing. The narrative literature review (Chapter 2) described the challenges to deprescribing in older, multimorbid patients as viewed by healthcare professionals. Overall medicines management in this patient population was challenged by the involvement of multiple prescribers with the perception that individual prescribers followed their own speciality treatment guidelines. This challenged the acquisition of a comprehensive review of a patient's medication which should ideally form the basis of deprescribing decisions. Consensus across studies was seen for the GPs to assume the responsibility for overall medicines management, including deprescribing, for older multimorbid people. Nonetheless, there was a reluctance from GPs to interfere with decisions made by other prescribers. A reluctance due to the fear of damaging professional relationships, poor communication between levels of care, patient demands, a lack of knowledge and experience with deprescribing, and a lack of guidelines to support deprescribing decisions. Patients' strong attachments and unwillingness to stop certain medications were other challenges described as well as a reluctance from the prescriber to communicate with patents about their life-expectancy, treatment goals and deprescribing opportunities. The support from

pharmacists to give recommendations in deprescribing was a welcomed opportunity for support viewed by both pharmacists and prescribers in the included studies but dependent on the prescriber-pharmacist relationship. Chapter 2 concluded that despite agreement of the GPs' role and the supportive role of the pharmacist in deprescribing, there was a need to further explore the interdisciplinary collaboration between GPs and pharmacists on deprescribing. Since the GP works in the primary care setting, it was deemed appropriate to target this setting and the supportive role of the community pharmacist.

The systematic literature review (Chapter 3) was conducted to summarise effectiveness of deprescribing interventions of reducing the number of medicines and PIP, and to identify behaviour change components determining the effectiveness. The systematic review found that following a plan, receiving clear instructions and social support, preferably from a credible source, were behaviour change components associated with intervention effectiveness. Another interesting finding in Chapter 3 was that the delivery of deprescribing recommendations, e.g. from a pharmacist was a key factor to effectiveness. Pharmacist recommendations were frequently enacted on in some studies, whilst a lower acceptance rate was demonstrated in other studies. This low uptake existed despite a shared belief of the need to deprescribe by pharmacists and GPs and highlights a need to further investigate the current collaboration between community pharmacists and GPs.

The secondary analysis of the population-based primary care cohort in Chapter 4 reported patterns of PPOs and PIMs over a five-year period in early-old aged people in an Irish setting. This study demonstrated that PPOs and PIMs are present in early old-aged community-dwelling people and is a persistent and growing problem as people progress to more advance old age. Prevalence of PPO and PIM were both significantly associated with a higher number of daily medicines, suggesting that preventing inappropriate should be focused on polypharmacy patients. The high prevalence of both PPO (31.2% increasing to 42.4%) and PIM (39.7% increasing to 45.6%) identified by the STOPP/START criteria substantiated the relevance of applying the criteria in primary care settings to identify patients for which deprescribing should be considered. Applying the STOPP/START criteria to

patients' medication data requires a comprehensive medical and pharmacological knowledge, clinical status of the patient and a complete list of the patients' medications. The application of STOPP/START may thus create an opportunity for the community pharmacists to support deprescribing by contributing with their pharmacological knowledge and knowledge of medications recently dispensed (prescription medication) and sold (OTC medications and herbal supplements) to the patient in order to identify patients in scope of deprescribing.

In Chapter 5, the study population from Chapter 4 was analysed for the next three years of follow-up, i.e. April 2015 to January 2018. Consistent with the findings of Chapter 4, PIMs were highly prevalent among the population (47-52%). This finding confirmed that PIP was still a significant problem affecting around half of the older population in Ireland. The NIC of PIMs at the final year of follow-up was €64,476.24 per annum and was the direct potential cost reduction of applying the STOPP criteria regularly to older people (aged 65 years and older). For the multimorbid community-dwelling patients with polypharmacy and in high risk of receiving PIMs, it is likely that they will visit the community pharmacy on a monthly basis to collect their prescription medications. Community pharmacists are thus able to review the prescriptions each month for appropriateness. This could provide an opportunity for community pharmacists to identify PIMs based on medication data and knowledge of the patient and to discuss these with the GP who has the clinical history of the patient. As a result, PIM prevalence and associated direct costs could be reduced.

The qualitative interview study described in Chapter 6 was designed to explore the views of community pharmacists to address some of the key areas identified in the previous chapters: barriers and facilitators to pharmacist support in reducing PIP (Chapter 2 and 3), and strategies to reduce the high and persistent levels of PIP identified in Chapter 4 and 5. Chapter 6 showed that the identification of PIP and recommendations about stopping medicines were not routine practices among community pharmacists in Ireland. Community pharmacists described a conflict between their perceived responsibility in reducing PIP as per their pharmacy training and their current role in practice. Some community pharmacists also described an

uncertainty of their role in PIP which constrained them from working outside of their current role and hindered their collaboration with other healthcare professionals. The study shed new light to the need for clearer descriptions of the role of the community pharmacist in reducing PIP together with clear communications of this role to stakeholders and patients. Collaboration between GPs and community pharmacists was believed to be challenged by a lack of understanding of each other's role and the absence of a shared platform with patient clinical information. The busy working environment they were both working in was also described to restrict them in prioritizing preventive actions such as screening for PIP and deprescribe inappropriate medications. Community pharmacists described themselves to be in an ideal role to support the reduction of PIP due to their pharmacological background and frequent patient consultations but highlighted the need for clinical information to improve the clinical relevance of their recommendations and guidelines to instruct the management of deprescribing.

The findings of Chapter 7 on the perceived barriers and facilitators to deprescribing and community pharmacist involvement echoed those of Chapter 2 and 6. Again, common barriers included lack of time and resources to prioritize preventive actions such as deprescribing. Other barriers pertained to lack of shared guidelines, poor communication and collaboration, patients' demands, a lack of awareness of the role of the community pharmacist, and an unclear role description of community pharmacists in deprescribing. Having a good relationship with the patient for both the GP and the community pharmacist was highlighted as a determinant of the patient's willingness to stop medicines. Community pharmacists and GPs both welcomed more pharmacist involvement in deprescribing. However, while GPs were pleased with their current interaction with community pharmacists about drug-interaction, switching to another medicine brand and patient medication adherence, community pharmacists experienced low uptake of their recommendations and had a feeling of picking at the GPs' practices. Current interaction between GPs and community pharmacists was described to be limited to rectifying errors identified by the community pharmacists, and this rather negative interaction was a suggested barrier to more collaboration. Chapter 7 pointed to a

need to improve and advocate the current pharmacist support to GPs with the aim to associate new pharmacists' responsibilities, e.g. advising on deprescribing, to existing positive interactions to improve the acceptance by GPs. The findings of Chapter 7 suggested that the pharmacy could have a quite central role in deprescribing in the community setting. With closer geographical proximity between patient and pharmacy compared to the GP practice in some rural areas, the pharmacy was a suggested way of bringing patient care services closer to the patients. Monitoring the discontinuation process and advocating life-style changes were other responsibilities believed to potentially be undertaken by the community pharmacist. Suggested ways of implementing new responsibilities to the community pharmacist role were to integrate the community pharmacist into the GP practices, having a structured process for deprescribing and agreeing on the frequency and extent of the pharmacist involvement in deprescribing. Other suggestions pertained to making the role more official by State- or union-led initiatives, and to integrate it into both the medical and pharmacy contracts and curriculums. Finally, interdisciplinary training and shared guidelines were suggested to improve collaboration between GPs and community pharmacists.

8.2 Interpretation of findings

The evidence-base of the improved benefits of deprescribing and pharmacist involvement in patient care continues to grow. Over recent years, a large number of papers have been published on these topics [72, 85, 112, 160, 175, 269, 286-292]. Existing research has explored strategies to integrate the pharmacist into areas of patient care, such as medicines usage reviews, patient consultations, vaccine administration and blood pressure monitoring [151, 288, 290, 292-294]. Lately, a trend of prescribing authority given to pharmacists is seen, and both the UK [295, 296] and Canada [297-299] have prescriber pharmacists. The principal contribution of this thesis has been the generation of evidence to support the role of the pharmacist in deprescribing in Ireland. The findings from this thesis adds to the evidence-base describing the extended role of the community pharmacist. It is the first thesis, to my knowledge, to formally look at the role of the community

pharmacist in deprescribing in an Irish primary care setting. This thesis substantiated that PIP is a persistent problem among Irish community-dwelling early old aged people. It is also evident from this thesis, that actions to prevent PIP, such as deprescribing, do not form part of a routine practice in the primary care setting. The role of the community pharmacist in deprescribing is welcomed both by community pharmacists and GPs but the successful integration has yet to be found. The findings of this thesis should serve to direct future research.

8.2.1 Extending the role of the community pharmacist to support deprescribing

With medication being the main focus of treatment to date together with the long-term preventive and treatment actions and the complexity of deprescribing, there is a need to get support from healthcare professionals with medication expertise, such as community pharmacists, more in the management of older multi-morbid patients. This support can potentially provide a more nuanced approach to the deprescribing process by offering inputs based different professional backgrounds, knowledge, experiences and expertise. From GPs and community pharmacists interviewed in Chapter 7, a suggested role for the community pharmacist is to recommend and advise deprescribing to the GP and to initiate the deprescribing conversation and/or to reinforce and support deprescribing decisions made by the GP, and to help monitor patients during the deprescribing process. As such, the community pharmacist could potentially identify patients for whom deprescribing would be beneficial, as well as supporting, monitoring, and empowering patients throughout the process. Despite this suggested role of the community pharmacist in deprescribing, one of the main challenges to the integration of this role into the community pharmacist's routine work was the lack of a clear definition of the role.

8.2.1.1 *Defining the role of the community pharmacist*

The first step towards a working definition of community pharmacists' roles and responsibilities in deprescribing is ensuring that none of the stakeholders is disenfranchised and that these responsibilities are in line with the needs of GPs. GPs interviewed in Chapter 7 felt that their role may be diminished professionally if community pharmacists take on new roles in the clinical management of older

patients, specifically those that they feel clearly fall within their remit. This finding echoes the conclusions of the literature reporting limited support from GPs for pharmacist role expansion into areas that could be thought to impinge on the GP's duties [282, 300-302]. The study by Bryant *et al.* [282] found that community pharmacist's roles that considered to encroach on the role of the GP were less acceptable, such as a role in prescribing. Almost 75% of the community pharmacists in the study agreed to a role of supervising repeat prescribing and making dosing adjustments to patients' medicines whereas between 15%-25% agreed to the community pharmacists taking these roles [282]. This may in turn partially explain GPs' reluctance to accept/implement pharmacists' recommendations as described in Chapters 3 and 7.

Another explanation to the low acceptance of pharmacists' recommendations by GPs experienced by the community pharmacists may be related to the setting in which community pharmacists practice. A low acceptance rate of community pharmacists' recommendations to medication management is a barrier particularly faced in community pharmacy practice settings. A review of 21 articles reporting community pharmacy interventions described that interventions in community pharmacy practice settings were less likely to report favourable intervention effects compared to interventions in other settings such as ambulatory care settings and hospital settings. The review highlighted that one of the factors accounting for the limited effectiveness of the community pharmacy-based interventions was the low acceptance rates of pharmacist recommendations [303]. Many of the factors that facilitate the effect of pharmacist-led interventions in other settings such as hospital settings and ambulatory care settings are rarely present in the community pharmacy settings. Community pharmacists usually have limited access to clinical patient information other than the medications that have been dispensed to them. This limits the clinical relevance of their recommendations, and this is a barrier to the uptake of community pharmacists' recommendations [303]. In Ireland, no system exists for sharing patient information with community pharmacists such as clinical status, diagnoses, laboratory tests and changes made during hospitalisations. The community pharmacies in Ireland are detached from this

information which limits the clinical ground on which they can build their prescribing and deprescribing recommendations to the GPs. Community pharmacists in Chapter 7 did acknowledge that due to the lack of clinical data, some of their recommendations were limited in terms of its clinical relevance. Under these circumstances, the community pharmacists had lower expectations of GP acceptance rates of their recommendations. In Chapter 5, community pharmacists also stressed a need for patient information on diagnoses and indications for medicines to be able to enter a more active role in preventing and reducing PIP. If we want to involve the community pharmacists more in advising GPs on deprescribing there is a need to ensure a clinical relevance of their recommendations in order to enhance the uptake of by the GPs. Being involved more in the deprescribing process it is important that the community pharmacists are equipped clinically to take on this role by giving them access to the required information. Described by Zhou et al. [68] one of the main barriers to pharmacist prescribing comparing initiatives from the UK, New Zealand, Canada and Australia is the lack of access to patients' clinical data. Making effective prescribing decisions by pharmacist prescribers without access to medical records can undermine patient safety [68]. Similarly, for pharmacists to give clinically appropriate advice on deprescribing, they need to know the patients' clinical history.

8.2.2 Equipping community pharmacists for a role in deprescribing

There is a need to ensure that any working definition of the role of the community pharmacist in deprescribing is used in academia as well as in practice. Community pharmacists interviewed in Chapter 6 and 7 refrained from interacting with GPs about reducing PIP and effecting deprescribing if they felt that they were working outside their scope. Changing the role of the community pharmacist from a drug-dispenser to entail more responsibility in clinical services such as advising deprescribing and monitoring patients during the cessation of drug asks new skills of the community pharmacist. In addition to providing community pharmacists with the clinical information needed to support deprescribing, there is a need to ensure that they are properly trained and equipped to take on this extended role. Community pharmacists interviewed in Chapter 6 also described that they did believe their pharmacology and therapeutics knowledge was sufficient to identify PIP but that they were not trained in the process of deprescribing it and stressed the need for

continuing professional education to bring their knowledge in line with new medications and most up-to-date guidelines on deprescribing. Some community pharmacists also described how they were not confident in recommending changes to a GP's prescription and that they then refrained from contacting the GPs. The community pharmacists did welcome more training in PIP and together with the GPs to also improve their collaboration. Although the community pharmacists in general believed they had sufficient knowledge, their suggestions to get more interdisciplinary training with GPs and more guidelines and continuous professional development may reflect a feeling of inadequate clinical knowledge to be able to recommend deprescribing to GPs. This perception is supported by the findings of Bryant *et al.* [282] reporting that less than 50% of the community pharmacists feel adequate dealing with GPs on clinical medicine-related issues, having sufficient confidence in their clinical knowledge and feeling sufficiently training [282]. Even though community pharmacists may report in the interviews that they have sufficient knowledge and we promote pharmacists to be experts in pharmacology and medicines, training is needed in diagnoses and clinical aspects of patient care if we expect them to be more engaged in deprescribing. As described in a systematic review on pharmacist prescribing by Zhou *et al.* [68], 26 of the included studies reported inadequate training of pharmacist related to diagnostic knowledge and skills as a barrier to pharmacist prescribing in practice. Barriers to pharmacist prescribing reflect that pharmacists do not traditionally have a role in clinical diagnosis and treatment, and the call for training in diagnostic knowledge and skills was prevalent across the studies [68]. These barriers to pharmacist prescribing could to an extent be similar to pharmacist support in deprescribing. Similar clinical information and knowledge is needed to identify medications to be deprescribing taking into account the patient's clinical status, prescribed list of medications and individual preferences.

8.2.3 Pharmacists involving patients in deprescribing

With the evidence of the benefits of patient-centred care (i.e. improved patient satisfaction, medication adherence, QoL and health outcomes), it seems logical to

engage patients in the deprescribing process as suggested by Reeve *et al.* [106]. In deprescribing, patient-centred care should include shared decision making, a holistic view of the patient and creation of a trusting relationship between the patient and the prescriber [106]. In Chapter 6 and 7 patients were described to either have no or very little interest in their medical therapy or being strongly attached to certain medicines, both barriers to deprescribing. Involving the patients in their medical treatment and educating them in the risks and benefits of taking medications were highlighted as necessary facilitators of deprescribing. In light of these findings and the findings by Reeve *et al.* [106], patient involvement is a key area to target in deprescribing.

According to most GPs and community pharmacists interviewed in Chapter 6 and 7, the Irish healthcare system does not allow sufficient time for non-acute issues to be resolved, and both GPs and community pharmacists felt that preventive actions receive less priority. The GPs interviewed reported neither sufficient time nor opportunity to discuss deprescribing with their patients during their regular consultations, and the topic was rarely brought up in discussion by the GP. The very limited time for most GP consultations points to an opportunity for the community pharmacist to counsel patients on deprescribing opportunities and benefits. A consultation with a trained community pharmacist may not require booking an appointment in advance, may be less costly and could provide a useful supplement to GP consultations for older patients with multimorbid illness and associated polypharmacy. The accessibility of the community pharmacist for patients with chronic diseases can position the community pharmacist well to undertake consultations pertaining to deprescribing. International experiences from Denmark are beginning to show the positive outcomes from community pharmacists offering medication consultations to all patients with chronic illness [304]. Patients with chronic conditions report a high level of acceptance of the pharmacist's consultation recommendations and feeling reassured and confident in the advice given during those consultations [304]. The community pharmacist in Ireland could have a similar role with comparably positive outcomes. Being positioned in the community, most pharmacists are an accessible source of information for patients and, as expressed in

Chapters 6 and 7, they are currently an underused healthcare resource. In a trusting patient-pharmacist relationship, the community pharmacist would be well positioned to inform patients about risks and benefits of medications and to act as an independent source of drug information. This pharmacist-patient relationship could position the community pharmacist favourably to influence older multimorbid patients on deprescribing matters and to empower them to initiate the conversation about deprescribing with their GPs. As demonstrated in the literature [288], pharmacist counselling has the potential to improve health-related outcomes by directing the counselling to a patient's health-related needs. Such benefits have been demonstrated in the areas of smoking cessation [305, 306], diabetes management [307, 308], hypertension [292, 309] and deprescribing of hypnotic Z-drugs [310]. As suggested in Chapter 7, pharmacist consultations with patients could provide GPs with useful support in the deprescribing process thereby reinforcing and monitoring the GP's deprescribing decisions and assuring patients that their medical treatment remains appropriate.

If extending the role of the community pharmacist to entail more clinical services to patients, patients' receptivity to the pharmacist providing these services needs to be considered. Interviewed in Chapter 7, community pharmacists described how some patients were willing to share all their clinical information with them and in some cases, more information than they would share with their GP. Other patients were thought to accept community pharmacist involvement in their treatment to little or no degree. Today, patients are mainly visiting the pharmacy to collect their prescription medications or buying OTC medications. Medication reviews and conversations about deprescribing are not currently part of community pharmacy practice in Ireland. Most patients do not expect clinical services to be offered at the pharmacy. Therefore, patients may not be aware of the services, understand why the services are being offered, know the benefits of these services and how these services are coordinated with their care from other healthcare providers, e.g. medication changes discussed during a GP-consultation [303]. This further advocates the improvement of the GP-pharmacist collaboration in deprescribing to ensure alignment in the treatment of patients and to ensure transparency in the services

offered by GPs and community pharmacists. In addition, it highlights a need to raise awareness of the community pharmacist services among patients.

8.2.4 Introducing new roles and responsibilities *into practice*

This thesis highlighted a need to consider the existing collaboration between GPs and community pharmacists in patient care when introducing new roles and responsibilities for the community pharmacist. As highlighted above, the views of pharmacists and GPs described in Chapter 7 diverged in terms of their current collaboration and this is very likely an area for future improvement. Clear definitions of roles as suggested above in deprescribing for community pharmacists and GPs was one suggested strategy, but the collaboration could also benefit from a complementary interdisciplinary training as suggested in Chapter 6 and 7. Interdisciplinary training was recommended by community pharmacists and GPs interviewed in Chapter 6 and 7 and that it should form a larger part of the undergraduate pharmacy and medical curricula as well as continuing into postgraduate practice by introducing it to the list of learning objectives for continuous professional development. The evidence supporting interprofessional training is well established, with studies showing positive outcomes of interdisciplinary training for pharmacy and medical students [311-314]. Interdisciplinary training has proven particularly useful in raising awareness of healthcare providers roles and contributions to patient care [315]. A US-based study compared the knowledge of pharmacy and non-pharmacy students on each other's roles and their contributions to patient care after attending an interdisciplinary training day. Nonpharmacy students who attended the interdisciplinary training day demonstrated greater awareness of pharmacy services such as patient counselling, patient education and dispensing medications than their counterparts who had not attended the training day [315].

In addition to interdisciplinary training, a suggestion raised from the findings of Chapter 7 was to improve the collaboration between community pharmacists and GPs by building on positive experiences from existing services. The GPs interviewed were satisfied with community pharmacists identifying their prescribing errors and

highlighting drug-interactions. They also wished for the community pharmacist to provide them with more information about patient medication non-adherence identified as this was perceived as valuable information in the deprescribing process. Highlighting positive outcomes and enhancing these existing pharmacy services are thus potential strategies for encouraging the collaborative work between community pharmacists and GPs and to pursue new areas of collaboration such as deprescribing in multimorbid older people. A US study with physicians substantiates these beliefs [265]. Physicians' perceptions of collaborating with community pharmacists were related to the expected outcomes of this collaboration. The surveyed physicians believed that collaborating with community pharmacists would improve medication adherence among patients, prevent drug-related problems and increase the use of cost-effective medicines. These believed outcomes made the physicians more inclined to collaborate with community pharmacists. In particular, the outcome of improved medication adherence was a strong predictor of positive attitude toward collaboration. Hence, physicians' beliefs that collaborating with pharmacists can result in improved outcomes is very likely to heighten their likelihood of collaborating with them. In line with the suggestion from Chapter 7, the US based study suggested that establishing new collaborative relationships between physicians and pharmacists may benefit from communicating and highlighting the value of the existing collaborations first [265].

Finally, as suggested by GPs and community pharmacists interviewed in Chapter 7, along with clear definitions of the community pharmacist's role in deprescribing, there is a need to make the role an official one, and to integrate the responsibilities into the pharmacist's contract to ensure successful implementation of deprescribing in practice.

8.2.5 Financial implications of pharmacist involvement in deprescribing

As demonstrated from the longitudinal data presented in Chapter 4 and 5, PIP is an increasingly growing and costly problem among the older population (≥65 years), a finding which is consistent with the literature [27, 37, 38, 46, 49, 153, 316]. A novel and important finding of Chapter 4 and 5 is that PIP is already an existing problem in

the early old-aged population (≥60 years) and continues to increase when following up the same population over an eight-year period. As people age, they are often using a higher number of daily medicines which significantly increases their risk of PIP. As the population of older people and prevalence of multimorbidity continue to grow, these demographic changes will present an ever-increasing challenge to healthcare systems. New and expensive diagnostic technologies and treatments add to both the complexity and costs of older patients clinical management [317]. The high consumption rate of medicines amongst the older population, along with the associated increased healthcare services required and the rising cost of the newer therapeutic interventions are adding to the pressures on healthcare systems which need to show that they are cost-effective [318, 319].

A report in 2016 by the internationally renowned auditing firm, PricewaterhouseCoopers (Pwc®), concluded that with the higher demands and increased costs of the ageing population in Ireland, there is a need to redistribute the publically funded health budget to achieve better patient health outcomes [320]. The report suggested the introduction of a principle of 'investing to save', whereby an intervention as a preventative measure can stop the condition developing to a higher level of acuity. The cost implications of treatment within the report generally increase substantially at higher acuity levels (i.e. the cost of a GP visit is c. €55 whereas the cost of a 24-hour hospital inpatient stay is approximately €1,000). The report concludes that if costs can be reduced, then the resultant savings could be reallocated more effectively to provide better outcomes [320]. Pharmacists could potentially have a significant role in containing / lowering costs by identifying and highlighting the high prevalence of PIP identified in Chapter 4 and 5 to the GPs. Previous studies have shown that pharmacist services contribute to cost reductions in a wide variety of care settings [317]. A pharmacist intervention study examining the cost avoidance achieved through the prevention of an ADE, reported a substantial net cost benefit of €626,279 and a cost benefit ratio of 8.64:1 [318]. It is likely, although not proven, that similar cost avoidance can be obtained if pharmacist interventions are deployed in primary care to reduce the prevalence of ADEs. Investing in pharmacist-led interventions to avoid adverse medications outcomes in

older multimorbid people could thus be a successful strategy to reduce the pressure on the healthcare system. However, as is evident from Chapter 6 and 7, there is a need for financial incentives and resources to expand the community pharmacist role in deprescribing as a means of 'investing to save'.

8.3 Recommendations for future work

This thesis provides an evidence-base to inform future research that aims to enhance deprescribing and the role of the community pharmacist in medication surveillance among multi-morbid older people exposed to polypharmacy living independently in the community setting. Based on the thesis findings, it is suggested that future research should focus on the areas outlined below:

1) Showing that deprescribing is effective in improving clinical patient outcomes
2) Standardising the deprescribing process
3) Defining the role of the community pharmacist in deprescribing based on the responsibilities suggested by community pharmacists and GPs.
4) Upgrading the pharmacy curriculum to reflect the expanded role of the pharmacist in community practice.
5) Strategies to incorporate more interdisciplinary training with other healthcare professional students (particularly medical students) focused on improved collaboration between pharmacists and other healthcare professionals in routine clinical practice.
6) Effects of sharing lessons learned and communication of the positive outcomes of existing pharmacy services on deprescribing.
7) Interventions to determine the feasibility and effectiveness of a pharmacist-led application of deprescribing guidelines and supporting standardised forms against which deprescribing recommendations are delivered to GPs by pharmacists.

8.4 Strengths and limitations

This thesis investigates the potential role of the community pharmacist in deprescribing and the perceived barriers and facilitators in an Irish primary care setting. Particularly novel was the behaviour change analysis of deprescribing interventions described in Chapter 3, and the longitudinal examination of PIP patterns among people in early old age ('young old') described in Chapter 4. Another important novel aspect of this thesis were the views of community pharmacists on deprescribing in Chapter 6 and 7. Research pertaining to deprescribing has primarily focused on GPs and/or hospital–based prescribers. The community pharmacist is one of the most accessible healthcare providers in the Irish healthcare system and a potentially useful support to the GP in deprescribing. The attitudes and opinions of community pharmacists are important if appropriate, safe and meaningful deprescribing is to be achieved, and Chapter 6 and 7 shed new light on their views and opinions. Deprescribing and expansion of the role of the community pharmacist to support more patient care services are both areas of increasing interest and possibly greater investment in the future by healthcare professionals, academics and policymakers. The research conducted as part of this doctoral thesis provides an evidence-base to guide some of the strategy development needed to enhance deprescribing.

One of the strengths of this thesis was that the individual primary research studies (Chapter 4-7) were designed from the findings of a narrative review and a systematic review of the available literature (Chapter 2-3). Systematically reviewing the literature provided a structured way of synthesising existing knowledge in order to make evidence-based decisions to fill the gaps in primary research studies.

The research described in this thesis had some limitations. The principal limitation was the fact that the primary research studies were conducted in one geographical area, i.e. the greater Cork region of southern Ireland. This could limit both the transferability and generalisability of study findings to other regions of Ireland, although the healthcare system in the Cork region is generally very similar to that of other regions of Republic of Ireland. A more detailed description of the

limitations and potential sources of biases are provided in the individual chapters above.

8.5 Conclusion

The overall aim of this community thesis was to identify challenges of deprescribing and to explore the role of the pharmacist in deprescribing in multimorbid older people in the primary care setting in Ireland. The findings presented in this thesis provide a detailed understanding of the current and potential future role of the community pharmacist in deprescribing, the potential benefits of such a role, and the barriers and facilitators to achieving that now role. Chapter 4 and 5 demonstrated that PIP is a highly prevalent problem with high associated costs among older people in Ireland. The pharmacist was identified as a useful but underexploited resource to reduce PIP from a supportive role in deprescribing in the other chapters. Several complex barriers challenge the deprescribing process in the primary care setting and the integration of the community pharmacist into the shared task of medication surveillance for PIP and logical and timely deprescribing. A busy working environment, suboptimal communication between care providers, a lack of a formalised structure or collaboration framework, lack of guidelines and patient influences must all be addressed thoroughly to enhance pharmacist involvement in deprescribing. Given the complexity and multiplicity of barriers, deprescribing interventions involving the community pharmacist are likely to require a multifaceted approach.

This thesis substantially contributes to the existing literature, through the provision of novel research on the areas for which pharmacist support is useful, and suggest the actions needed to facilitate the successful implementation of the role with regards to deprescribing. The community pharmacist is in a favourable position to bring pharmaceutical care closer to the patient through patient counselling and close collaboration with the patient's GP. To integrate the role of the community pharmacist with that of the GP in practice, there is a need to consider the mode of pharmaceutical service delivery and to expand the collaboration between pharmacists and GPs by building on existing positive experiences of collaboration.

The insights gained from this thesis provide directions for future research into two target areas: (i) improved interdisciplinarity between pharmacists and GPs and (ii) system changes to existing healthcare structures.

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9 Appendices

9.1 Appendix I - Publications

Peer-reviewed Publications

Hansen CR, Walsh EK, Bradley CP, Sahm LJ. Teaching prescribing: Just what the doctor ordered? A thematic analysis of the views of newly qualified doctors. Pharmacy [Internet]. 2017 Jun [cited 2019 Mar 26];5(32):1-9. Available from: https://www.mdpi.com/2226-4787/5/2/32.

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Walsh EK, **Hansen CR**, Sahm LJ, Kearney PM, Doherty E, Bradley CP. Economic impact of medication error: a systematic review. Pharmacoepidemiology and Drug Safety. 2017;26(5):481-497.

Peer-reviewed published abstracts

Hansen CR, Byrne S, O'Mahony D, Cullinan S, Sahm LJ, Kearney PM. The influence of potentially inappropriate medications on healthcare needs and medication use: a retrospective cross-sectional study. In: Age and Ageing, 45(Suppl_2). Proceedings of the 64th Annual and Scientific Meeting of the Irish Gerontological Society Developing Cultures of Excellence in Ageing and Exploring the Needs of Marginalised Groups; 2016 Sep 30 to Oct 01; Killarney. London: British Geriatrics Society; 2016. p. ii13-ii56. (Poster presentation).

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Challenges of deprescribing in the multimorbid patient

Shane Cullinan,[1] Christina Raae Hansen,[1] Stephen Byrne,[1] Denis O'Mahony,[2] Patricia Kearney,[3] Laura Sahm[1]

[1]School of Pharmacy, University College Cork, Cork, Ireland
[2]Department of Geriatric Medicine, Cork University Hospital, Cork, Ireland
[3]Department of Epidemiology and Public Health, University College Cork, Cork, Ireland

Correspondence to
Dr Shane Cullinan, School of Pharmacy, University College Cork, Cork, Ireland; Shane.cullinan@ucc.ie

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ABSTRACT

Older patients often have multimorbidity, frequently resulting in polypharmacy. Independently, multimorbidity and polypharmacy are among the biggest risk factors for inappropriate medication, adverse drug reactions, adverse drug events and morbidity, leading to patient harm and hospitalisations. After a medication review, discontinuation of medication or deprescribing is one of the most common recommendations but is likely to be ignored. The deprescribing process includes some or all of the following elements: a review of current medications, identification of medications to be discontinued, a discontinuation regimen, involvement of patients and a review with follow-up. In addition to the complexity presented by prescribing or deprescribing for older multimorbid patients, other factors act as barriers to discontinuation of medications in these patients; these include interprofessional relationships, difficulties with medication reviews, deficiencies in knowledge and evidence and patients' preferences/resistance to change. These challenges are compounded by the need to manage the shared treatment of multiple conditions by several prescribers from different specialties based on disease-specific guidelines without evidence of effects on the older, frailer, multimorbid patients. The interdisciplinary effort in the treatment of such patients needs to improve to ensure that we treat the patient holistically and not just the individual conditions of the multimorbid patient, according to guidelines. We must first, however, equip prescribers to identify instances where deprescribing is appropriate and then make the necessary changes to pharmacotherapy.

INTRODUCTION

Within the 34 member countries of the Organisation for Economic Co-operation and Development (OECD), people born today have an average life expectancy of 80.1 years.[1] This is a 10-year increase compared with just 45 years ago. Sixty-five year olds today have an average life expectancy of 19.25 years, almost a 6-year increase from 1960. Of these extra 19 years, nine are likely to be 'healthy years'.[2] In 1960, 8.6% of the OECD population was aged ≥65 years. Today, that figure is 15.4% and set to rise to 27.2% by 2050.[3 4] The global population is ageing. With this come many socioeconomic burdens and increased pressures at all levels of care.

Older patients often have to contend with multimorbidity, which in turn leads to polypharmacy. Together, multimorbidity and polypharmacy are among the biggest risk factors for inappropriate medication, adverse drug reactions (ADRs), adverse drug events and morbidity, leading to patient harm and hospitalisations.[5 6] Suboptimal prescribing in older patients has been well-established as a significant problem in healthcare today.[7–9] In recent years, the focus of research into optimisation of medicines for older patients has shifted from quantitatively measuring the deficiencies in prescribing for this cohort, to qualitatively uncovering the root causes of suboptimal prescribing.

Instead of asking how bad the problem is, attention is now turning to why does it happen and how can we deal with it? Published reports of qualitative research attempting to answer and deal with these questions have increased.[10–13] From this research, new avenues for exploration have emerged that may optimise prescribing for older multimorbid patients through targeted interventions and new procedures for medication reviews.[14–16] However, one of the most common recommendations after a medication review—discontinuation of medication or deprescribing—is one of the least likely to be followed.[17 18] The deprescribing process includes some or all of the following elements: a review of current medications, identification of medications to be discontinued, a discontinuation regimen, involvement of patients and a review with follow-up.[19] Our review highlights some of the potential reasons for this lack of deprescribing and the challenges to discontinuing drugs for these patients.

WHY DEPRESCRIBE?

Recent research by our group examined the effect of a structured pharmacist review on the appropriateness of medications as well as adverse outcomes such as ADRs in patients with multimorbidity and polypharmacy.[15 16] In a cluster randomised controlled trial, patients in the intervention group underwent a thorough medication review by a pharmacist using a computerised decision support system (CDSS) to aid the generation of recommendations. Of the 577 recommendations made in 296 patients about the appropriateness of pharmacotherapy, 297 (51%) advised stopping at least one medication, based on the Screening Tool of Older Person's Prescriptions (STOPP) criteria.[20 21] The results of the recommendations were (i) an improvement in overall appropriateness of medications (illustrated by a significant improvement in Medication Appropriateness Index score), (ii) a significant improvement in ADR rates in the intervention group compared with the control group (13.9% vs 20.7%, p=0.02), (iii) a shorter hospital stay but with no statistically significant difference between the groups (8 vs 9 days, p=0.44). While discontinuation of medications was not the only

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'appropriateness' recommendation provided to medical teams, it was the most common and the most widely implemented. However, acceptance rates were still only 45%. Fewer than half the deprescribing recommendations were implemented, yet significant improvements in ADR rates and medication appropriateness were still achieved. Improving the acceptance rates would therefore appear to be a justified exercise.

CHALLENGES TO DEPRESCRIBING

The low acceptance rates of deprescribing recommendations mentioned above and elsewhere,[17 18] invite inquiry into the reasons why despite the potential benefits. Deprescribing is a difficult task for practitioners in all patients but is further complicated in older multimorbid people owing to the need to consider life expectancy in addition to age-related changes in pharmacokinetics (PK) and pharmacodynamics (PD).[22] PK/PD changes are important indicators of deprescribing, enabling us to distinguish between drug-related adverse events and general age-related symptoms and identification of drugs and doses that are potentially inappropriate. Prescribing and deprescribing should be regarded as equally important in considering the drug-induced harm that is to be ameliorated or prevented through deprescribing, the benefits and risks and the assessment and management of the withdrawal.[23] The same insight and understanding of a patient's clinical situation is thus required to facilitate both safe prescribing and deprescribing.

Despite existing tools such as STOPP, Beer's Criteria, Medication Appropriateness Index and Medstopper and clinical guidelines on safe withdrawal of drug dependence to guide discontinuation of inappropriate drugs safely, there is still a gap in the management of polypharmacy and the use of drugs for chronic conditions where therapeutic alternatives do not exist.[24]

However, factors other than complexity play a part, which contribute to prescribers' reluctance to deprescribe.

INTERPROFESSIONAL RELATIONSHIPS

In the treatment of multimorbid older patients, the involvement of several healthcare professionals is common.[25–32] This often results in individuals following his/her specialty treatment guideline(s) and dominating the patient's treatment with their own particular focus.[26] Similarly, some physicians believe that they are solely responsible for the medicines management within their specialty and that the overall management is the responsibility of others.[31] Lack of communication between the various levels of care is a known source of suboptimal prescribing.[11 12]

The literature abounds with studies illustrating this confusion over where responsibility lies. In some instances, it has been shown that primary care physicians welcome the help of pharmacists to support them in polypharmacy management and most pharmacists are in favour of the suggested clinical role for them in treating multimorbidity.[31] However, in other instances the perceived value of a pharmacist's recommendations varies between the general practitioners (GPs),[32] and seems to be determined by the relationship between the medical and the pharmacy profession. In one study it was shown that junior doctors felt that GPs and consultants were the main healthcare professionals responsible for deprescribing, followed by senior house officers, junior doctors and pharmacists.[33] Recent literature reviews of pharmacy-led interventions[34] have described a positive impact on the appropriateness of prescribing in older patients. Promising results were reported from both interventions of pharmacists working independently or as part of a multidisciplinary team. Despite different levels of clinical significance of the interventions reviewed, both reviews highlighted the important role of pharmacists in improving the quality of medication use among older patients.

Elsewhere, it has been reported that GPs feel that the responsibility to review a patient's overall health status and quality of life is theirs. Hence, they believe that they have a coordinating role in reviewing the patient's medical treatment, including lowering the doses, quantifying the medication use and reducing the number of inappropriate drugs. However, they also described the challenges of these tasks, which include a heavy workload on top of their regular work.

> It's a great idea to reduce medication if you can do it in a safe manner that's not going to make us have to go out to the nursing homes 55 more times:[32]

Another factor is a reluctance to interfere with medication that has been prescribed by a colleague or a specialist.[32] Our research group has encountered this, both through our work in developing and implementing the STOPP/Screening Tool to Alert doctors to Right Treatment (START) criteria[20 21] and our qualitative work exploring the barriers to appropriate prescribing in older patients.[10 12] Prescribers described a fear of offending other doctors, including specialist doctors and GPs.[10] If, for example, a doctor noticed something potentially inappropriate in a patient's prescription, they would be less likely to intervene if that patient was under the care of a specialist. Similarly, when transferring information —for example, from hospital to primary care, it was noted that information might be limited owing to a fear of causing offence to patients' GPs. This fear of offending other doctors is compounded by a fear of upsetting a medication regimen. There is a culture of 'don't rock the boat' when it comes to making changes.

> Doctors described reluctance to discontinue a medication that has been taken for a long time by a patient in order to avoid worry and spoke of not wishing to disrupt patients' clinical stability.[10]

It can be argued that the medical treatment of chronic diseases takes place after hospital discharge and that problems of polypharmacy and inappropriate medication use are resolved in primary care. The GPs may therefore be the key players. However, the focus of the current deprescribing debate is on hospital specialists who are called to "take the lead in deprescribing".[23] The reported reluctance among practitioners to interfere with decisions made by a specialist highlights a need to change the medical culture and improve the communication between levels of care. The transition between primary and secondary care is often associated with miscommunication and a lack of clarity of the roles and responsibility for a patient's medical treatment, including deprescribing. A debate as to who needs to take the lead in deprescribing and in what setting the process should take place may therefore involve a discussion on improving collaboration between levels of care to optimise safe medication use. This cultural change and discussion applies to the physicians and practitioners, but might also be relevant to the roles of hospital pharmacists and pharmacists in primary care.

MEDICATION REVIEW DIFFICULTIES

Before any deprescribing takes place, a thorough medication review needs to be carried out, which is often challenging in the older multimorbid patient. Multiple prescribers usually mean that a clear overview of the patient's medical treatment is difficult to achieve.[26 29 31] This is further compounded by the lack of interprofessional communication described above, in

particular poor documentation of changes made to a treatment — for example, initiation, amendments and discontinuation. In turn, this poor documentation is a barrier to deprescribing as it hinders the understanding of other doctors' motivations for the initiation or continuation of a particular treatment.[26 29 31 32]

Apart from poor documentation by prescribers, the difficulty in obtaining an updated list of patients' medications further hinders deprescribing. Shemeili *et al*[31] reported that the main difficulty with medication review was the need to consult several sources—for example, pharmacy, patient, family and GP, to complete the list, coupled with uncertainty about which source provides the optimal list of drugs taken by the patient. Not knowing which medications should be included on the list —for example, 'as required' (PRN) analgesics or topical medicines, was another challenge mentioned.[31] The literature also describes how *incomplete* information is perceived as a barrier to making a decision about deprescribing—that is, which drugs to discontinue and when.[30] Poor acquisition and documentation of patient information from nurses has also been suggested as a barrier to deprescribing:

> It's a matter of educating them [nursing staff] that they need to provide information about that resident that's documented well and correctly so that we can use that information.[32]

A medication review is a critical step in assessing a patient's pharmacotherapy and ultimately deprescribing for that patient, and warrants attention. Our group has investigated the use of a CDSS-supported, Structured Pharmacist Review of Medication (SPRM) and the Structured HIstory taking of Medication use (SHIM) tool to streamline the medication review process. Both approaches improved the accuracy and reliability of patient data obtained.[15 16 35] We did find, however, that any pro forma used, still relied on basic communication between levels of care and adequate documentation by prescribers.

KNOWLEDGE AND EVIDENCE BASE

Simply not knowing what can be safely discontinued or indeed what should be discontinued is in itself a barrier to deprescribing. We have found that medical students and junior doctors are not equipped to make these decisions about older patients as there is little or no distinction made between them and the general adult population in their training,[12] even though they are entirely different populations. As previously mentioned, altered PKs and PDs, reducing renal and hepatic function and altered body fat/lean muscle ratios all make prescribing for older patients notoriously difficult. If physicians are not being trained to prescribe for them, how can we expect them to effectively deprescribe for them?

> It's a different knowledge set. And it's difficult you know because there isn't a huge amount of data out there or its not communicated to us very well[12]

The lack of evidence for the use of or discontinuation of a particular drug by older patients limits structured deprescribing, mainly owing to the exclusion of multimorbid older patients in clinical trials.[25–27 30] The available evidence is perceived by many as insufficient in relation to the effect of multiple drug treatments in older patients[25] and the effects of preventive medication in the oldest patients.[26 27 30] A low level of evidence often underlies recommendations in existing treatment guidelines and many commonly used recommendations are based on expert opinions and 'standard of care'.[36 37] As a result, although there is an abundance of prescribing guidelines, their application to older, multimorbid patients is unsatisfactory for the following reasons:

1. They are based on trial data involving younger patients.[30]
2. They provide only a standardised set of recommended medications for each indication regardless of a patient's additional comorbidities.[30]
3. They are too disease-specific.[38]
4. They do not include recommendations for deprescribing.[27]

Despite these misgivings, in the absence of alternative evidence, many clinical guidelines become widely used and prescribers feel under pressure to adhere to them instead of prioritising the medical treatment and deprescribing where appropriate.[26 29 30] A prescriber's tendency to deprescribe may therefore be affected by the lack of evidence-based guidelines and also by the particular medical culture. The lack of guidance for the multimorbid patient warrants further research. Until evidence-based recommendations are incorporated into succinct and validated guidelines, any efforts to systematically deprescribe will be based on the same 'expert opinion' approach previously seen. Although this has its benefits, a more standardised and robust system for optimising a patient's prescriptions is required. A barrier to this has been the exclusion of older, multimorbid patients from clinical trials but, encouragingly, two ongoing trials are focusing on these very patients. The SENATOR trial is assessing the impact of a CDSS, incorporating the STOPP/START criteria, on ADR rates in older multimorbid patients (http://www.senator-project.eu/). The OPERAM project is also assessing the impact of a CDSS in these patients, with drug-related admissions as the primary outcome. It is hoped that the findings from these trials will facilitate a significant step towards evidence-based prescribing guidance for multimorbid patients. Evidence, or lack of evidence, of ADRs is also something that influences prescribing decisions. Damestoy *et al*[39] reported that many of the physicians interviewed prescribed as they did because they did not often see side effects. Dickinson *et al*[40] reported that GPs did not perceive a significant problem with long-term prescribing of antidepressants as they had not seen any evidence to indicate serious harm to the older patient. What is not clear in these instances is whether ADRs simply were not occurring or the prescriber was just not aware of them.

PATIENT

The patient has an important influence on the deprescribing process because:

1. Some patients' unintentionally withhold information about adverse drug events because they attribute these to ageing rather than the side effects of medicines.[26]
2. Some patients are more likely to report their symptoms to healthcare professionals such as hospital specialists or nurses other than their GPs , which means that the GP is not being fully aware of the problems experienced by the patient[26]
3. Patient characteristics, such as cognitive impairment, functional dependency, level of education and old age, hinder a patient's explanation of problems with their current medications and the need for deprescribing.[25 26]
4. Some patients do not wish to stop familiar medications.[26 29]
5. Patients' demands, wishes and expectations and those of their families may have an influence.[25 29 30 32 38]
6. Practitioners are reluctant to talk to patients about their life expectancy.[26]

In this research group's experience, all of the above can be significant obstacles to deprescribing—particularly, points (4) and (5). We have found that doctors are commonly influenced

by patients or patients' families when it comes to prescribing, which often results in them prescribing something that they know may not be technically appropriate or even required.[10 12]

> Many of the physicians thought patients would seek out another physician if they were not satisfied with their prescription and they took this into account before prescribing.[10]

> As a doctor sometimes, you feel that you have to do something, you get pressurized by either nursing staff, relatives or patients. You have to give them something. So you end up giving something that you are not 100% happy with.[12]

These outside influences are difficult to deal with. However, procedures for teaching medical students 'non-technical skills', such as dealing with patients and their families, have recently been proposed,[41] and would appear to be warranted. There is also a consensus among the medical profession that increased targeted patient education would help to improve communication between doctor and patient.[12]

OVERCOMING THE CHALLENGES

Dealing with the challenges outlined above by improving the lines of communication between levels of care, making it explicit who has the ultimate responsibility for ensuring the appropriateness of a patient's medical treatment, improving the medication review processes, including the patient in the decision-making process, better educating our young doctors and patient education, will all aid deprescribing.

However, two areas should be the focus of immediate attention and the hospital pharmacist is ideally suited to deal with both. In order to facilitate deprescribing, we must (i) be able to identify instances where discontinuation of medications would be appropriate and (ii) know what to change and how. Several sets of explicit criteria have been developed to aid in the identification of instances where deprescribing would be beneficial. The two most established are the Beers criteria,[42] mainly used in the USA, and the STOPP/START criteria,[20 21] developed by our team in Cork. While these are useful tools and describe clear, practice-based situations where deprescribing might be beneficial, we have found that doctors are either unaware of them or do not know how to implement them.[12] Providing prescribers with information about these tools and training is critical. To know what to do once polypharmacy/inappropriate prescribing is detected and to know what to discontinue requires experience. But doctors could be given a much better start than is currently the case. Major deficiencies in geriatric pharmacotherapy training have been uncovered through interviews with doctors.[12] Prescribers need to be made aware at an earlier stage the vast differences between older and younger patients.

CONCLUSION

The challenges of deprescribing in older patients are compounded by the need to manage the shared treatment of multiple conditions by several prescribers from different specialties based on disease-specific guidelines which do not contain evidence on the older, frailer, multimorbid patient population. Interdisciplinary effort in the treatment of older patients with multimorbidity needs to be improved to make sure that we treat the patient holistically and do not merely treat the individual conditions. We must first, however, equip prescribers to identify instances where deprescribing is appropriate and then make the necessary changes to pharmacotherapy.

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SYSTEMATIC REVIEW AND META-ANALYSIS

Identification of behaviour change techniques in deprescribing interventions: a systematic review and meta-analysis

Correspondence Christina R. Hansen, Pharmaceutical Care Research Group, School of Pharmacy, Cavanagh Pharmacy Building, University College Cork (UCC), College Road, Cork, Ireland. Tel.: +353 21 490 1690; E-mail: christina.raaehansen@ucc.ie

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Christina R. Hansen[1,2], Denis O'Mahony[3,4], Patricia M. Kearney[5], Laura J. Sahm[1,6], Shane Cullinan[7], C.J.A. Huibers[8], Stefanie Thevelin[9], Anne W.S. Rutjes[10], Wilma Knol[8], Sven Streit[11] and Stephen Byrne[1]

[1]*Pharmaceutical Care Research Group, School of Pharmacy, Cavanagh Pharmacy Building, University College Cork, Cork, Ireland,* [2]*Section for Social and Clinical Pharmacy, Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen Ø, Denmark,* [3]*Department of Medicine, University College Cork, Cork, Ireland,* [4]*Department of Geriatric Medicine, Cork University Hospital, Cork, Ireland,* [5]*Department of Epidemiology & Public Health, UCC, Cork, Ireland,* [6]*Pharmacy Department, Mercy University Hospital, Cork, Ireland,* [7]*School of Pharmacy, Royal College of Surgeons of Ireland, Dublin, Ireland,* [8]*Department of Geriatric Medicine and Expertise Centre Pharmacotherapy in Old Persons, University Medical Centre Utrecht, Utrecht, The Netherlands,* [9]*Clinical Pharmacy Research Group, Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium,* [10]*Institute of Social and Preventive Medicine, University of Bern, Switzerland & Institute of Primary Health Care (BIHAM), University of Bern, Switzerland, and* [11]*Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland*

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AIMS

Deprescribing interventions safely and effectively optimize medication use in older people. However, questions remain about which components of interventions are key to effectively reduce inappropriate medication use. This systematic review examines the behaviour change techniques (BCTs) of deprescribing interventions and summarizes intervention effectiveness on medication use and inappropriate prescribing.

METHODS

MEDLINE, EMBASE, Web of Science and Academic Search Complete and grey literature were searched for relevant literature. Randomized controlled trials (RCTs) were included if they reported on interventions in people aged ≥65 years. The BCT taxonomy was used to identify BCTs frequently observed in deprescribing interventions. Effectiveness of interventions on inappropriate medication use was summarized in meta-analyses. Medication appropriateness was assessed in accordance with STOPP criteria, Beers' criteria and national or local guidelines. Between-study heterogeneity was evaluated by I-squared and Chi-squared statistics. Risk of bias was assessed using the Cochrane Collaboration Tool for randomized controlled studies.

RESULTS

Of the 1561 records identified, 25 studies were included in the review. Deprescribing interventions were effective in reducing number of drugs and inappropriate prescribing, but a large heterogeneity in effects was observed. BCT clusters including *goals and planning*; *social support*; *shaping knowledge*; *natural consequences*; *comparison of behaviour*; *comparison of outcomes*; *regulation*; *antecedents*; and *identity* had a positive effect on the effectiveness of interventions.

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CONCLUSIONS

In general, deprescribing interventions effectively reduce medication use and inappropriate prescribing in older people. Successful deprescribing is facilitated by the combination of BCTs involving a range of intervention components.

Introduction

Older people (aged ≥65 years) are more vulnerable to medication-related harm and inappropriate prescribing than younger chronically medicated people [1, 2]. Age-related physiological changes contribute to iatrogenic vulnerability in older people, but it is equally a consequence of their multimorbidity and frequent use of multiple medications [1, 3–7]. Vulnerability, polypharmacy and multimorbidity represent complex challenges in the care of older people and often exclude them from clinical trials [6, 8–10]. Therefore, some prescriptions in multimorbid older people are without clear-cut evidence to support them and inappropriate prescribing is highly prevalent [11–13]. Excessive inappropriate prescribing in older people has turned the focus of current research towards deprescribing – the systematic process of identifying and discontinuing drugs in patients for which existing and potential harms outweigh the benefits [14]. Making informed decisions to deprescribe with the goal of reducing inappropriate prescribing and improving patient outcome is hampered by a lack of evidence of withdrawal effects in older people and is further challenged by prescriber- and patient-related factors [15, 16].

Research has demonstrated safety and effectiveness of deprescribing in older people (aged ≥65 years) [17] whilst reluctance of prescribers to deprescribe a medication commenced by another prescriber is described as well [18]. Although evidence suggests that pharmacist involvement and patient-centred interventions are effective, the best ways to engage and support prescribers in deprescribing remain unclear [16, 19–23]. Previous reviews examining the effects of deprescribing interventions on clinical outcomes call for a better understanding of successful implementation of deprescribing [6, 17–19].

Within the clinical context of patient care, there is a need to ensure that behaviour change is a part of any intervention design in order to maximize the chance that prescribers are enacting on recommendations [24, 25]. Recent advances in behavioural science provide insight into the components of complex interventions aiming at behaviour change. The Behaviour Change Techniques (BCTs) taxonomy version 1 (BCTTv1) [26] is designed to assist in the identification of BCTs of interventions. A BCT is defined as 'an observable, replicable, and irreducible component of an intervention designed to alter or redirect causal processes that regulate behaviour' [27]. A clear description of BCTs will clarify the essential content of these complex interventions in a consistent way to assist in future replication of effective interventions [28]. The application of the BCT taxonomy to deprescribing is novel. This review was designed to complement previous reviews [6, 17, 19] on deprescribing by offering a broader analysis of behaviour change techniques in deprescribing interventions.

The aims of this review are (i) to identify behaviour change techniques used more frequently in interventions effective in reducing number of drugs and inappropriate prescribing, (ii) to describe other characteristics of deprescribing interventions and (iii) to determine intervention effectiveness on drug use, prescribing appropriateness and Medication Appropriateness Index (MAI) score in meta-analyses.

Methods

A systematic search of the primary, secondary and grey literature to identify randomized controlled trials (RCTs) on deprescribing was undertaken on December 14, 2016. This systematic review was reported according to the PRISMA guidelines for systematic reviews and meta-analyses [29], and was registered in Prospero (record no. CRD42016037730).

Search strategy

The search strategy was designed in conjunction with an experienced medical librarian (JM) who was trained in systematic review methodology. A combination of text words and subject headings (such as MeSH terms) related to the intervention was used, without restricting publication date or language (Table S1).

The following electronic bibliographic databases were searched: MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trials, Web of Science and Academic Search Complete. Grey literature was searched via the Google Scholar® search engine and from screening reference lists of included studies as well as relevant systematic reviews. Additional searches were done in the System for Information on Grey Literature in Europe (OpenSIGLE) and the clinical trial registries, namely ClinicalTrials.gov, International Standard Registered Clinical/soCial sTudy Number (ISRCTN), WHO International Clinical Trials Registry Platform (ICTRP) and the Australian New Zealand Clinical Trials Register (ANZCTR).

Study selection

One reviewer (C.H.) screened titles of all retrieved citations. Two reviewers (C.H. and S.C.) independently screened abstracts and full-texts for eligibility according to protocol-defined inclusion and exclusion criteria. Any disagreements between reviewers were resolved by consensus and both reviewers agreed on the final inclusion of studies.

Inclusion and exclusion criteria

Inclusion was restricted to randomized controlled study design, including randomized controlled trials (RCTs) and cluster RCTs. The control group could involve either active interventions or inactivity, e.g. sham or no intervention. This

study design was chosen to allow for between-study comparison of intervention effectiveness in meta-analyses. Studies were included if they reported on interventions encouraging the deprescribing of existing drugs or the reduction of existing inappropriate prescribing. Only those interventions involving older patients (aged ≥65 years) or a healthcare professional with prescribing, dispensing or administration authority were included. No restrictions were applied to language, clinical setting of the intervention, sample size, blinding procedures or other design characteristics. We excluded interventions specifically focusing on the clinical effects of drug withdrawal processes, e.g. opioid withdrawal effects.

Risk of bias assessment

Risk of bias was assessed separately by two reviewers (C.H. and A.R.) using the Cochrane Collaboration Tool for randomized controlled studies [30] with a descriptive purpose of summarizing the quality of the studies that met inclusion criteria. Studies were not excluded from data analysis because of methodological flaws if they otherwise met inclusion criteria. Incomplete outcome data was in general rated as high risk of bias if the loss of patients to follow-up was 20% or higher and rated as low risk of bias if the loss was 10% or less. Imbalance in the numbers lost to follow-up between intervention and control groups was also considered to introduce bias. The risk of bias assessment is described in detail in Table S2.

Data extraction strategy

Data were collected using a pre-agreed data extraction form (see Table S3). Two reviewers (C.H. and L.S.) independently pilot tested the form on two randomly chosen studies both included in the review. Thereafter data extraction on all studies was completed independently by L.S. and C.H. Disagreements on study inclusion/exclusion were resolved by discussion leading to consensus; where consensus could not be achieved, the study was excluded. Primary outcomes were: (i) number of total and inappropriate prescriptions and/or drugs as defined in the individual studies according to prescribing appropriateness criteria, e.g. STOPP criteria, Beers' criteria and local or national prescribing guidelines; (ii) proportion of participants with a reduction in number of total and inappropriate prescriptions and/or drugs; and (iii) implementation of recommendations. Secondary outcome was change in MAI score.

Behaviour change techniques coding

Coding of BCTs was performed independently by two reviewers (C.H. for all interventions and C.J.A., S.T. and L.S. for a subset of interventions each) by identifying BCTs for each intervention using the BCTTv1 [26]. C.H. had completed online training in BCTTv1. A coding manual and instructions made by C.H. were given to the other reviewers and, exercises from the online training were made available to them. Any questions about the coding were solved by discussion and consensus between the reviewers. The target behaviour was the decision making to discontinue a drug or an inappropriate prescription. Findings were tabulated across studies by computing frequencies. The information was used to determine the BCTs used more frequently in studies that reported effectiveness of interventions to reduce number of drugs and/or improve prescribing appropriateness.

Statistical analysis

We calculated odds ratios (OR) with standard deviations (SD) for each of the reported outcomes and used RevMan v5.3 to statistically combine the outcome data [31]. Continuous outcomes were expressed as difference in means between groups with a 95% confidence interval (95% CI). The level of between-study heterogeneity was evaluated by calculation of the I^2 and Chi-squared statistics. Where possible, stratified random effects meta-analyses was used to identify factors affecting intervention effectiveness. Subgroup analyses were performed by risk of bias assessment, intervention setting and intervention target. If the level of reporting did not allow for inclusion of a study in one or more meta-analyses, additional information was sought from the study authors. If the information was not made available, the study was excluded from the meta-analysis.

Results

Literature search and review process

The database search identified 1444 records, and grey literature yielded 117 records. After removal of duplicates and title screening, 178 abstracts were screened for eligibility and 58 of these met the inclusion criteria. Assessment of full texts resulted in 25 studies included in this review [32–56]. Study selection and reasons for exclusion are illustrated in Figure 1.

Study characteristics

Included studies were RCTs (n = 22) [32–41, 43–45, 47, 49–56] and cluster RCTs (n = 3) [42, 46, 48] with a follow-up period from 6 weeks [45] to 13 months [42]. A total of 20 812 patients were enrolled in the studies ranging from 95 [41] to 1188 per study [55]. Detailed study characteristics are provided in Table 1. Three studies aimed primarily to reduce the number of drugs taken by patients [41, 44, 46]. Other objectives included reduced prevalence of inappropriate medications [32, 33, 38, 39, 42, 49], improved prescribing appropriateness [34–36, 47, 50–55], or better patient health outcomes and medicines management [35, 40, 48, 56]. Ten out of the 25 studies included in this review showed evidence to support intervention effectiveness [34, 35, 37, 40, 41, 45, 46, 50, 53, 56]. Most of the studies reporting intervention effectiveness of the key outcomes of this review delivered recommendations or feedback to the prescriber orally, often face-to-face, and many of them followed up on the recommendations/feedback given. Recommendations and feedback were given immediately after identification of a problem or at the time of prescribing using an on-demand service. For studies reporting no intervention effectiveness on the key outcomes, some delivered recommendations using written communication and many of the interventions did not follow up on the recommendations with the prescriber. None

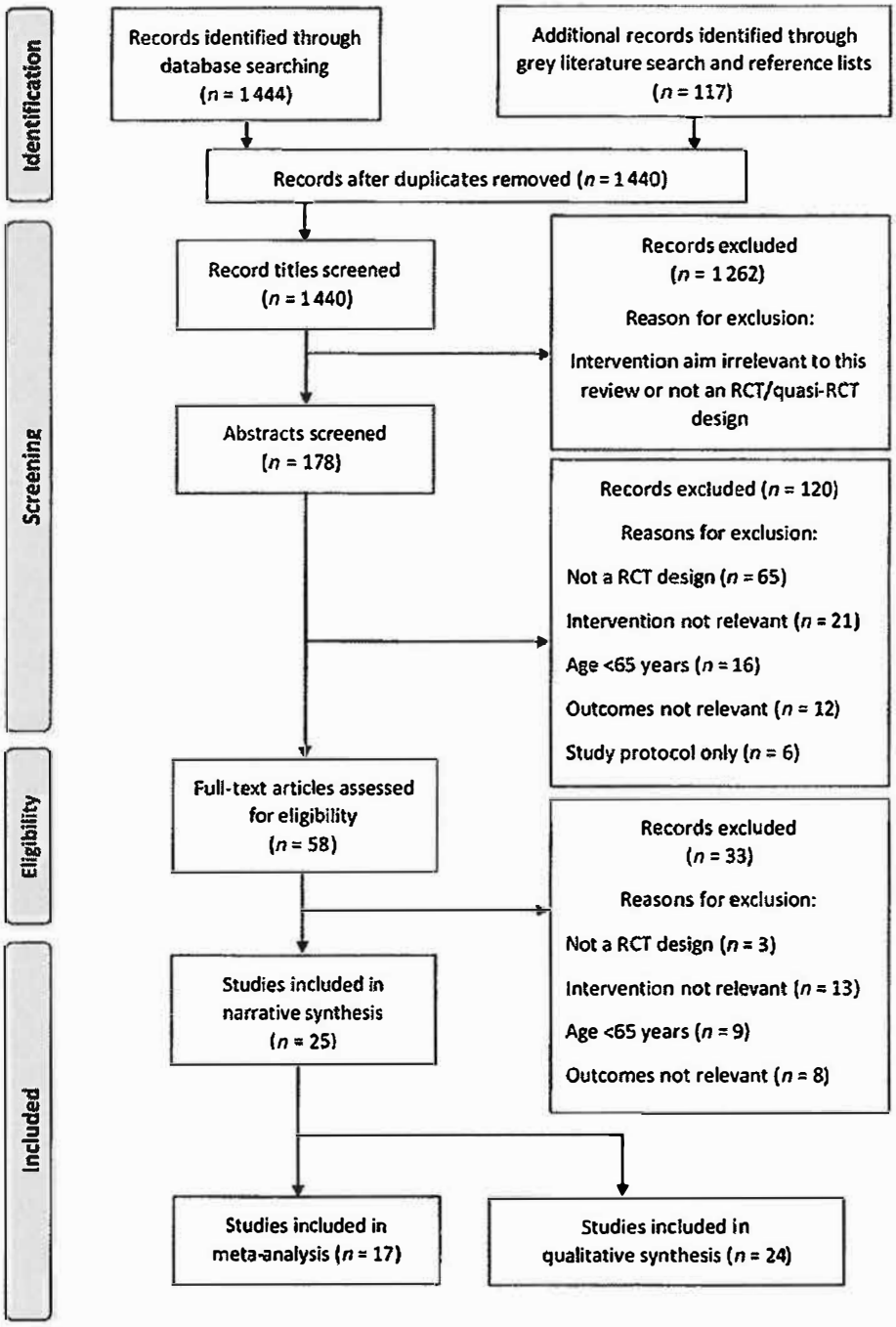

Figure 1
PRISMA flow chart of study selection

of the included studies reported the use of explicit theories of behaviour change as part of the interventions and no study reported the use of a systematic and theoretical approach, such as the UK Medical Research Council's complex intervention framework [57], in the intervention design. Reported educational interventions were based on the principles of constructive learning theory in one study [39] and social constructivist learning and self-efficacy theory in another study [46].

Risk of bias

Risk of bias assessment is illustrated in Figure 2. Risk of bias not pertaining to any of the defined categories were categorized as 'others' and these are described in Table S2.

Behaviour change techniques

All but one study [48] reported the behaviour change components underpinning the intervention. The BCT coding is

Table 1

Characteristics of included studies (n = 25)

Author (year)	Country Setting	No. of patients % Female	Mean age of patients (±SD), years	Intervention (I) Delivered by (D)	Target behaviour Target person(s) (P)
Allard *et al.* (2001) [32]	Canada Community	266 67.7%	80.6 (4.5)	(I) Medication review and suggestions made and mailed to GPs (D) Multidisciplinary team of physicians, pharmacists and nurses	Reducing the number of potentially inappropriate prescriptions given. (P) GPs.
Bregnhøj *et al.* (2009) [47]	Denmark Primary care physician practice	212 66.1%	76.5 (7.2)	(I) Interactive educational meeting (single intervention) and combined with individualized feedback on prescribed medication (combined intervention) (D) Clinical pharmacologist and pharmacists	Improving prescribing appropriateness. (P) GPs.
Crotty *et al.* (2004) [48]	Australia Nursing home	154 59.6%	84.5 (5.0)	(I) Medication review and case conferences (D) Multidisciplinary team of geriatrician, pharmacist, representative of the Alzheimer's Association of South Australia	Improving medication appropriateness. (P) Residential care staff and residents' GPs.
Dalleur *et al.* (2014) [33]	Belgium Teaching hospital	146 63.0%	85.0 (5.2)	(I) Medication review and recommendations provided to discontinue medications based on the STOPP criteria (D) Multidisciplinary team of nurses, geriatricians, dietician, occupational therapist, physiotherapist, speech therapist and psychologist	Discontinuation of PIMs (P) Hospital physicians
Fick *et al.* (2004) [49]	USA Primary care physician practice	Not specified	Not specified	(I) Decision support service comprising educational brochure, list of suggested inappropriate medications based on the STOPP criteria, and list of patients with STOPP criteria identified (D) Research team and expert panel of physicians and pharmacists	Changing prescribing behaviour and decreasing PIM use. (P) GPs
Frankenthal *et al.* (2014) [56]	IsraelChronic care geriatric facility	239 66.6%	82.7 (8.7)	(I) Medication review and recommendations provided based on the STOPP/START criteria (D) Study pharmacist	Improving clinical and economic outcomes by giving STOPP/START recommendations. (P) Chief physicians.
Gallagher *et al.* (2011) [34]	Ireland Teaching hospital	382 53.1%	75.6 (7.3)	(I) Medication review and recommendations provided to change medications based on the STOPP/START criteria (D) Research physician	Improving prescribing appropriateness (P) Hospital physician and medical care team
García-Gollarte *et al.* (2014) [35]	Spain Nursing home	1018 73.0%	84.4 (12.7)	(I) Educational workshops, material and on-demand advice on prescriptions (D) Nursing home physician with geriatric expertise	Improving the quality of prescriptions (P) Nursing home physicians
Hanlon *et al.* (1996) [36]	USA Ambulatory clinic	172 1.0%[a]	69.8 (3.8)	(I) Medication review and prescribing recommendations provided	Improving prescribing appropriateness (P) GPs and patients

(continues)

Table 1

(Continued)

Author (year)	Country Setting	No. of patients % Female	Mean age of patients (±SD), years	Intervention (I) Delivered by (D)	Target behaviour Target person(s) (P)
				(D) Pharmacists	
Lenaghan *et al.* (2007) [37]	UK Primary care physician practice	136 65.6%	84.3[b]	(I) Medication review and development of action plan of agreed amendments (D) Pharmacists	Reducing hospital admissions and number of drug items prescribed (P) GPs and patients
Meredith *et al.* (2002) [50]	USA Home health setting	317 74.9%	80.0 (8.0)	(I) Medication review and development of action plan to address identified problem (D) Multidisciplinary team of physicians, nurses and pharmacists	Improving medication use (P) Nurses and patients
Milos *et al.* (2013) [38]	Sweden Nursing home and community	374 74.9%	87.4 (5.7)	(I) Medication review and feedback given to physician on drug-related problems (D) Pharmacists	Reducing the number of patients using PIMs (P) GPs
Pitkälä *et al.* (2014) [39]	Finland Nursing home	227 71.0%	83.0 (7.2)	(I) Staff training and list of harmful medications provided to encourage nurses to bring this to the physician's attention (D) Research team	Improving the use of potentially harmful medications (P) Nurses
Pope *et al.* (2011) [40]	Ireland Hospital	225 62.9%	82.9[b]	(I) Clinical assessment by a senior doctor and multidisciplinary medication review using Beer's criteria. Recommendations given to GP (D) Consultant or senior specialist registrar and a multidisciplinary panel of consultant geriatricians, specialist registrars, hospital pharmacists and senior nurse practitioners	Reducing the number of drugs prescribed (P) GPs
Potter *et al.* (2016) [41]	Australia Nursing home	95 52.0%	84.0 (7.0)	(I) Medication review and cessation plan of non-beneficial medications (D) Research team of GP and geriatrician	Reducing the total number of medicines taken (P) GPs and patients
Richmond *et al.* (2010) [51]	UK Primary care trusts	760 43.2%	80.4 (4.1)	(I) Pharmaceutical care including medication reviews (D) Research team	Improving prescribing appropriateness (P) GPs
Saltvedt *et al.* (2005) [52]	Norway Teaching hospital	254 65.0%	82.1 (5.0)	(I) Comprehensive geriatric assessment and treatment of all illnesses (D) Multidisciplinary team of geriatrician, nurses, residents, occupational therapists and physiotherapists	Increasing the number of drugs withdrawn (P) Medical care team
Schmader *et al.* (2004) [53]	USA Hospital	864 2.5%[a]	46% aged 65–73 54% aged ≥74 years	(I) Treatment in a geriatric evaluation and management unit (GEMU) in either inpatient or outpatient care or both (D) Pharmacists and a multi-disciplinary team of geriatrician, social worker and nurse	Improving prescribing (P) Medical care team

(continues)

Table 1
(Continued)

Author (year)	Country Setting	No. of patients % Female	Mean age of patients (±SD), years	Intervention (I) Delivered by (D)	Target behaviour Target person(s) (P)
Spinewine *et al.* (2007) [54]	Belgium Hospital	203 69.4%	82.2 (6.6)	(I) Pharmaceutical care including medication review and development of a therapeutic care plan with prescribing recommendations (D) Pharmacists	Improving prescribing appropriateness (P) Medical care team and patients
Tamblyn *et al.* (2003) [42]	Canada Primary care physician practice	12 560 62.7%	75.4 (6.3)	(I) Electronic alerts instituted in the electronic patient prescription record to identify prescribing problems (D) Research team	Reducing inappropriate prescribing (P) GPs
Tannenbaum *et al.* (2014) [46]	Canada Community pharmacy	303 69.0%	75.0 (6.3)	(I) Educational booklet to empower and encourage patients to discontinue benzodiazepines (D) Research team	Discontinuation of benzodiazepines (P) Patients
Vinks *et al.* (2009) [43]	The Netherlands Community pharmacy	196 74.7%	76.6 (6.5)	(I) Medication review and prescribing recommendations provided (D) Pharmacists	Reducing the number of potential DRPs and the number of drugs prescribed (P) GPs
Weber *et al.* (2008) [44]	USA Ambulatory clinic	620 79.3%	76.9[b]	(I) Electronic messages sent to physician via electronic medication record to give prescribing recommendations (D) Pharmacist and geriatrician	Reducing medication use (P) GPs
Williams *et al.* (2004) [45]	USA Ambulatory clinic	140 57.1%	73.7 (5.9)	(I) Medication review based on MAI and prescribing recommendations provided and action plan made (D) Pharmacists	Simplifying medication regimens (P) Patients
Zermansky *et al.* (2001) [55]	UK Primary care physician practice	1188 56.0%	73.5 (6.5)	(I) Prescription review and treatment recommendations given to patients (D) Pharmacist and physician	Making changes to repeat prescriptions and reducing the number of medicines taken (P) Patients

[a]The low percentages of females reported was explained by the nature of male patients in Veterans Affairs (VA) clinics
[b]The SDs were not reported and could not be retrieved from the authors

presented in Table S4. Based on the reported results, 10 of the 25 studies showed an effect on the key outcomes (i) or (ii) of this review when comparing the intervention group to the control group [34, 35, 37, 40, 41, 45, 46, 50, 53, 56]. No direct pattern was seen between the number of individual BCTs used and reported intervention effectiveness. The median number of BCTs used were similar for studies reporting effective and non-effective interventions (6 BCTs, IQR 3–8 and 5 BCTs, IQR 4–7, respectively). BCT clusters coded more frequently in studies reporting effectiveness [34, 35, 37, 40, 41, 45, 46, 50, 53, 56] compared to studies reporting no effectiveness were: *goals and planning*; *social support*; *shaping knowledge*; *natural consequences*; *comparison of behaviour*; *comparison of outcomes*; *regulation*; *antecedents*; and *identity* (see Figure 3).

Intervention effectiveness

(a) Drug use

Overall, the mean number of drugs post-intervention was significantly lower among intervention participants compared to the control participants in the presence of moderate between-study heterogeneity (mean difference −0.96, 95%

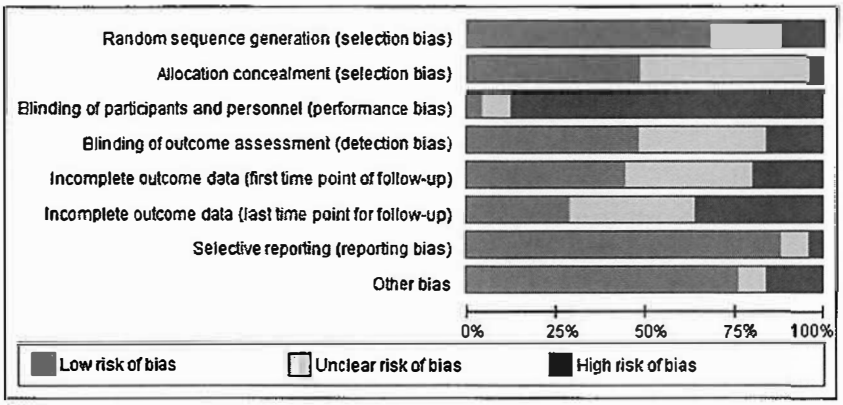

Figure 2

Results of risk of bias assessment

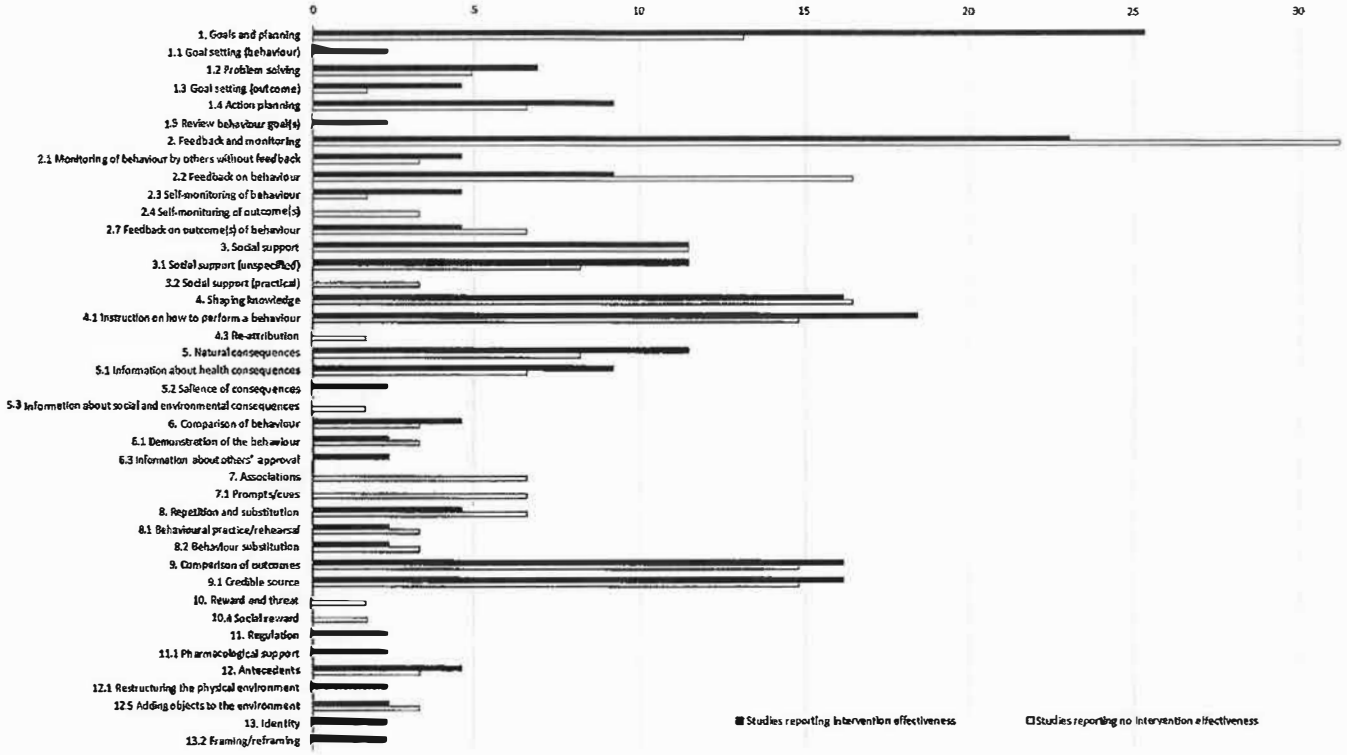

Figure 3

Frequency of behaviour change techniques (BCTs) coded for studies reporting intervention effectiveness on the key outcomes of this review compared to studies reporting no effectiveness of interventions. The frequencies are weighed values based on the number of studies in each group, i.e. effectiveness versus no effectiveness

CI −1.53, −0.38, heterogeneity I^2 = 70% and P = 0.002, Figure S1). Regarding the difference in change in the number of drugs taken per patient, deprescribing interventions lowered the number (−0.74, 95% CI −1.26, −0.22), but effects varied greatly across studies (I^2 = 92%, $P < 0.001$) (Figure 4). Stratified analyses by: (i) whether the intervention was patient-centred or targeting solely healthcare professionals (Figure S2), (ii) intervention setting (Figure 4) and (iii) study quality (Figure S3) showed no effect of these factors on summary estimates. In addition, the unexplained variation within subgroups remained large.

(b) Prescribing appropriateness

Deprescribing interventions demonstrated a relatively small effect and a high level of heterogeneity on the number

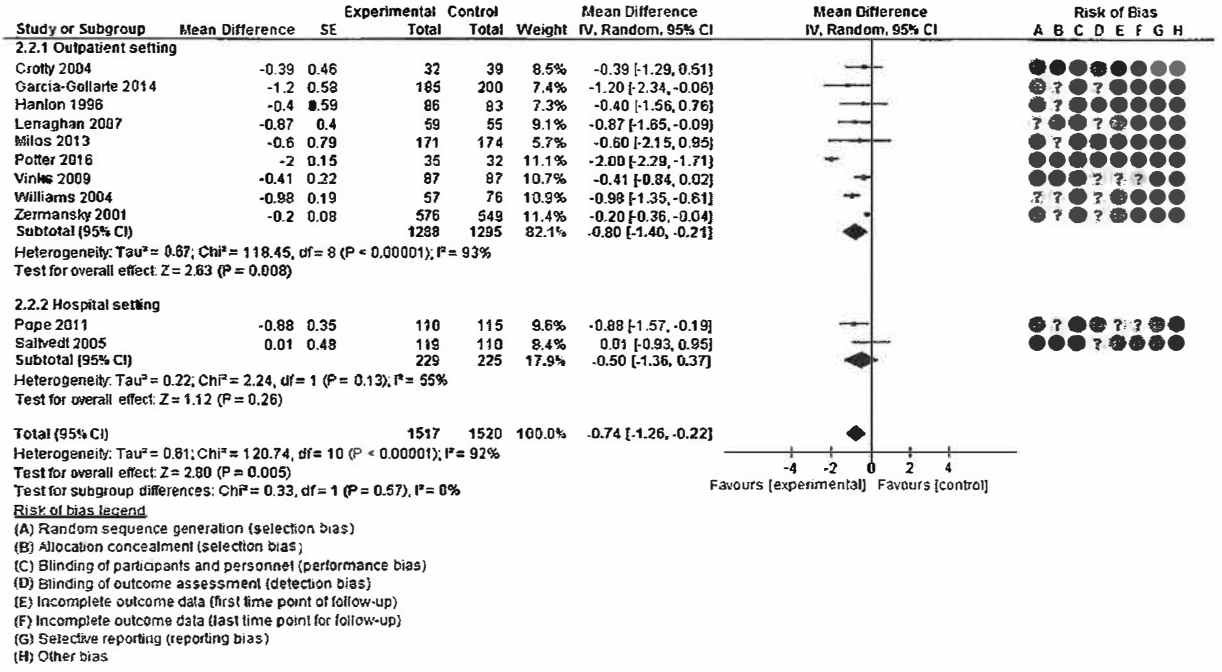

Figure 4

Mean difference in the change in number of drugs comparing experimental (intervention) group and control group. Subgroup analysis on intervention setting (outpatient setting versus hospital setting)

of inappropriate drugs per participant comparing intervention and control groups post-intervention (−0.19, 95% CI −0.40, 0.02, heterogeneity I^2 = 90% and P = 0.07, Figure S4). The proportion of participants with at least one inappropriate drug, as defined in the individual studies, were reduced when a deprescribing intervention was applied, but confidence intervals were wide, and a high level of heterogeneity was present (Figure 5).

(c) Implementation of recommendations

Only four studies reported implementation rates of recommendations to discontinue a medication or change a medication [36, 38, 43, 49]. Action was taken in 55.1% of recommendations given by a pharmacist compared to only 19.8% of the nurse recommendations as part of usual pharmaceutical care [36]. In the study by Vinks *et al.* [43], 27.7% of pharmacists' recommendations were implemented, and action was taken in 56% of drug-related problems identified by a pharmacist in Milos *et al.* [38]. A lower recommendation implementation rate of 15.4% was shown in Fick *et al.* [49]. This result was based on self-reported action taken by the physicians; only 71% of physicians reported this, which may explain the lower frequency of action observed.

(d) MAI score

Seven studies reported changes in MAI scores for participants pre- and post-interventions [34, 36, 47, 48, 51, 53, 54]. Across studies, deprescribing interventions demonstrated a significant effect on reducing the MAI score comparing intervention and control groups post-intervention (−5.04, 95% CI −7.40, −2.68, heterogeneity I^2 = 88% and P < 0.0001, Figure S5).

Discussion

Effectiveness of deprescribing interventions is determined by a combination of factors. Consistent with the findings of recent reviews [6, 17], our meta-analysis showed that deprescribing interventions are effective in reducing the number of drugs and inappropriate prescribing (reduced MAI scores) in older people, although the evidence is heterogeneous.

Based on the findings of the BCT coding exercise, effective deprescribing interventions included: (i) a goal and an action plan to solve prescribing problems, (ii) monitoring of behaviour, (iii) social support and the use of a credible source, and (iv) clear instructions and guidance on implementation to the prescriber and information about health consequences of doing/not doing the behaviour. Support from colleagues and information about potential risks and benefits to the patients in the presence/absence of a behaviour change may also be effective techniques of deprescribing.

Differences in the delivery of prescribing recommendations were seen in the studies reporting intervention effectiveness compared to studies reporting no effect on key outcomes of this review. Studies reporting effectiveness [34, 35, 37, 40, 41, 45, 46, 50, 53, 56] used oral and face-to-face communication to discuss and implement deprescribing recommendations consistent with the principles of educational outreach to inform clinical decision making as described by Soumerai and Avorn [58]. Investigation of the delivery of recommendations to deprescribe may provide useful information on the delivery of a successful deprescribing intervention in addition to the use of BCTs.

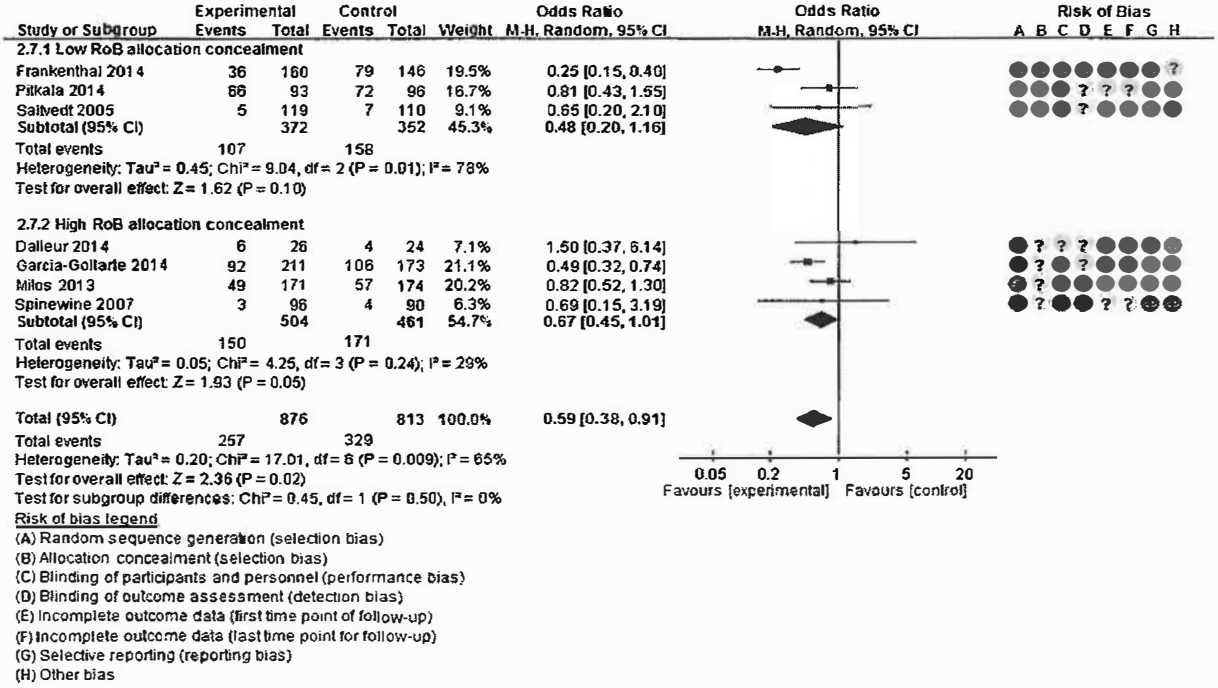

Figure 5

Number of participants with inappropriate drugs comparing experimental (intervention) group and control group. Subgroup analysis on risk of bias assessment (allocation concealment)

Pharmacist recommendations to reduce drug intake and inappropriate prescribing were frequently enacted on in some studies [36, 38], consistent with previous literature reporting benefits of pharmacist-led interventions to optimize medication use in older people [21, 59]. Other studies [43, 49] reported a lower acceptance rate of pharmacist recommendations, between 15% and 28% of recommendations enacted on. Recent research has demonstrated a high level of agreement between prescribers and pharmacists in the assessment of potential target medications for deprescribing [60, 61]. In contrast, other research studies indicate that acceptance rates for recommendations made by pharmacists are lower than those made by their physician colleagues [62]. The lower uptake of pharmacist recommendations despite a high level of agreement about deprescribing is noteworthy. It may indicate that challenges to deprescribing are in fact dependent on the particular ways deprescribing interventions are delivered, particularly when there is a question of behaviour change. Based on the findings of this review, we suggest that future research should investigate the behaviours associated with the acceptance and rejection of deprescribing recommendations to gain a better understanding of a successful delivery of deprescribing interventions.

This is the first review to identify BCTs in deprescribing interventions necessary to achieve a change in behaviours towards deprescribing. Our findings complement previous reviews on deprescribing [17, 19] by offering a broader analysis of BCTs that are effective for deprescribing.

Limitations and strengths

The review findings are based on a comprehensive search of the literature. The novel aspect of this review is in the use of a validated taxonomy to describe intervention content that facilitates behaviour change. Limitations of this review reside mostly in the limited data available. RCTs to date are of a relatively small size (often ≤100 participants) and usually with short follow-up periods. Other limitations relate to the high-risk blinding procedures; these were needed because the interventions in question required blinding of the personnel whose behaviour was targeted, and this was logistically difficult. Absence of blinding procedures for outcome assessors were not considered to introduce important bias because the study outcomes, e.g. number of drugs taken, was not a particularly subjective measure. Random sequence generation and allocation concealment were considered high importance biases in this review because participant characteristics such as multimorbidity, age and polypharmacy could have an impact on the number of drugs taken and risk of inappropriate prescribing [1, 5–8].

The meta-analysis was reliant on published or reported data and, while some reported outcomes were adjusted for baseline patient characteristics, others were not, which makes the direct comparison of intervention effect on specific outcomes open to question. Similarly, and as described in a previous review [27], the BCT coding was limited to the intervention descriptions reported in the studies. Limited reporting on interventions used to encourage deprescribing could have resulted in BCTs being undercoded

and others overcoded due to assumptions made about the strategies used based on the information available. For example, we assumed that the reporting of prescribing recommendations given to the prescriber would involve BCT codes: *instructions on how to perform a behaviour* and *feedback on behaviour.* Prescribing recommendations were a commonly used intervention in the studies and this may have resulted in these two BCTs being overcoded. One study was also excluded from the BCT coding due to lack of information which could have potentially impacted the true findings of this review. Furthermore, we were unable to code BCTs in the control groups due to limited reporting of the control conditions. The control conditions such as usual care in hospital settings or in outpatient settings could include BCTs with potential implications on the interpretation of the review findings. Reporting of future behaviour change interventions and control conditions will benefit from the use of comprehensive checklists, such as the TIDieR [63], and give reviewers the ability to adequately code BCTs and extensively appraise the reporting quality of such interventions. This will improve the identification of relationships between BCTs used and intervention effectiveness.

The main limitation of our pooled estimates is the presence of typically large between-study variation and, for some of the analyses, the wide confidence intervals including trivial effects. Some may argue that a meta-analysis should not be done in the presence of important heterogeneity. Meta-analytical methods, however, allow for the exploration of sources of heterogeneity and we fully acknowledge that the magnitude of the summary estimates should be interpreted with care. To minimize the level of heterogeneity due to different study designs, we also decided to limit the inclusion criteria to randomized controlled studies and cluster randomized controlled studies only. Although the direction of effect was favouring deprescribing, the magnitude of effect was very variable. This inconsistency, together with the imprecision and risk of bias issues lower our confidence in the estimates of effect so that the magnitude of effect is very low.

Conclusion

Deprescribing interventions are effective in reducing the number of drugs taken by patients and improving prescribing inappropriateness. Their success may be explained by a combination of BCTs spanning a range of different intervention functions, although we could not empirically show this. The use of BCTs and delivery of such behaviour change interventions should be considered of importance to facilitate successful implementation of deprescribing. This review contributes to the existing evidence by critically analysing the content of deprescribing interventions in terms of behaviour change, clearly demonstrating that the current evidence base is too small to derive strong conclusions on determinants of success.

Contributors

C.H., S.C., L.S. and S.B. conducted the study selection for this review, performed data extraction and evaluated study quality. A.R. verified quality assessments. C.H., P.K., L.S., S.T. and C.J.A. performed the quantitative meta-analyses and the behaviour change analysis. C.H. drafted the manuscript with contributions from D.O.M., P.K., S.B., L.S., S.C., W.K., S.T., C.J.A. and S.S. A.R. helped in the interpretation of results. All authors read and approved the final manuscript. S.B. was the senior author.

Competing Interests

In cases where a co-author of this review was also a co-author of an included study, the author in question was not involved in the study selection, quality evaluation or data analysis.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13742/suppinfo

Table S1 Search strategy
Table S2 Risk of bias assessment
Table S3 Data extraction form
Table S4 Behaviour change techniques taxonomy version 1 (BCTTv1) applied to the included studies and the prevalence of each BCT and BCT cluster
Figure S1 Mean number of drugs per patient post-intervention comparing experimental (intervention) group and control group
Figure S2 Subgroup analysis on target person (patient or healthcare professional) for mean difference in the change in number of drugs per patient
Figure S3 Subgroup analysis on risk of bias assessment (random sequence generation) for mean difference in the change in number of drugs per patient
Figure S4 Mean difference in the number of inappropriate drugs per participant comparing experimental (intervention) group and control group
Figure S5 Mean difference in the change in MAI score per participant comparing experimental (intervention) group and control group

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page # (Page numbering according to the paper published in BJCP)
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2716
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2716-17
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2717
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Table S1
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2717
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2717-18
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2717
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2717-18
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2718
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Table S2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	2718
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2718
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	2718

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	2718
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	2718
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	2718-19
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	2718-24
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	2718-24
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	2718-24
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	2718-24
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	2724-25
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	2725-26
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	2725-26
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2726

[1]H

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Effectiveness of deprescribing interventions in older people: a systematic review and meta-analysis

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6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Ms Christina Raae Hansen

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Ms Hansen

7. * Named contact email.

Give the electronic mail address of the named contact.
christina.raaehansen@ucc.ie

8. Named contact address

Give the full postal address for the named contact.
Pharmaceutical Care Research Group,

School of Pharmacy, University College Cork

Cavanagh Pharmacy Building, College Road

Cork City

Ireland

9. Named contact phone number.

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National University of Ireland, University College Cork

Organisation web address:

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11. * Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Ms Christina R. Hansen. Pharmaceutical Care Researcg Group, School of Pharmacy, University College Cork, Cork, Ireland and Section for Social and Clinical Pharmacy, Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
Dr Shane Cullinan. School of Pharmacy, Royal College of Surgeons, Dublin, Ireland
Professor Patricia M. Kearney. Department of Epidemiology and Public Health, University College Cork, Cork, Ireland
Professor Denis O'Mahony. Department of Medicine, University College Cork and Geriatric Medicine, Cork University Hospital and St. Finbarr's Hospital, Cork
Dr Sven Streit. Institute of Primary Health Care BIHAM, University of Bern, Bern, Switzerland
Dr Laura Jane Sahm. Pharmaceutical Care Research Group, School of Pharmacy, University College Cork and Mercy University Hospital, Grenville Place, Cork, Ireland
Professor Stephen Byrne. Pharmaceutical Care Research Group, School of Pharmacy, University College Cork, Cork, Ireland
Ms C.J.A. Huibers. Department of Geriatric Medicine and Expertise Centre Pharmacotherapy in Old Persons, University Medical Centre Utrecht, Utrecht, The Netherlands.
Ms Stefanie Thevelin. Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium
Ms Anne W. S. Rutjes. University of Chiete-Pescara, Chiete-Pescara, Italy.
Dr Wilma Knol. Department of Geriatric Medicine and Expertise Centre Pharmacotherapy in Old Persons, University Medical Centre Utrecht, Utrecht, The Netherlands

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

The systematic review is being conducted as part of Christina Raae Hansen's PhD. This work is part of the project "OPERAM: OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly" supported by the European Commission (EC) HORIZON 2020, proposal 634238, and by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 15.0137. The opinions expressed and arguments employed herein are those of the authors and do not necessarily reflect the official views of the EC and the Swiss government. Dr Shane Cullinan and Ms Christina Raae Hansen are both funded by the OPERAM project.

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are

not listed as review team members.

Mr Joe Murphy. Hospital Library, Mercy University Hospital, Grenville Place, Cork, Ireland

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

To determine the effectiveness of deprescribing interventions in reducing prescribed medications in adults.

To identify behaviour change components present in interventions and whether they are deemed to be effective or non-effective.

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Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

The following electronic bibliographic databases will be searched for relevant literature: MEDLINE, EMBASE, CINAHL, The Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and Academic Search Complete. Grey literature will be searched from relevant sources. The search strategy will include only terms relating to or describing the intervention.

There will be no language or time restrictions.

17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy.Do NOT provide links to your search results.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Deprescribing

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Older people (aged = 65 years) prescribed medication.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

The interventions to be reviewed are interventions to discontinue existing drug prescriptions and reduce drug dosages; targeting deprescribing in adults (aged = 18 years); and involving a healthcare professional with

prescribing authority and/or adult patients.

Inclusion criteria: Original primary research, full-text availability, controlled trials of interventions.

Exclusion criteria: Interventions targeting appropriateness of prescribing and interventions focusing on Opioid withdrawal or Nicotine Replacement Therapy.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

No control group, a non-exposed control group or a control group receiving 'treatment as usual' or 'standard care' at the time that the particular eligible study was done.

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

Controlled trials of interventions to deprescribe medications in adults will be included (i.e. randomised controlled trials, non-randomised controlled trials and before-and-after studies). Studies in primary, secondary and tertiary care evaluating the effect of a deprescribing intervention to reduce number of prescriptions and dosages per patient will be included. Exclusion of studies that evaluates interventions to prevent inappropriate prescribing and evaluating withdrawal of Opioid and Nicotine Replacement therapies.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

Studies in primary, secondary and tertiary care including ambulatory and inpatient settings.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Number of prescriptions per patient and/or change in dosages of prescriptions per patient

Timing and effect measures

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

Medication Appropriateness Index (MAI).

Timing and effect measures

26. * Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Retrieved citations from the search strategy will be screened for eligibility based on citation titles, abstracts and full-texts. The titles of studies will be reviewed by the primary researcher. Subsequent abstract review of potentially eligible studies will be conducted independently by the primary researcher and another member of the review team. Full texts of potentially eligible studies will be retrieved and the articles will be reviewed by the two researchers. The reviewing process will be performed according to the pre-specified inclusion criteria. Any disagreements between the two reviewers will be resolved by consensus and a third reviewer will be consulted if this cannot be obtained. A pre-agreed data extraction form will be used to collect the relevant data by the primary researcher. This will include information on study characteristics such as study design, methods, setting, participants, intervention and outcomes. Where applicable, intervention characteristics such as delivery, theory, target component, behaviour components and prescriber component will be extracted.

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Risk of bias (quality) assessment will be performed independently by two reviewers for each study included individually using an appropriate Cochrane risk of bias tool. Disagreements between the reviewers will be resolved by discussion, with involvement of a third reviewer where necessary.

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

The findings of the individual studies will be combined in a meta-analysis to estimate the effectiveness of the interventions. The level of heterogeneity between the studies will be evaluated by two reviewers based on the data extraction. A sensitivity analysis will be conducted on study quality. If a meta-analysis is not appropriate due to heterogeneity of the studies reviewed, the findings will be combined thematically in a narrative synthesis.

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

Where applicable in the studies, a subgroup analysis will be conducted to identify the presence and

frequency of behaviour change components as per the Behaviour Change Technique Taxonomy v1 described by Michie S, et al. (2013): "The Behaviour Change Technique Taxonomy (v1) of 93 Hierarchically Clustered Techniques: Building an International Consensus for the Reporting of Behaviour Change Interventions."

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
No

Other
No

Health area of the review

Alcohol/substance misuse/abuse

No
Blood and immune system
No
Cancer
No
Cardiovascular
No
Care of the elderly
Yes
Child health
No
Complementary therapies
No
Crime and justice
No
Dental
No
Digestive system
No
Ear, nose and throat
No
Education
No
Endocrine and metabolic disorders
No
Eye disorders
No
General interest
No
Genetics
No
Health inequalities/health equity
No
Infections and infestations
No
International development
No
Mental health and behavioural conditions
No
Musculoskeletal
No
Neurological
No
Nursing
No
Obstetrics and gynaecology
No
Oral health
No
Palliative care
No
Perioperative care
No
Physiotherapy
No
Pregnancy and childbirth
No
Public health (including social determinants of health)

No
Rehabilitation
No
Respiratory disorders
No
Service delivery
No
Skin disorders
No
Social care
No
Surgery
No
Tropical Medicine
No
Urological
No
Wounds, injuries and accidents
No
Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.
Ireland

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

A paper will be submitted to a leading journal in this field.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Deprescribing

Behaviour Change

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For newregistrations the review must be Ongoing.
Please provide anticipated publication date

Review_Completed_published

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

The findings of this review will be used to inform further research to be conducted as part of the PhD of the primary researcher

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Hansen CR, O'Mahony D, Kearney PM, Sahm LJ, Cullinan S, Huiber CJA, Thevelin S, Rutjes AWS, Knol W, Streit S, Byrne S. Identification of behaviour change techniques in deprescribing interventions: a systematic review and meta-analysis. Br J Clin Pharmacol. 2018;84:2716-28. Doi:10.1111/bcp.13742

Give the link to the published review.

https://doi.org/10.1111/bcp.13742

https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/bcp.13742

9.6 Appendix VI - Chapter 3 Data extraction form

Author (year)	Country	Setting primary/secondary/tertiary (specified)	Aim
Intervention type (e.g. medication reviews, electronic alerts, education etc.)	Intervention description	Control type (e.g. usual care, different education/training)	Who delivered the intervention? (researcher, pharmacists etc.)
Intervention target person (i.e. whose behaviour was changed/targeted?)	Follow-up duration	Primary outcome	Secondary outcomes
Tool /Measure to identify target/outcome (only for prescribing appropriateness)	Number of participants enrolled in total and for individual arm	N (participants, total)	Gender female (%) (both total, intervention group and control group)
Age of study population (specify mean or median)	Average of Mean (SD)	Ethical considerations (yes/no/cant' tell)	The study conclusion (short!)
Trial design	Where were participants recruited from?	How were participants recruited? (database, telephone etc.)	Sample size calculation/consideration reported (yes/no)
Data collection (i.e. source of information)	Blinding (who was blinded or what process what blinded?)	Randomisation strategy	Eligibility criteria of study subject/patients (who was invited?)
Inclusion criteria (study subjects/patients)	Exclusion criteria (study subjects/patients)	Medication use/prescribing rate at baseline	Number of participants experiencing reduction in number of prescriptions (in all intervention and control groups) Event/Intervention and event/control

Author (year)	Country	Setting primary/secondary/tertiary (specified)	Aim
Number of participants experiencing reduction in number of medication (in all control and intervention groups)	Number of participants experiencing reduction in number of PIPs/PIMs (in all control and intervention groups)	Change in number of PIPs/Rx/Drugs/Dosages	Change in MAI-score
Healthcare services utilization (hospital admission, GP visits etc.)	ADRs/ADEs prevalence	Medication costs	Other comments on outcomes (if relevant to the review)

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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Longitudinal patterns of potentially inappropriate prescribing in early old-aged people

Christina Raae Hansen[1] · Stephen Byrne[1] · Shane Cullinan[2] · Denis O'Mahony[3,4] · Laura J. Sahm[1,5] · Patricia M. Kearney[6]

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Abstract

Purpose It is contentious whether potentially inappropriate prescribing (PIP) is predominantly a phenomenon of late life or whether it has its origins in early old age. This study examined the pattern of PIP in an early old-aged population over 5 years.

Methods Secondary data analysis of a population-based primary care cohort, of patients aged 60–74 years. Medication data were extracted from electronic patient records in addition to information on comorbidities and demographics. Explicit START criteria (PPOs) and STOPP criteria (PIMs) were used to identify PIP. Generalised estimating equations were used to describe trends in PIP over time and adjusted for age, gender and number of medicines.

Results A total of 978 participants (47.8%) aged 60–74 years were included from the cohort. At baseline, PPOs were detected in 31.2% of patients and PIMs were identified in 35.6% at baseline. Prevalence of PPOs and PIMs increased significantly over time (OR 1.08, 95% CI 1.07; 1.09 and OR 1.04, 95% CI 1.0; 1.06, respectively). A higher number of medicines and new diagnoses were associated with the increasing trend in both PPO and PIM prevalence observed over time, independent of PPOs and PIMs triggered by drug combinations.

Conclusions Potentially inappropriate prescribing is highly prevalent among early old-aged people in primary care and increases as they progress to more advanced old age, suggesting that routine application of STOPP/START criteria in this population would significantly improve medication appropriateness.

Keywords PIM · Polypharmacy · Longitudinal patterns

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00228-017-2364-6) contains supplementary material, which is available to authorized users.

✉ Christina Raae Hansen
christina.raaehansen@ucc.ie

[1] Pharmaceutical Care Research Group, School of Pharmacy, University College Cork, Cavanagh Pharmacy Building, College Road, Cork, Ireland

[2] School of Pharmacy, Royal College of Surgeons of Ireland, 123 St. Stephen's Green, Dublin 2, Ireland

[3] Department of Medicine, University College Cork, Brookfield Health Sciences Complex, College Road, Cork, Ireland

[4] Department of Geriatric Medicine, Cork University Hospital, Wilton, Cork, Ireland

[5] Pharmacy Department, Mercy University Hospital, Greenville Place, Cork, Ireland

[6] Department of Epidemiology and Public Health, University College Cork, Western Gateway Building, Western Road, Cork, Ireland

Introduction

Optimisation of pharmacotherapy is a core part of the care of older people [1, 2]. Medical treatment in older people is often challenged by age-related physiological changes affecting pharmacokinetic and pharmacodynamic responses to drugs, with increasing risk of adverse drug-disease and drug-drug interactions [2, 3]. For that reason, many drugs must be used with caution in older people [1, 2]. The use of five or more daily drugs (i.e. polypharmacy) is increasing in older people and is associated with a higher risk of potentially inappropriate prescribing (PIP) for this population [4, 5]. PIP includes both the omission of a medical treatment that is clinically indicated in the patient for irrational or ageist reasons, potential prescribing omissions (PPOs) or the use of a medical treatment in

which the risks outweigh the benefits through the use of potentially inappropriate medications (PIMs) [3, 6, 7].

Recent work by Cooper et al. [8] indicates high PIP prevalence in middle-aged (45–64 years) people using Prescribing Optimally in Middle-aged People's Treatments (PROMPT) criteria. Using prescription databases PIP prevalence rates among middle-aged people were found to be 21.1 and 42.9%, in Northern Ireland and the Republic of Ireland, respectively [9]. The high level of PIP in middle age suggests that the well-recognised high prevalence of PIP in advanced old age (those aged ≥ 75 years) arises in late middle age/early old age [8]. However, to date, limited data exist to explore when in the life course of PIP emerges.

PIP is well described in the older population [10–13] and is shown to be associated with increasing age [3, 12]. The acknowledged high prevalence of PIP in late life is thought to result directly from high levels of multi-morbidity and polypharmacy in this population [3, 11, 12, 14]. More information is needed on PIP in younger populations to assess potential benefits of minimising PIP before people enter older age. Given the lack of published data on PIP in the latter age group, we aimed to determine the longitudinal pattern of PIP in people aged between 60 and 74 years.

The central aim of the present study, therefore, was to assess the levels of PIP in early old age and to follow the trend of PPO and PIM prevalence over a 5-year interval in order to determine the patterns of PPO and PIM prevalence longitudinally.

Methods

We undertook a secondary analysis of a previously described population-based cohort from a large primary care centre in Ireland [15]. The cohort includes a total of 2047 men and women aged 50–69 years at recruitment in 2010, and provides information on demographics, general health, medication use and private health insurance status. Updated information on clinical status, diagnoses and medications were obtained by researchers from annual screenings of electronic patient records, and thus provided ongoing passive follow-up of participants between waves of active data collection. The follow-up screenings were scheduled every year, the first one commencing in April 2010 until April 2011, and following the patients to the end of the 5-year follow-up in October 2015. Patients were lost for the active follow-up of the original cohort study [15] but this did not impact the passive follow-up data that were used in this study. We obtained detailed information on all prescribed medications from electronic patient records from enrolment in 2010–2011 until the end of 2015 [15]. The original medication data from baseline and all annual screenings were coded by the WHO Anatomical Therapeutic Chemical (ATC) classification system [16]. Management of the original clinical data at baseline was completed and linked at patient-level to the coded medication data.

The Screening Tool to Alert doctors to Right Treatment (START) and Screening Tool for Older Persons' Prescriptions (STOPP) version 2.0 criteria [17, 18] were retrospectively applied to the medication data from baseline and annual screening of the electronic patient records in order to determine the prevalence of PPOs (START) and PIMs (STOPP) at annual time points over a prospective five-year period [17]. Participants were dichotomised according to presence or absence of any PPOs and PIMs at baseline. For a subanalysis, the START/STOPP criteria triggered by the presence of more than one drug were removed to explore the effect of polypharmacy independent of those PPOs and PIMs triggered by drug combinations.

Statistics

The study population was summarised using descriptive statistics including means and standard deviations or median and interquartile range as appropriate for continuous variables, and proportions and percentages for categorical variables. Participant groups were compared using Pearson's chi-square test or Fisher's exact test for categorical variables, Mann-Whitney *U* test for nonparametric continuous variables, and paired *t* test for normal distributed continuous variables. The proportions of people with any PPOs or PIMs were compared for two consecutive years and for baseline and end of follow-up (year 6) using McNemar's test for paired groups [19]. We used negative binomial regression models or Spearman's rank correlation model, where appropriate, to describe the correlation between the presence of any PPOs and any PIMs and the reported number of medicines and age for each year of follow-up. Generalised estimating equation (GEE) models with exchangeable correlations were fitted for overall PPO and PIM prevalence from baseline to follow-up, and followed by multivariate GEE analysis which adjusted for gender, age, numbers of medicines and number of new diagnoses over the five-year time frame to determine associations between these and PPO and PIM prevalence [20, 21]. The results are presented as both unadjusted and adjusted odds ratios (OR and aOR, respectively) with 95% confidence intervals (95% CI). Data analyses were performed using Stata software version 13 (StataCorp. College Station, TX. 2013) with a significance level of $p < 0.05$.

Results

Baseline characteristics

From the total cohort of 2047 patients, 978 participants (47.8%) were aged 60 to 74 years at recruitment and were

eligible for inclusion in the current study. Due to incomplete data, four participants were not included in the analysis. Baseline participant characteristics are presented in Table 1. There were no significant differences in baseline characteristics between participants with PPOs and without PPOs. The proportion of people with ≥ 2 medications was higher for participants with PIMs compared to participants without PIMs (28 versus 19%, $p = 0.001$); this is to be expected, given the known association between polypharmacy and PIM occurrence [3, 9–12]. Differences between participants with and without PIM were non-significant for all other characteristics (Table 1).

STOPP/START

Based on data availability, 27 of 34 (79.4%) START criteria and 64 of 81 (79.0%) STOPP criteria were applied (additional data are given in Online Resource). PPOs were detected in 304 participants (31.2%) and PIMs were identified in 347 participants (35.6%) at baseline (Table 1). Anxiety and rheumatological disorders were most often associated with PPOs, whilst hypno-sedatives (benzodiazepines and Z-drug hypnotics) and angiotensin-converting-enzyme (ACE) inhibitors were the most common drug classes accounting for PIMs (additional data are given in Online Resource). Three START criteria and ten STOPP criteria that were triggered by drug combinations were excluded from the sub-analysis (additional data are given in Online Resource).

PPO prevalence

The number of patients with at least one PPO increased significantly between consecutive years from baseline to year 3 of follow-up with a continuing increasing, but non-significant, trend until the end of follow-up. After 5 years, an additional 11% of participants ($n = 33$) had a PPO ($p < 0.001$) (see Online Resource). However, the mean number of PPOs per participant did not significantly change from baseline to end of follow-up with a mean of 0.45 (SD 0.82) PPOs per participant at baseline and 0.42 (SD 0.49) at year 6 ($p = 0.259$). Unadjusted odds ratio (OR) showed a significant increase in the PPO prevalence comparing 5-year follow-up to baseline (OR 1.08, 95% CI 1.07; 1.09. Table 2). The multivariate GEE model showed that number of medicines and number of new diagnoses were significantly associated with the change in PPO prevalence and the change in prevalence comparing follow-up to baseline was not significant after adjusting for these variables. The multivariate analysis showed no significant association of age and gender with change in PPO prevalence (Table 2). A positive but non-significant correlation was found between the number of PPOs and older age for all years of follow-up (see Online Resource). The number of

Table 1 Baseline characteristics of the study sample ($n = 978$) excluding $n = 4$ participants with incomplete data

Baseline characteristics		Study population ($n = 978$)	With no medications ($n = 96$, 9.9%)	With PPO ($n = 304$, 31.2%)	Without PPOs ($n = 670$, 68.8%)	*P* value	With PIMs ($n = 347$, 35.6%)	Without PIMs ($n = 531$, 54.5%)	*P* value
Age, years	Mean (SD)	64.8 (2.96)	64.3 (3.00)	64.7 (2.99)	64.8 (2.96)		64.9 (2.92)	64.8 (2.99)	
Age, years	Median (IQR)	64.2 (61.8–67.3)	64.2 (61.8–66.4)	64.2 (61.8–67.3)	64.2 (61.8–67.3)	0.896	65.1 (61.8–67.3)	64.2 (61.8–67.3)	0.850
60–64 years		499 (51.0)	53 (55.2)	153 (50.3)	343 (51.2)		169 (48.7)	274 (51.6)	
70+ years		15 (1.5)	1 (1.0)	3 (1.0)	12 (1.8)		7 (2.0)	7 (1.3)	
Gender, female	*N* (%)	505 (51.6)	46 (47.9)	148 (48.7)	353 (52.7)	0.247	184 (53.0)	271 (51.0)	0.564
Chronic conditions									
0	*N* (%)	225 (23.0)	22 (22.9)	80 (26.3)	142 (21.2)	0.200	79 (22.8)	121 (22.8)	0.931
1		238 (24.4)	30 (31.3)	69 (22.7)	169 (25.2)		80 (23.0)	128 (24.1)	
≥2		515 (52.8)	44 (45.8)	155 (51.0)	359 (53.6)		188 (54.2)	282 (53.1)	
Number of medications	Mean (SD)	2.1 (3.1)	0 (0)	2.4 (3.6)	2.0 (2.9)		3.2 (4.3)	1.8 (1.9)	
0	*N* (%)	100 (10.2)	96 (100.0)	33 (10.9)	63 (9.4)	0.144	0 (0)	0 (0)	< 0.001*
1		682 (69.7)	0 (0)	200 (65.8)	482 (71.9)		250 (72.0)	432 (81.4)	
≥2		196 (20.0)	0 (0)	71 (23.4)	125 (18.7)		97 (28.0)	99 (18.6)	
Current smoker	*N* (%)	108 (11.0)	11 (11.5)	37 (12.2)	71 (10.6)	0.552	36 (10.4)	61 (11.5)	0.499
Private health insurance	*N* (%)	582 (59.5)	58 (59.5)	186 (61.2)	393 (58.7)	0.457	213 (61.4)	308 (58.0)	0.319
Living situation									
Living alone	*N* (%)	146 (14.9)	12 (12.5)	41 (13.5)	105 (15.7)	0.379	57 (16.4)	77 (14.5)	0.352
Living with others		638 (65.2)	67 (69.8)	203 (66.5)	435 (64.9)		218 (62.8)	353 (66.5)	
Unspecified		194 (19.8)	17 (17.7)	60 (19.7)	130 (19.4)		72 (20.7)	101 (19.0)	

*$p < 0.05$, i.e. significant difference in the median number of medications between participants with and without PIMs

Table 2 Univariate and multivariate GEE models for PPO and PIM prevalence showing the changes in the proportion of patients with a PPO or PIM during the study period and the association with the potential covariates; gender, age and number of medicines. Study population $n = 974$ for PPO and $n = 878$ for PIM, excluding $n = 96$ with no medications at baseline

	Any PPO	Any PIM
Unadjusted odds ratio (95% CI)		
Follow-up vs. baseline	1.082* (1.071; 1.093)	1.042* (1.029; 1.055)
Adjusted odds ratio (95% CI)		
Follow-up (vs. baseline)	1.037 (0.995; 1.080)	1.005 (0.963; 1.047)
Age (per year older)	1.033 (0.992; 1.075)	1.023 (0.984; 1.065)
Gender (female vs. male)	0.813 (0.639; 1.033)	0.909 (0.717; 1.151)
Number of medicines (per higher number)	1.02*1 (1.011; 1.030)	1.103* (1.084; 1.123)
Number of new diagnoses[a] (per higher number)	1.054* (1.043; 1.065)	1.016* (1.022; 1.030)

*$p < 0.05$, i.e. statistically significant

[a] new diagnoses refer to the diagnosed conditions after baseline data collection

PPOs and number of medicines were positively correlated for all years with the exceptions of baseline and year 4 of follow-up (see Online Resource).

When excluding the START criteria triggered by drug combinations, a higher number of medicines and new diagnoses were still significantly associated with the change in PPO prevalence in the multivariate GEE analysis (aOR 0.99, 95% CI 0.98; 0.99 and aOR 1.06, 95% CI 1.05; 1.07, respectively). The number of PPOs was not positively correlated with number of medicines after excluding the criteria triggered by drug combinations ($p > 0.05$ for all individual years). Additional data are given in Online Resource.

PIM prevalence

Prevalence of PIMs increased significantly between consecutive years from baseline to year 2 of follow-up and decreased slightly thereafter ending with a significant decrease between year 5 and year 6 (see Online Resource). Despite this, the overall PIM prevalence from baseline to end of follow-up increased significantly from 39.7% of participants receiving a PIM at baseline to 45.6% at end of follow-up. The unadjusted GEE model showed a significant increase in the PIM prevalence comparing follow-up to baseline (OR 1.04, 95% CI 1.03, 1.06, $p < 0.001$; Table 2). The mean number of PIMs per participant did, however, decrease significantly from 0.82 (SD 1.53) at baseline to 0.45 (SD 0.5) at end of follow-up ($p < 0.001$). Adjusted odds ratios showed that higher numbers of medicines and higher number of new diagnoses were positively and significantly associated with change in PIM prevalence (aOR 1.10; 95% CI 1.08; 1.12 and aOR 1.02, 95% CI 1.00; 1.03, respectively), consistent with the published literature. No significant association was found between PIM prevalence and age or gender (Table 2). A positive correlation between the number of PIMs and older was, however, seen for all years (see Online Resource). The regression models showed a significant positive correlation between the number of daily medications and the number of PIMs prescribed at baseline and all years of follow-up (see Online Resource). The odds of receiving any PIM were affected by the number of new diagnoses but there was no significant correlation between the number of PIMs and number of diagnoses (see Online Resource).

Excluding the STOPP criteria triggered by drug combinations, both a higher number of medicines and new diagnoses were still significantly associated with the change in PIM prevalence in the multivariate GEE analysis (aOR 1.07, 95% CI 1.06; 1.08 and aOR 1.02, 95% CI 1.01; 1.03, respectively). A positive correlation between the number of PIMs and number of medicines was still shown for all years of follow-up ($p < 0.001$ for all individual years). Additional data are given in Online Resource.

Discussion

This study illustrates that inappropriate prescribing is present even in early old-aged community-dwelling people. This prescribing challenge comprises both prescribing omissions and use of inappropriate medications to similar degrees. It is also a persistent problem with a tendency to increase over time as people progress to more advanced old age.

Our findings showed that over time the number of people with a PPO increases significantly, and that the odds of a PPO increase with higher number of medicines and new diagnoses independent of PPOs triggered by drug combinations. These findings are similar to those of Moriarty et al. [12] that showed an increasing trend in PPO prevalence in people aged ≥ 65 years significantly associated with age, higher number of medicines and chronic conditions. The associations between higher number of medicines with PPO prevalence found in Moriarty et al. [12] and this current study may hypothesise that older people experience side effects from their medication resulting in new diagnoses and new treatments, both of these generating a higher number of PPOs. Similarly, a continuing prevalence of underuse (PPOs) and misuse (PIMs) in multimorbid older people results in poorer health outcomes. As per Wauter et al., [22] in those aged ≥ 80 years, every additional

PPO increases the rate of hospitalisation (26%) and mortality (36%).

In early old-aged people, our findings showed that the odds of receiving a PIMs over time (OR 1.04, 95% CI 1.03, 1.06) were similar to that of an older population studied by Moriarty et al. [12] (1.08; 95% CI 1.03, 1.13). Polypharmacy was found to be significantly associated with a higher risk of PIMs in our study, a finding that is well documented in the literature [3, 9–12], and was also shown to be independent of PIMs triggered by drug combinations. In addition, our findings showed a significant impact of the number of new diagnoses on PIM prevalence. Although PIM prevalence increased, the mean number of PIMs per patients decreased over time. This finding highlights that a subset of this cohort was accumulating more and more PIMs rather than an increase in mean number of PIMs across the board. A preliminary characterisation of this subset of participants showed a similar mean age compared to the entire study population (65.0 versus 64.8 years) and a similar gender distribution (48.3 versus 51.6%). The subset was taking a higher number of medicines at baseline compared to the entire population (9.2 versus 2.1) and a third of the subset suffered from high blood pressure (33.3%), a fourth (26.7%) suffered from low back pain and nearly a fifth (18.3%) had osteoarthritis at baseline. This is an area that needs to be explored further to identify causative factors and future studies may examine a more detailed clusterisation of patients based on their number of PIMs.

Our data did not show a significant association between changes in either PPO or PIM prevalence and age in this early old-aged population (mean age 64.8 years (SD 3.0). In contrast, Moriarty et al. [12] found that advancing age was significantly associated with both increasing PPO and PIM prevalence in people aged ≥65 years (mean age 74.8 years, SD 6.2 years). These contrasting findings suggest that in early old-aged patients, age may not have the same influence on PPO or PIM prevalence as it does in older patients after the age of 70 years. It has also been observed that in the 'old old' population (i.e. those aged over 85 years), age alone may no longer have such a significant impact on PPO and PIM prevalence, as was found by Wahab et al. [3].

The present study findings indicate that PPOs and PIMs, which are recognised to be highly prevalent in the older population aged 75–84 years [23] and 'old old' population (85 years and older) [3, 9], are also present in early old age. Our data indicate that PPO prevalence and PIM prevalence gradually increases over a five-year period as people progress from early old age towards more advanced old age. Albeit a quite small effect of the increase in PPO and PIM prevalence (ORs of 1.08 and 1.04 for PPOs and PIMs, respectively), the findings highlight an increase in the prevalence of inappropriate prescribing that may reach a clinically significant level over time. Long-term follow-ups from prospective cohort studies are needed to examine this potential clinical relevance of PPO and PIM prevalence. Already known is that a substantially high prevalence of potentially inappropriate prescribing has a negative impact on medication management and adherence in older patients increasing the likelihood of adverse drug events (ADEs) and drug-related hospital admissions caused by overuse, underuse or misuse of prescribed medication [2, 22]. Non-adherence to pharmacotherapy is known to be associated with a higher number of daily medicines, such that there is an estimated increase of 16% non-adherence for each one-unit increase in the number of daily medicines taken [24]. Improving medication adherence by preventing potentially inappropriate prescribing (PIP) could therefore play an important role in reducing the need for healthcare services among older adults and improve their medical therapy. The findings of this study make a strong argument for minimising PIP among early old aged people in primary care, using screening tools such as STOPP/START criteria. In the elderly multi-morbid hospitalised population, STOPP/START criteria have been shown to significantly improve prescribing appropriateness [6] and to minimise adverse drug reactions (ADRs) [25]. It is likely (although not yet proven) that routine application of STOPP/START criteria in late middle-aged/early old aged patients in the primary care setting would significantly improve the medication appropriateness and reduce the incidence of both ADRs and ADEs in this cohort also.

Recent clinical trials demonstrate tangible clinical benefit of applying STOPP/START criteria, albeit in older patient populations in settings other than primary care [6, 14, 25, 26]. There are two large scale multi-centre clinical trials currently in progress designed around software-assisted application of STOPP/START criteria to the medication lists of older people in hospital [27, 28]. Computer-assisted prescribing systems may provide a useful way of implementing routine screening for PIP and these trials may approve to be highly relevant to prescribing surveillance if they show positive results. The first results of the SENATOR trial (software engine for the assessment and optimization of drug and non-drug therapy in older persons) will be known in 2018, and will possibly have direct relevance to PIP prevention in older community-dwelling people [28]. In addition, future studies should examine the effect of training primary care physicians in the use of STOPP/START criteria on the prevalence of PIP in primary care.

The present study is the first, to our knowledge, to report the pattern of PIM and PPO prescribing over a five-year period in early old-aged people (60–74 years). The use of longitudinal data describing prescription medication in this study provides important information on long-term patterns of PIP.

Our study was, however, limited in that some of the required information was not available when applying the STOPP/START criteria, and as a consequence, not all STOPP/START criteria were applied. Additionally, some criteria may have been over triggered due to a lack of detail for diagnoses such as anxiety. A prolonged use of benzodiazepines (more than 4 weeks) may be appropriate among patients with severe mental illnesses or personality disorders. Equally, omission of medical treatment of mild forms of anxiety would not necessarily reflect an omission of treatment for anxiety but rather these may have been treated using non-pharmacological approaches e.g. cognitive behavioural therapy, not recorded in this study. Despite this, both under-diagnosis and under-treatment of anxiety in old age is quite common and the study findings may be a reflection of the suboptimal treatment of anxiety with benzodiazepines in this group. Another limitation of the current dataset is that it lacks any information on medication adherence. Nevertheless, our data indicate that PIP in early old age very likely contributes significantly to the high prevalence of PIP in more advanced old age. Based on the similarities of our findings with comparable studies [11, 12, 22], we consider our findings to be relevant to other European countries.

In conclusion, this is the first study to examine the longitudinal pattern of PIP among people in early old age in the primary care setting. Our data show that approximately one in three persons aged 60 to 74 years has one or more PIMs or PPOs and that over a 5-year follow-up interval, PPO prevalence rises significantly to over 40% whilst PIM prevalence exceeds 45%. Polypharmacy and multi-morbidity have a significant impact on the odds of receiving PPOs and PIMs independent of those triggered by drug combinations. These findings alongside the data emerging from recent clinical trials [6, 25] that describe the positive impact of STOPP/START criteria as an intervention support the use of STOPP/START criteria in the routine review of medication lists of patients in early old age (60–74 years) in the prevention of PIP among older people in primary care.

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Compliance with ethical standards Local ethical approval was obtained to analyse the data and the original study was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals.

Conflict of interest The authors declare that they have no conflicts of interest.

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9.8 Appendix VIII - Chapter 4 STOPP/START

Data on the STOPP/START criteria identified in the study population (n=974).

START criteria version 2.0 identified in the study population (n=974), described as the number of people with each individual criteria for each year of follow-up.

START Criteria	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A1 – Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation	1	1	5	10	13	14	15
A3 – Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease	28	29	33	42	49	56	59
A4 – Antihypertensive therapy where systolic blood pressure consistently >160 mmHg and/or diastolic blood pressure consistently >90mmHg; if systolic blood pressure >140 mmHg and/or diastolic blood pressure >90mmHg, if diabetic	23	22	21	21	21	22	21
A5 – Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is >85 years	13	15	15	21	24	27	28
A6 – Angiotension Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease	16	15	15	15	15	17	17
A7 – Beta-blocker with ischaemic heart disease	4	4	8	10	17	21	22
A8 - Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvediol) with stable systolic heart failure.	0	0	0	0	0	0	0
B1 – Regular inhaled Beta-2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or COPD	31	36	40	45	48	57	56
C1 - L-DOPA or dopamine agonist in idiopathic Parkinson's disease with functional impairment and resultant disability	0	0	1	4	4	4	4
C2 – Non-TCA antidepressant drug in the presence of persistent major depressive symptoms	39	40	46	49	53	53	53
C3 - Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine) for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine)	0	0	1	0	2	2	2
C4 - Topical prostaglandin, prostamide or beta-blocker for primary open-angle glaucoma	0	0	2	3	4	4	4

START Criteria	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
C5 – Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated) for persistent severe anxiety that interferes with independent functioning.	73	73	73	72	75	75	75
C6 - Dopamine agonist (ropinirole or pramipexole or rotigotine) for Restless Legs Syndrome, once iron deficiency and severy renal failure have been excluded	0	1	1	3	2	2	2
D1 – PPI with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation	2	6	9	11	13	13	13
D2 – Fibre supplements (e.g. bran, isphaghula, methylcellulose, sterculia) for diverticulosis with a history of constipation	5	5	5	5	5	5	5
E1 – Disease-modifying anti-rheumatic drug (DMARD) with active, disbling rheumatoid disease	77	77	79	79	81	83	83
E2 – Bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy	18	41	34	32	28	31	22
E3 – Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or (Bone Mineral Density T-scores more than -2.5 in multiple sites)	36	37	40	43	46	51	52
E4 – Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab) in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores > -2.5 in multiple sites)	36	37	41	45	50	54	55
E5 – Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is >-1.0 but < -2.5 in multiple sites)	3	4	7	10	13	18	19
E6 – Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat) with a history of recurrent episodes of gout	1	2	5	9	10	16	17
E7 – Folic acid supplement in patients taking methotrexate	0	0	2	0	0	0	0
G1 - Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary	0	0	8	16	19	21	21
G2 - 5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary	0	0	8	15	18	20	20

START Criteria	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
G3 - Topical vaginal oestrogen or vaginal oestrogen pessary for symptomatic atrophic vaginitis	0	0	0	0	0	1	1
H2 – Laxatives in patients receiving opioids regularly	18	28	33	32	35	30	27

STOPP criteria version 2.0 identified in the study population (n=974), described as the number of people with each criteria for all five years of follow-up.

STOPP Criteria	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A3 – Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants (optimisation of monotherapy within a single drug class should be observed prior to considering a new agent)	127	179	247	256	233	221	177
B1 - Digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit)	0	0	0	0	0	0	0
B3 – Beta-blocker in combination with verapamil or diltiazem (risk of heart block)	2	2	2	2	2	2	2
B4 – Beta-blocker with bradycardia (<50/min), type II heart block or complete heart block (risk of complete heart block, asystole)	12	9	9	9	9	9	8
B6 – Loop diuretic as first-line treatment for hypertension (safer, more effective alternatives available)	3	5	6	7	8	10	10
B8 – Thiazide diuretic with current significant hypokalaemia (i.e. serum K+ <3.0 mmol/l), hyponatraemia (i.e. serum Na+ <130mmol/l), hypercalcaemia (i.e. corrected serum calcium >2.65 mmol/l) or with a history of gout (hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic)	0	0	0	0	0	0	0
B9 – Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence)	7	8	9	9	9	9	7
B11 – ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia	1	1	0	1	1	1	1
B13 – Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) in severe heart failure characterised by hypotension i.e. systolic BP<90 mmHg, or concurrent nitrate therapy for angina (risk of cardiovascular collapse)	1	1	1	1	1	2	2
C2 – Aspirin with a past history of peptic ulcer disease without concomitant PPI (risk of recurrent peptic ulcer)	0	0	0	0	0	0	0
C3 – Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding	1	2	2	2	3	4	4

STOPP Criteria	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
risk, i.e. incontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding) (high risk of bleeding)							
C4 – Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy)	8	9	10	11	8	9	8
C5 – Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patietns with chronic atrial fibrillation (no added benefit from aspirin)	1	1	2	1	1	1	2
C6 – Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease (no added benefit from dual therapy)	5	7	9	10	10	8	10
C7 – Ticlopidine in any circumstances (clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects)	0	0	0	0	0	0	0
C8 – Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for >6 months, (no proven added benefit)	0	0	0	0	0	0	0
C9 – Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for >12 months (no proven added benefit)	0	0	0	0	0	0	0
C10 – NSAID and vitamin K antagonist, direct thrombin inhibitor or factors Xa inhibitors in combination (risk of major gastrointestinal bleeding)	3	8	11	16	15	9	8
C11 – NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis (increased risk of peptic ulcer disease)	18	20	30	23	26	24	23
D1 – Tricyclic antidepressants (TCAs) with dementia, narrow angle glaucome, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of worsening these conditions).	1	1	2	2	2	2	3
D2 – Initiation of Tricyclic antidepressants (TCAs) as first-line antidepressant treatment (higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs)	10	15	13	12	13	14	15

STOPP Criteria	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
D3 – Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol) with a history of prostatism or previous urinary retention (high risk of urinary retention)	0	0	0	0	0	1	1
D4 – Selective serotonin re-uptake inhibitors (SSRIs) with current or recent significant hyponatraemia i.e. serum Na+ <130 mmol/l (risk of exacerbating or precipitating hyponatraemia)	0	0	0	0	0	0	0
D5 – Benzodiazepines for ≥4 weeks (no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for more than 4 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly)	77	107	108	117	110	113	109
D6 – Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease (risk of severe extra-pyrimidal symptoms)	0	0	0	0	0	0	0
D8 – Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment)	0	0	0	0	1	1	1
D11 – Acetylcholinesterase inhibitors with a known history of persistent bradycardia (<60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil (risk of cardiac condiction failure, syncope and injury)	74	78	80	78	78	76	78
D12 – Phenothiazines as first-line treatment, since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care)	6	11	17	20	12	15	15
D13 – Levodopa or dopamine agonists for benign essential tremor (no evidence of efficacy)	0	0	0	0	0	0	0
D14 – First-generation antihistamines (safer, less toxic antihistamines now widely available)	1	1	1	1	1	1	1

STOPP Criteria	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
E2 – Direct thrombin inhibitors (e.g. dabigatran) if eGFR <30ml/min/1.73m2 (risk of bleeding)	0	0	0	0	0	0	0
E3 – Factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR <15 ml/min/1.73m2 (risk of bleeding)	0	0	0	0	0	0	0
E4 – NSAIDs if eGFR<50 ml/min/1.73m2 (risk of deterioration in renal function)	1	1	1	1	1	1	1
E5 – Colchicine if eGFR <10 ml/min/1.73m2 (risk of colchicine toxicity)	0	0	0	0	0	0	0
E6 – Metformin if eGFR < 30ml/min/1.73m2 (risk of lactic acidosis)	0	0	0	0	0	0	0
F1 – Prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating Parkisonian symptoms)	0	0	0	0	0	0	0
F3 – Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where non-constipating alternatives are available (risk of exacerbation of constipation)	0	0	1	2	1	1	1
G1 – Theophylline as monotherapy for COPD (safer, more effective alternative; risk of adverse effects due to narrow therapeutic index)	0	0	0	0	0	0	0
G2 – Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD (unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available)	1	1	1	1	1	1	1
G3 – Antimuscarinic bronchodilators (e.g. ipratropium, tiotropium) with a history of narrow angle glaucoma (may exacerbate glaucoma) or bladder outflow obstruction (may cause urinary retention)	0	0	0	0	1	1	1
G4 – Non-selective beta-blocker (whether oral or topical for glaucoma) with a history of asthma requiring treatment (risk of increased bronchospasm)	1	1	1	1	1	1	1
G5 – Benzodiazepines with acute or chronic respiratory failure i.e. pO2 <8.0 kPa±pCO >6.5 kPa (risk of exacerbation of respiratory failure)	1	1	1	1	1	1	1
H1 – Non-sterodial anti-inflammatory drug (NSAID) other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist (risk of peptic ulcer relapse)	1	1	1	2	3	2	2

STOPP Criteria	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
H2 – NSAID with severe hypertension (risk of exacerbation of hypertension) or severe heart failure (risk of exacerbation of heart failure)	1	0	2	4	5	8	5
H4 – Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis (risk of systemic corticosteroid side-effects)	2	6	3	5	3	4	3
H5 – Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis (risk of systemic corticosteroid side-effects)	0	0	0	0	0	0	0
H6 - Long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor (e.g. allopurinol, febuxostat) (xanthine-oxidase inhibitors are first choice prophylactic drugs in gout)	0	0	0	0	0	0	0
H7 – COX-2 selective NSAIDs with concurrent cardiovascular disease (increased risk of myocardial infarction and stroke)	0	3	2	6	3	4	2
H8 – NSAID with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease)	4	7	9	10	4	10	6
H9 – Oral bisphophonates in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding (risk of relapse/exacerbation of oesophagiti, oesophageal ulcer, oesophageal stricture)	0	1	1	1	2	2	2
I1 – Antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow-angle glaucoma (risk of acute exacerbation of glaucome), or chronic prostatism (risk of urinary retention)	0	0	0	1	2	2	2
I2 – Selective alpha-1 selective alpha blockers (prazosin, doxazosin, tamsulosin, terazosin) in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope)	0	0	0	0	0	0	0
J1 – Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus (risk of prolonged hypoglycaemia)	1	2	2	2	2	2	2
J2 – Thiazolidenediones (e.g. rosiglitazone, pioglitazone) in patients with heart failure (risk of exacerbation of heart failure)	0	0	0	0	0	0	0

STOPP Criteria	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
J4 – Oestrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence)	0	0	1	1	1	1	1
J6 – Androgens (male sex hormones) in the absence of primary or secondary hypogonadism (risk of androgen toxicity; no proven benefit outside of the hypogonadism indication)	0	0	0	0	0	0	0
K1 – Benzodiazepines (sedative, may cause reduced sensorium, impair balance)	100	108	115	134	122	120	116
K2 – Neuroleptic drugs (may cause gait dyspraxia, Parkinsonism)	27	35	45	44	39	45	41
K3 - Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers) with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥20mmHg (risk of syncope, falls)	0	0	0	1	2	2	2
K4 – Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia)	71	79	86	79	85	85	79
L1 – Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first line therapy for mild pain (WHO analgesic ladder not observed)	8	10	12	14	11	16	11
L2 – Use of regular (as distinct from PRN) opioids without concomitant laxative (risk of severe constipation)	23	43	66	56	53	58	46
L3 – Long-acting opioids without short-acting opioids for break-through pain (risk of persistence of severe pain)	0	0	1	0	0	0	0
N – Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines) (risk of increased antimuscarinic/anticholinergic toxicity)	1	1	1	1	2	1	1

STOPP/START criteria not applied to the dataset.

START criteria version 2.0 that were not applied to the dataset due to unavailable clinical information.

START Criteria
A2 - Aspiring (75 mg - 160 mg once daily) in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.
B2 - Regular inhaled corticosteroid for moderate-severe asthma or COPD, where FEV1<50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.
B3 - Home continuous oxygen with documented chronic hypoxaemia (i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%).
F1 - ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor) in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria (>30mg/24 hours) with or without serum biochemical renal impairment.
H1 - High-potency opioids in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective.
I1: Seasonal trivalent influenza vaccine annually.
I2: Pneumococcal vaccine at least once after age 65 according to national guidelines.

STOPP criteria version 2.0 that were not applied to the dataset due to unavailable clinical information.

STOPP Criteria
A1 - Any drug prescribed without an evidence-based clinical indication.
A2 - Any drug prescribed beyond the recommended duration, where treatment duration is well defined.
B2 - Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure).
B5 - Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmia (higher risk of side-effects than beta-blocker, digoxin, verapamil or diltiazem).
B7 - Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure (leg elevation and/or compression hosiery usually more appropriate).
B10 - Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives (centrally-acting antyhypertensives are generally less well tolerated by older people than younger people).
B12 - Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalaemia i.e. >6.0 mmol/l - serum K should be monitored regularly, i.e. at least every 6 months).
C1 - Long-term aspirin at doses greater than 160mg per day (increased risk of bleeding, no evidence for increased efficacy).
D7 - Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications (risk of anticholinergic toxicity).
C9 - Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed (increased risk of stroke).
C10 - Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls).

STOPP Criteria
E1 - Digoxin at a long-term dose greater than 125µg/day if eGFR < 30 ml/min/1.73m2 (risk of digoxin toxicity if plasma levels not measured).
F2 - PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated)..
F4 - Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate > 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate > 1800 mg/day; no evidence of enhanced iron absorption above these doses.
H3 - Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief).
J3 - Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycaemic symptoms).
J5 - Oral oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer).

STOPP/START criteria triggered by drug combinations and excluded in the sub-analysis.

START criteria version 2.0 triggered by drug combinations.

START Criteria
E2 - Bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy.
E7 - Folic acid supplement in patients taking methotrexate.
H2 - Laxatives in patients receiving opioids regularly.

STOPP criteria version 2.0 triggered by drug combinations.

STOPP Criteria
A3 – Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants (optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).
B3 – Beta-blocker in combination with verapamil or diltiazem (risk of heart block).
C4 – Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy).
C5 – Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patietns with chronic atrial fibrillation (no added benefit from aspirin).
C6 – Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease (no added benefit from dual therapy).
C10 – NSAID and vitamin K antagonist, direct thrombin inhibitor or factors Xa inhibitors in combination (risk of major gastrointestinal bleeding).
C11 – NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis (increased risk of peptic ulcer disease)
D11 – Acetylcholinesterase inhibitors with a known history of persistent bradycardia (<60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil (risk of cardiac conduction failure, syncope and injury).
H8 – NSAID with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease).
N – Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines) (risk of increased antimuscarinic/anticholinergic toxicity).

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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Qualitative analysis of community pharmacists' opinions on their involvement in reducing potentially inappropriate prescribing

Christina Raae Hansen[1,2] · Stephen Byrne[1] · Denis O'Mahony[3,4] · Patricia M. Kearney[5] · Laura J. Sahm[1,6]

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Abstract

Purpose Older people are at risk of potentially inappropriate prescribing (PIP) due to polypharmacy arising from multi-morbidity. Despite available explicit criteria to reduce PIP, it is highly prevalent. Whilst community pharmacists have the required knowledge to help reduce PIP, they are not currently engaged with the problem. This study explores the views of community pharmacists on their potential involvement in reducing PIP and determines the challenges to its implementation.

Methods Semi-structured interviews with pharmacists working in community pharmacies in Ireland. The theoretical domains framework (TDF) was used to develop the topic guide and to analyse the transcripts. Domains of highest relevance for PIP reduction were identified based on their frequency or whether the participants emphasised the impact of constructs within a domain. Local ethical approval was obtained.

Results Of 18 participants, 12 were female, median age was 30 years (IQR, 27–35) with a median of 6 years (IQR, 3–8) of experience. Seven TDF domains were identified as relevant to PIP reduction. Pharmacists were uncertain about their role in reducing PIP and reluctant to challenge physicians' prescribing decisions. Challenges pertained to the environment, knowledge, social influences, professional role and identity.

Conclusions Pharmacists welcomed new responsibilities in reducing PIP as part of their daily practice but expressed a need for removal of social and environmental barriers as well as, provision of relevant guidelines and education about PIP. This study provides useful insights into the target domains for overcoming barriers of pharmacist involvement in reducing PIP.

Keywords Pharmacist · Primary care · Older patients · Prescribing · Qualitative

Introduction

Older multi-morbid people are at substantial risk of having potentially inappropriate prescribing (PIP) [1, 2]. The risk of PIP increases as people grow older and is strongly associated with the higher number of daily medicines, i.e. polypharmacy, used to treat multi-morbid illness [3–5]. Patient safety is at risk when older people are exposed to PIP because of the associated adverse drug events (ADEs) and drug-related hospitalisations of PIP [6, 7]. Previous studies indicate a high

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✉ Christina Raae Hansen
christina.raaehansen@ucc.ie

[1] Pharmaceutical Care Research Group, School of Pharmacy, Cavanagh Pharmacy Building Room UG06, University College Cork, College Road Cork, Cork, Ireland

[2] Section for Social and Clinical Pharmacy, Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen Ø, Denmark

[3] Department of Medicine, School of Medicine, University College Cork, Western Gateway Building Room 2.59, Western Road, Cork, Ireland

[4] Department of Geriatric Medicine, Cork University Hospital, Wilton, Cork, Ireland

[5] School of Public Health, University College Cork, Western Gateway Building 4th Floor, Western Road, Cork, Ireland

[6] Pharmacy Department, Mercy University Hospital, Greenville Place Centre, Cork, Ireland

prevalence of PIP throughout the primary care setting in Ireland, with prevalence estimates of 21–57% [3, 5, 8, 9]. Similar prevalence estimates have been reported in the neighbouring country, Northern Ireland (34%) [10] and in other European countries, e.g. Spain (38–46%) [11] and the Netherlands (35–85%) [4]. No intervention has succeeded in reducing the substantial PIP prevalence in primary care despite the existence of explicit criteria to identify PIP for over 10 years, and the evidence that they are effective in reducing PIP in hospitalised, older patients [2, 4, 12]. Two of the most commonly cited sets of PIP criteria are Beers' criteria [13–17] and screening tool of older people's prescriptions (STOPP) and screening tool to alert to right treatment (START) criteria [1]. There are currently four randomised clinical trials showing the clinical efficacy of applying STOPP/START criteria to reduce PIP [2, 18], falls incidence and overall medication cost [19], as well as incidence of ADRs [12] in the hospital and nursing home settings.

Reviewing new and repeat prescriptions and completing medication reviews are recognised ways of identifying PIP. Medication review is a broad term covering several interventions carried out by prescribers themselves or by other practitioners providing advice to prescribers (e.g. pharmacists) with the overall aim of improving the quality, safety and appropriateness of use of medicines [20]. Studies in primary care settings have demonstrated a significant positive effect of medication reviews on the reduction of PIP in older people [21–24], and also in community pharmacy settings [24]. Pharmacists are in a position to identify and help reduce PIP. However, prevalence data of PIP among community-dwelling older people indicate that pharmacists are not undertaking this important role of identifiers of PIP with a further remit of PIP prevention [25–27].

When designing an intervention to change traditional working practice, it is fundamental to understand the processes underlying the behaviour [28, 29]. In the case of pharmacists, it is essential to understand the barriers and facilitators for the involvement, or lack thereof, of community pharmacists in reducing PIP. The theoretical domains framework (TDF) was originally developed by Michie et al. [30] and later updated by Cane et al. [31]. The TDF considers a wide range of possible theoretical explanations for the relevant behaviours [28, 32, 33]. The 12 domain TDF [30] has been widely used in health research to define behaviours and to identify barriers and facilitators to that behaviour [28, 33, 34]. The identification of such domains relevant for a specific behaviour change is an important step in the design of an intervention [31, 35]. In this study, the 14 domain TDF was employed to identify barriers and facilitators of pharmacist involvement in reducing PIP. The 14 domain TDF has previously been used to explore a similar topic: the utilisation of a screening tool in medicines usages reviews (MURs) by community pharmacists [35] and was deemed appropriate to investigate their involvement in reducing PIP.

Whilst large randomised controlled trials are examining various ways to assess the interventions targeted at prevention of PIP in hospital care settings [2, 36, 37], little research is being carried out in primary care. To date, the views of the community pharmacists on reducing PIP have been given little attention [35]. Therefore, this study aimed to explore the views of community pharmacists on their potential involvement in reducing PIP, and to determine the perceived barriers and facilitators to the implementation of PIP reduction in community pharmacy practice.

Methods

Sampling

Community pharmacists working in community practice in Cork in Ireland were recruited using convenience sampling based on a sampling matrix. The convenience sampling method was chosen due to time constrictions of the study and to increase the likelihood of respondents. Hence, a close geographic proximity allowed the researcher (CH) to conduct face-to-face interviews with participants at suitable location. Pharmacies located in Cork were identified and contacted by telephone. The study was introduced to the pharmacist on call at that actual time, and the pharmacist was asked to take part in the study. An agreed interview date, time and location were then arranged. Currently working in community practice was the only inclusion criterion, and there were no exclusion criteria.

A sampling matrix was designed to ensure variation of important participant characteristics in the study population (see Online Resource I). The design of the matrix was done by three researchers (CH, LS and SB) together with a panel of pharmacists with backgrounds in academia and community pharmacy practice. The final matrix design was approved by all authors. Matrix parameters chosen were (i) experience from working with nursing homes (either from working in a nursing home or from working in a pharmacy serving nursing homes), (ii) years of experience working as a community pharmacist (< 3 years, ≥ 3 years and ≥ 10 years) and (iii) number of pharmacists working simultaneously in the pharmacy. A cutoff of 3 years of community experience was chosen as a matrix parameter because pharmacists in Ireland after a 3-year period can choose to take up employment subsequently as supervising/superintendent pharmacist.[1] Being a supporting or a supervising pharmacist was considered to influence the

[1] The supervising/superintendent pharmacists is the person responsible for the day-to-day management and operation of the pharmacy and must have a minimum of 3 years post-registration experience (http://www.thepsi.ie/gns/Pharmacy_Practice/practice-guidance/Guidance_for_pharmacists/Guidance_for_Supervising_Pharmacists.aspx).

level of confidence and knowledge. A threshold of 10 years or more experience was then agreed by the authors and the expert panel due to an expected seniority after 10 years which might have influenced their opinions and answers. Experience of working in a nursing home was considered to have an influence on the pharmacists' answers relating to medication reviews and polypharmacy issues as these are commonly undertaken by pharmacists in Irish nursing homes. The number of registered pharmacists on duty in the pharmacy at any one time was believed to have an impact on their perceived capability to perform medication reviews compared to those pharmacies with a single pharmacist on duty. Although not matrix parameters, the areas in which the pharmacists worked, i.e. urban or rural as well as associated affluence or disadvantage were considered when recruiting. Areas with social affluence and disadvantage were identified from the deprivation index viewer (available from www.pobal.ie) [38].

Interview topic guide

An interview topic guide (see Online Resource II) was designed to explore the 14 domains of the framework [30, 31] whilst also allowing the participants to freely share their opinions. Using the TDF to design the topic guide is a helpful tool in formulating questions that will enable the identification of the behaviour and the barriers and facilitators to that behaviour. The use of a TDF-formulated topic guide has also been shown to effectively elicit responses from the interviewees that they would not otherwise report [29]. The topic guide was refined by consensus among all authors and with an expert panel of pharmacists with backgrounds in academia and community pharmacy practice. The topic guide was pilot tested in two community pharmacists. During the study, it was refined on an iterative basis after each interview was transcribed to allow for emerging themes to be explored in subsequent interviews. Interviews were conducted until the point of thematic saturation as described by Francis et al. [39]. The interviews were introduced with some general questions regarding their awareness and beliefs about PIP and medication reviews. Participants were shown the recently developed deprescribing algorithms and asked to give their opinion about the content, layout and usefulness in their daily practice [40–43]. Participant demographic details were also collected including gender, age and number of years of experience in community pharmacy.

Data collection

Semi-structured interviews with pharmacists working in community pharmacies in Ireland conducted by one researcher (CH). This type of interviews was chosen as it encourages interviewees to share the views and opinions that are important to him/her [44]. Interviews were conducted face-to-face or over the telephone. At the time of the interviews, the participant received an information letter and gave their written consent. Interviews were audio recorded and transcribed verbatim. Transcripts were returned to participants for review, but no one accepted this offer.

Qualitative data analysis

Transcripts were anonymised and transferred to the QSR NVivo® Version 11 software. In line with framework analysis, a familiarisation process took place whereby the researcher (CH) repeatedly listened to the interview audio recordings and read the interview transcripts. From the transcribing process and familiarisation process, the researcher (CH) attained an overview of specific beliefs within the data [45]. Following this step, CH coded excerpts from the interview transcripts into one or more of the 14 TDF domains. Three randomly selected transcripts were coded by a second researcher (LS) to assure validity and reliability of the data analysis. Disagreement in coding between the two researchers was resolved through discussion and consensus. Domains for which transcript excerpts were coded into were summarised by CH. Supporting excerpts were attached to each domain summary. The summaries were reviewed by LS. The two researchers determined the domains of relevance for PIP reduction using a similar approach to previous studies [28, 35]. A domain was deemed relevant if excerpts were coded frequently into this or if the participants emphasised the significant impact of barriers and/or facilitators within a domain on their involvement in reducing PIP.

Results

A total of 21 pharmacists were approached of whom 18 agreed to participate. One pharmacist refused to participate and the remaining two were unavailable at the time of the study. There were no dropouts in this study. Interviews were conducted in the period from June to end of August 2017. The interviews were a mean length of 19 min (SD 6.00) and took place at the pharmacy in which the participant worked. Data saturation was reached after 15 interviews with no new themes emerging from conducting an additional three interviews. Characteristics of the participants are described in Text box 1.

Text box 1 Characteristics of interview participants (N = 18)

- Community pharmacists interviewed worked in pharmacies placed in urban (n = 15) and rural (n = 3) areas, of which 13 areas were categorised as affluent and 5 were deprived areas according to data from www.pobal.ie.
- 12 female and 6 male pharmacists were interviewed and were a median age of 30 years (interquartile range, IQR 27–35).

- The pharmacists had a median of 6 years of experience from working in a community pharmacy (IQR 3–8) and 8 pharmacists had experience from working in or for a nursing home. Seven pharmacists had graduated before 2010 and 11 pharmacists after 2010.
- Eight pharmacists were working in a pharmacy with only one licenced pharmacist and 10 pharmacists worked in a pharmacy with 2 or more licenced pharmacists on duty. 16 pharmacists had help from technician staff in the pharmacy whilst 2 did not have technician staff.

Pharmacists were familiar with the term 'inappropriate prescribing' and defined this as: (i) any medication prescribed that has the potential to cause harm, side effects or drug interactions; (ii) overprescribing or prescribing without a documented indication; (iii) prescribing a medicine to relieve side effects of another medicine that the patient is taking; (iv) prescribing any medication for longer than indicated and (v) prescribing a medicine not suitable for older people. A few pharmacists mentioned the explicit STOPP/START criteria [1, 46] to identify PIP but the majority referred to treatment guidelines such as the NICE guidelines [47] and no pharmacist used explicit set of criteria to identify PIP in their daily work. The pharmacists perceived the presented deprescribing algorithms [40–43] to give a good overview and to be user-friendly. However, some pharmacists also believed that the information on the algorithms was well known among pharmacists, and did not believe algorithms to have significant influence on their involvement in reducing PIP.

Pharmacists described medication reviews as the systematic process of reviewing patients' medications and identifying drug-related problems. No pharmacist had experience of doing medication reviews in community pharmacy setting but some had experience from educational sessions or from working in hospitals or nursing homes. No pharmacist interviewed was carrying out medication reviews as part of their current routine practice.

Qualitative analysis themes

Transcript excerpts were most frequently coded into five domains: (i) *beliefs about capabilities*, (ii) *environmental context and resources*, (iii) *knowledge*, (iv) *social influences and* (v) *social professional role and identity*. The two domains *memory, attention and decision processes* and *reinforcement* were less frequently coded. However, those participants who made comments coded into these domains attached significant importance to the factors identified. The interview data coded into these seven domains are summarised in Table 1 with illustrative quotations.

Beliefs about capabilities

Pharmacists perceived themselves as appropriate healthcare providers to identify PIP. Competencies were attributed to: being trained to do it; being good at identifying PIP; having a good relationship with patients due to the nature of patients visiting their pharmacy more often than their General Practitioner (GP) and looking at older patients' prescription drugs with fresh eyes.

Beliefs about capabilities were affected by a pharmacist's level of confidence and this subsequently influenced the likelihood of the pharmacist communicating any recommendations to the GP. One pharmacist's self-perceived duty as a pharmacist gave her the confidence to act when an instance of PIP was identified (Table 1). Another, younger pharmacist (1.5 years of experience) described how her lack of confidence restrained her from actively giving her input despite her beliefs about her role (Table 1).

Environmental context and resources

Being busy with serving many patients and doing administrative work were believed to restrict time to do medication reviews and to have follow-up contact with prescribers to discuss potential changes. Pharmacists described a need to prioritise their time and focus on more immediately unsafe issues, such as major drug-drug interactions, rather than reviewing medication lists for PIP, which was felt to have more medium or long-term implications for the patient (Table 1). Protected time to review medications facilitated by extra pharmacist staff was a suggested solution.

Another challenge was a lack of communication between healthcare providers, e.g. between pharmacists and GPs, and was thought to lead to confusion about medication changes and to impede the implementation of these changes. Pharmacists described being unsure where the responsibility for stopping PIP resides. Suggested improvements included more direct lines of communication and willingness to collaborate from all parties. Geographic proximity and face-to-face interaction were believed to be key facilitators of a good collaborative relationship (Table 1).

Other challenges pertained to a lack of patient information, e.g. diagnosis or indication for a drug. Receiving hospital discharge letters and gaining access to a centralised clinical record system for sharing patient information between pharmacists and GPs were suggested improvements.

Knowledge

Pharmacists believed their pharmacology/therapeutics knowledge to be sufficient to identify PIP but stressed the need for continuing professional education to bring their knowledge in line with new medications and most up-to-date guidelines. Interdisciplinary training was suggested as one way to meet these educational needs whilst simultaneously improving collaboration between pharmacists and GPs (Table 1).

Table 1 Interview quotations supporting the individual theoretical domains identified as relevant for PIP prevention in primary care

TDF domain	Supporting quotes
Beliefs about capabilities	"I would not go down the route and ring up a doctor and saying: 'You should not be on this'. The patient has been on this for longer than two weeks, you should not be giving this anymore'. I just do not. That is probably my role to some extent but I would not like going down that route of complaining to another healthcare professional about what they are doing, so." [Pharmacist 6, Code: Beliefs about capabilities]. "I'd be fairly confident. I'd be kind of, just thinking in my own head: 'Look, I have a duty of care' and if the doctors are a little bit annoyed with me, I'll take that." [Pharmacist 17, Code: Beliefs about capabilities]. "I would be happy enough to have a look through somebody's medicine, if you are given a bit of time to go through it beforehand. Instead of the cuff kind of walking off the street: 'Oh here's my 42 medicines in a brown paper bag'(...) But if you have time to go through stuff beforehand and had a bit of time to spend with the patient then definitely I think it would be both cost-effective and much, much more beneficial to the patient in the long term." [Pharmacist 18, Code: Beliefs about capabilities].
Environmental context and resources	"I think communication is a huge issue because (...) if something [prescription] comes out from the hospital, the GP might not want to stop it. You know the hospital's intention might have been 'let us go on this for 6 weeks'. But then the GP puts it on the repeat and then it comes to the pharmacist and I am looking at it and they have been on it for two months. I am not going to ring the GP after two months and say 'oh, it's probably inappropriate for you to stop this now'. It's kind of like who actually [should tackle instances of PIP], and where does the buck stop. Who should say 'this is where it stops' or 'this is where it starts' or." [Pharmacist 15, Code: Environment] "Well it's just, I guess, everybody's busy. Ehm, things maybe are not reviewed as often as they should bet (...). So, you know, it does not, it it just flies by and you know, you have got a number of other reasons, which are far more immediate in terms of inappropriate prescribing, that you need to look out for. So, you know, those are the ones that you are gonna go for, the ones that are immediately unsafe, I guess." [Pharmacist 2, Code: Environment] "I suppose between the doctor and the pharmacist. It's a two-way thing. There needs to be better relationship, I suppose, between the prescribing doctor and the pharmacist. Then again, I think it just depends on which doctor you talk to. Some of them are happy about engaging with the pharmacist and some of them are not. Some do not want to, so. I suppose, so." [Pharmacist 16, Code: Environment]
Knowledge	"I think interdisciplinary training would be very good. Get all the GPs and all the pharmacists into the room. Get a little bit of a talk, a lecture, have a dinner, and let them [GPs] understand how we [pharmacists] work and the position that we are in, because we [GPs and pharmacists] often do not understand our jobs and they can explain. I mean we [phannacists] go to visit the GP for our own thing. So, we kind of have a little bit more of an understanding [of the GP's work]. But they [GPs] may ever come to a pharmacy and they may not know how we operate." [Pharmacist 12, Code: Knowledge] "Maybe if there was some sort of training about how to review those [PIP] that would be good. (...) and some sort of training so then it makes us aware that 'right, we are going to look out for' you know" [Pharmacist 9, Code: Knowledge and Memory, attention and decision] "It is useful [deprescribing algorithms] but like at the same time like I feel like it's something that we all already know (...) I do not think it's the spotting is the big problem. It's the like what do you do when you do spot it? So, it's the training of what are we actually supposed to do. So, I suppose you do spot it but like I do not necessarily know like what you are supposed to do with it." [Pharmacist 15, Code: Knowledge]
Social influences	"I suppose for our part it's just time and for the patient's part it's just the interest in it. ..... There are some patients who want to know everything that they are on and every reason. And then other patients who genuinely .....have great belief in the doctor and pharmacist and they just think if they were ever prescribed [any medication] they need to take it." [Pharmacist 13, code: Social influences] "A lot of it is: 'well, if the doctor said' or 'if you said' or you know, someone else said. They do not kind of listen to themselves or do what they think they should do or what as I say, that maybe they are not informed enough." [Pharmacist 17, Code: Social influences] "I sometimes, depending on the doctor, encourage the patient to go back and ask. If you just say to the doctor, eh to the patient: 'maybe say to the doctor ehm could you check your levels'. So, like you say it in a nice way so they do not go like 'well the pharmacist said'. But you know that they kind of think themselves and maybe they should be questioning it. You are kind of empowering them a bit." [Pharmacist 5, Code: Social influences] Sometimes it, it can be quite difficult as a pharmacist to deal with certain doctors or certain doctors in the hospitals. Not for the fact that they are authoritarian or anything like that but it's that they are busy too. They just do not want the hassle of it. They are the almighties sometimes (...) The channels need to be a bit more open. Sometimes they are very closed and if they [the doctors] were a bit more open and a bit more receptive to what our [pharmacists] role as like a professional could be. Which I think some, some of them are not, then I think it would help a lot." [Pharmacist 18, Code: Environment]
Social professional role and identity	"We should be doing more but we are doing less [to reduce PIP than we should]. Whether that's business or whether that's some people are... shying away from it because they are afraid that they are out of touch, [such as some] older pharmacists. I am not sure, but definitely there's this un-realisation of what our role should be in [reducing PIP] for sure." [Pharmacist 18, code: Social/Professional role] "I think it's, the overall responsibility I think is a two-way think. I think it's between the GP and pharmacy, and I do not think either holds the overall responsibility (...) I suppose we would not review. I would not see it as a role, no. As a primary role. It would only be if there was an issue with the prescription or if there was an interaction [that the pharmacist would contact the prescriber]. But other than that I would not, no." [Pharmacist 3, Code: Soc. Prof. role] "I take an active interest into the medication. I have no problems ringing a doctor about anything, any time. Even if it's something small lif I think it's gonna benefit the

Table 1 (continued)

TDF domain	Supporting quotes
	patient. Within reason. I am not going to be annoying them without reason over stuff either. You know. I always try to put patient benefit over profit first." [Pharmacist 5, Code: Soc. Prof. role]
Memory, attention and decision processes	"Well those IPU [Irish Pharmacy Union] and HSE [Health Services Executive] campaigns about generic medications for example, have been very successful. I think a similar campaign along the lines of 'do you need everything you are taking?'. Or encouraging patients to go to their doctor. I think to a certain extent; the prescription levy did this very well. Where people went to their doctor and asked 'do I really need to be taking all this?'" [Pharmacist 10, Code: Memory, attention & decision process] "Probably advertising it a bit more in so that, and even advertising it in doctor surgeries. Cause I did have someone ask me before about a person that could do, a certain doctor that would do a medication review, and I was pretty confused, and I said 'but you know that everyone doctors and pharmacists can do it?'. But they'd heard from one person that there was this one doctor that does medication reviews and that was the answer. So, I suppose maybe it's not advertised as a service or advertised as something that people can, pharmacists and doctors can do." [Pharmacist 6, code: Memory, attention & decision process] "Well definitely there was one GP, when it all came out [regulations on benzodiazepine prescribing in Ireland], kind of contacted us and said: 'how am I? Like, am I prescribing more benzodiazepines than any other GP?'. And like that's an interesting one. Just to be able to say like, on a scale you are prescribing more. It might kind of open their eyes up a little (...) It would be hard, but it would be a nice study for someone to do at some stage. To say: 'look, as a GP you are prescribing this amount as opposed to the national average of such and such'." [Pharmacist 11, code: Memory, attention & decision process]
Reinforcement	"I suppose it's [PIP] a bit under the radar in a lot of my daily work because you are not incentivised to look for it (...) Well it's really a case of your incentives. You know, you are not incentivised to do it. It does not really benefit you directly at all." [Pharmacist 2, Code: Reinforcement] "If it [medication reviews] could be incorporated into your CPD [continuing professional development], I know pharmacists who would be much more inclined to do it because we are all trying to clock up our CPD hours (...) it should be a thing that if you do your certain medicine reviews you can log this as CPD. You know that the PSI [the Pharmaceutical Society of Ireland], or the IPU would support us in that way. The IPU [Irish Pharmacy Union], support us in that way and encourage us." [Pharmacist 5, Code: Reinforcement] "But I think if you try and force people to do it [medication reviews] for even for like a financial thing. Reimbursement or anything like this, it's just going to come to like the same thing as we do with say the HSE claims or something. Say, you are doing it for the wrong reasons and even in that case you might not do it properly." [Pharmacist 7, Code: Reinforcement]

Guidelines were perceived to be valuable information sources partly because of their generally easy application to daily practice and partly for the evidence-base guidance to pharmacists' recommendations. However, some pharmacists criticised guidelines for limitations such as describing how to identify PIP without specific guidance on how to manage it (Table 1).

Social influences

Patient demands and their relative interest in medication were noted to strongly influence the changing or discontinuation of medication. Some patients were described as demanding treatment and not being content to adjust their medication due to fear of change or loyalty to the doctors' prescription orders (Table 1).

Pharmacists also noted however that their regular contact with patients put them in a position to influence the patients' behaviours. Pharmacists described how negative interactions with GPs resulted in loss of confidence in their own recommendations, conversely, being acknowledged by patients' GPs motivated pharmacists to discuss potential changes with those GPs (Table 1).

Social professional role and identity

Pharmacists described their current role to include: (a) informing patients about their medication, (b) maintaining patient safety perspective over financial benefits for the pharmacy and (c) being familiar with patients' particular medication needs. Pharmacists agreed that they had a role in PIP prevention but were divided regarding the extent to which they should intervene when PIP is detected. A clear description of the pharmacist's role in reducing PIP and an acceptance of this role among healthcare professionals was suggested as a way in which to increase the involvement of pharmacists (Table 1).

Memory, attention and decision process

Raising awareness of PIP to pharmacists, doctors and patients was thought to enhance PIP reduction. Suggested initiatives were campaigns from health authorities to patients and/or healthcare providers (Table 1). The purpose of these campaigns should be to inform patients or GP about particularly problematic drug classes and raise awareness (Table 1).

Reinforcement

State reimbursement, or professional acknowledgement, for doing medication reviews was both considered to be motivating factors to do medication reviews. However, concerns were raised about the quality of government mandatory medication reviews and how incentives may shift focus away from patient benefits to financial and personal benefits instead.

Discussion

This study used a theoretical approach to explore the views of community pharmacists on their involvement in reducing PIP in older people and their perceived barriers and facilitators to this. Despite beliefs about capability and responsibility for reducing PIP structured medication, reviews and recommendations about stopping medications do not form a routine part of daily practice for community pharmacists in Ireland. It is clear from this study that for some pharmacists, there was a sense of conflict in what they knew to be the identifiable instances of PIP and what they actually did to reduce PIP.

Pharmacists in expressed uncertainties about the extent of what their role in reducing PIP should be. They described a reluctance to work outside of their current role and to challenge prescribing decisions taken by GPs, such as recommending drug discontinuation. The consequences of this uncertainty about the pharmacist's role in patient care, such as reducing PIP, have also been described in the literature [23, 26]. In the study by Patterson et al. [23], the inconsistent description of pharmacists' responsibilities in a primary care team was considered to hinder collaboration between pharmacists and other healthcare professionals. They described how some healthcare professionals felt that pharmacists do not adequately handle their responsibilities and described a likely relationship between this belief and a general lack of awareness of the role of the pharmacist [23]. Schindel et al. [26] described how a lack of consistency in the pharmacy service influences patients' expectations in that they may be informed variably about pharmacist services.

When asked specifically about stopping medications, pharmacists in our study described uncertainty of where final responsibility for PIP avoidance lies. In a recent review, this same theme caused confusion for GPs and also differing opinions of GPs regarding pharmacist support [48]. Extending the role of the pharmacist to include patient care may therefore require a clear description of the tasks and responsibilities expected to be undertaken by pharmacists that this is clearly communicated to all stakeholders.

Our findings suggest a need for a shared goal of medicines optimisation, and that by having more interdisciplinarity within training in medication reviews; this may be achieved. Consistent with our findings, the study by Patterson et al. [23] described that collaboration between pharmacists and GPs was challenged by (i) a lack of understanding of each other's professional role in combination with (ii) the busy professional practice environment and (iii) the absence of a shared platform with patient information. To date, there is no centralised system in which patient information is shared between community pharmacies and GP practices in the Republic of Ireland. It would be reasonable to suggest that having access to diagnoses and comorbidities would increase the clinical relevance of pharmacist recommendations and improve communications with other healthcare providers. Sharing patient clinical data was suggested in our study as one fundamentally important way to improve communication and collaboration between community pharmacists and GPs. This was also suggested in the study by Bergman et al. [25] as a mean of improving satisfaction among some GPs with pharmacist recommendations, which were often criticised for lacking consideration of patient context. Keller et al. [27] also showed how shared patient information enhanced the communication between pharmacists and physicians and increased mutual professional trust between them.

Pharmacists in the present study welcomed more education and guidelines on reducing PIP. These guidelines should ideally give instructions on the steps following the identification of a PIP, be up-to-date and be used by all, including prescribers. To date, guidelines on stopping inappropriate medications in older people have been criticised for being too disease specific and not addressing the steps of stopping and/or changing a medication identified as inappropriate [48–50]. There is a need to design guidelines that meet the needs of healthcare professionals in busy medical and pharmacy clinical practice in terms of content, instructions and relevance. The existing Beers' criteria and the STOPP/START criteria as well as the recently developed deprescribing guidelines and algorithms by Farrell et al. [40, 43], Bjerre et al. [41] Pottie et al. [42], Reeve et al. [51] and the newly developed STOPP Frail criteria [52] may meet these criteria. However, a recent study by Cardwell et al. [35] has highlighted a number of barriers to the utilisation of screening tools by community pharmacist in daily practice—those barriers being similar to those of this study. Future investigation on the application of these deprescribing guidelines in primary care setting is thus warranted and may provide useful insights into the implementation of more deprescribing to reduce PIP in primary care.

Whilst some studies to date have shown a positive impact of pharmacist involvement in reducing PIP in primary care [21], more research is needed into the effective implementation of such interventions. The majority of barriers and facilitators identified in this study fall under the TDF domains of *environment, knowledge, social professional role and social influences.* The design of future interventions should target these domains. Our findings suggest that future research should focus on the creation of

guidelines that suit the primary care setting as well as investigating new strategies to improve the collaboration and communication between healthcare professionals both across and within care settings. Policy makers and the educational sector, such as universities, could support the work of community pharmacists in preventing PIP by offering continuous training and encouraging interprofessional education, whilst also researching new ways of making more patient-specific information available to the pharmacist.

A strength of this study is its use of a robust theoretical framework to analyse the interview data. Using the TDF ensures that a large variety of factors on behaviour are considered compared to a more restricting set of factors being explored when using individual theories of behaviour change [35]. The use of TDF allows the mapping of findings to theory and is a useful way of identifying mediators of change. Although the use of a pre-specified framework to develop the interview topic guide and to analyse the data can prevent the emergence of non-predefined themes of relevance; nevertheless, the TDF has been applied successfully in previous studies to describe topics similar to this study [28, 33–35]. This study was not without limitations. The sample size of 18, although acceptable for qualitative research, is small. The nature of qualitative analysis is subjective and despite the use of a sampling matrix to recruit participants, the findings of this study, as with any qualitative research, are not generalisable to all community pharmacists. Additionally, the convenience sampling methods has its limitations to the generalisability of the study population, and the self-selected study population may have introduced self-selection biases. However, the findings of this study may still be relevant to healthcare providers in other countries.

In conclusion, pharmacists were generally aware of PIP in older people and its related problems. Pharmacists mostly welcomed responsibilities into their involvement of reducing PIP but described challenges of overcoming social and environmental barriers, compounded by a lack of relevant guidelines for reducing PIP and education on the subject of PIP. This study identified barriers and facilitators of more pharmacist involvement in reducing PIP in community practice. The findings pointed to the need for greater collaboration between physicians and pharmacists in reducing PIP through clearer descriptions and mutual awareness of their individual roles and responsibilities in this process. This study provides useful insights into the target domains for overcoming barriers of pharmacist involvement in reducing PIP in community practice and may prove useful in the design of future pharmacist-led interventions to reduce PIP. Although exclusive to Irish community pharmacists, the findings may be of use in the expansion of the role of the community pharmacist in other countries.

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Compliance with ethical standards

Ethical approval for this study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals prior to recruitment. Written informed consent was obtained from all participants included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee

Tel: + 353-21-490 1901
Fax: + 353-21-490 1919

Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

Our ref: ECM 4 (c) 09/05/17

26th April 2017

Professor Stephen Byrne
Head of School of Pharmacy
University College Cork
Room UG06
Cavanagh Building
College Road
Cork

Re: Inappropriate prescribing in the older person – the voice of the community pharmacist.

Dear Professor Byrne

Approval is granted to carry out the above study at:

- Community Pharmacies in Munster.

Please note that should you wish to carry out this study in areas that do not come under the remit of CREC you may need to seek approval from other committees in the other areas.

The following documents have been approved:

- Cover Letter
- Application Form signed 3rd April 2017
- Participant Information Letter Version 1.0 dated April 2017
- Consent Form Version 1.0 dated April 2017
- Topic Guide Version 3.0
- Study Protocol Version 2.0
- Evidence of Insurance.

We note the co-investigators involved in the study will be:

- Professor Denis O'Mahony, Professor Patricia Kearney, Department of Epidemiology, Dr Laura Sahm, Senior Lecturer and Christina Raae-Hansen.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospital

Interview topic guide used for the qualitative interviews with community pharmacists in Chapter 5.

Part 2 - Interview questions

1) What do you understand by the term "inappropriate prescribing"? (example, no indication, risk of side-effects)
2) How significant a problem is inappropriate prescribing in the older people? (often/rare in older, multiple meds)
3) What do you think contributes to inappropriate prescribing for older people? (time, hospital transition)
4) What do you understand by the term 'medication review'?
5) We are not expecting pharmacists to conduct medication reviews, but if you experience with it, what kind of review have you then performed? (sources, discussion with pts/GP/carer)
6) Think back to a situation where you noticed inappropriate prescribing (wrong drug, side effects, interaction) in one of your older patients. What was your next step? (contact GP/patient) What was the outcome?
7) How do you think medication reviews would benefit your older costumers? (health, adherence, QoL)
8) How easy do you find it to perform medication reviews in your daily practice (community pharmacy)? (time, information source, knowledge)
9) What are the challenges in conducting medication reviews as part of your daily practice? (time, staff, GP, pts)
10) What changes could be made to make it easier for you to do medication reviews as part of a routine practice? (education, information, collaboration)
11) How confident would you say you are to suggest to stop a medication to a patient/carer or relative/GP? (very/not, reasons for that)
12) How easy do you find the communication with the patient/carer or GP/hospital about stopping a medication?
13) How would you describe your role as a pharmacist in ensuring appropriate patient care? (give information, recommend changes to GP/patient/carer, adherence)
14) Where do you feel the overall responsibility for medicines management lies? (GP, hospital, patient)
15) In what way could you support the person (based on question 16) in medicines management?
16) Do you think that the pharmacist is the appropriate individual to identify inappropriate prescribing and suggest stopping medications?

17) How can we involve the community pharmacist more in suggesting changes to the GPs such as stopping medications that no longer beneficial to the patient? (communication, structured process, education)
18) How can we involve the patient more in their medical treatment and to follow medication changes such as stopping a medication?
19) What type of information or training (in terms of content) would you like to get about stopping inappropriate medicines in older people? (dosing, e.g. in renal impairment, age-related changes, co-morbidities)
20) How would you like to receive the information to be used when reviewing older people's medications and suggesting changes to their GPs? (apps/booklets/algorithms/online tutorial)
21) What do you know about prescribing guidelines and tools? (useful in your practice and how?)
22) Can you propose one or more essential things that you think would address inappropriate prescribing in older people? (barriers and facilitators)
23) Is there anything else you would like to add?

Part 3 - Demographics

- Gender:
- Can I ask you how old you are?
- How many years have you worked as a community pharmacist? Full- time and/or part time?
- Pharmacist grade (supervising, manager, intern, support):
- Have you previously worked in a hospital?
- When did you complete your undergraduate and/or postgraduate training?
- Is your pharmacy serving a nursing home?
- How many pharmacists work with you on a regular basis?
- Do you have pharmacy technician(s) working with you?

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Fax: + 353-21-490 1919

Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

Our ref: ECM 4 (c) 09/05/17 & ECM 3 (rrrr) 03/07/18

6th July 2018

Professor Stephen Byrne
Head of School of Pharmacy
University College Cork
Room UG06
Cavanagh Building
College Road
Cork

Re: Inappropriate prescribing in the older person – the voice of the community pharmacist.

Dear Professor Byrne

The Chairman approved the following:

- Cover Letter dated 6th June 2018 (received 18th June 2018)
- Application Form signed 6th June 2018
- Participant Information Letter for Pharmacists Version 2.0 dated 6th June 2018
- Participant Information Letter for General Practitioners Version 2.0 dated 6th June 2018
- Consent Form Version 2.0 dated 6th June 2018
- Focus Group Topic Guide Version 1.0 dated 6th June 2018
- Roles and Responsibilities Version 1.0 dated 6thJune 2018
- Study Protocol Version 3.0 dated 6th June 2018.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospital

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

UCC

Tel: + 353-21-490 1901
Fax: + 353-21-490 1919

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Clinical Research Ethics Committee

Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

Our ref: ECM 4 (c) 09/05/17 & ECM 3 (uu) 04/09/18

31st August 2018

Professor Stephen Byrne
Head of School of Pharmacy
University College Cork
Room UG06
Cavanagh Building
College Road
Cork

Re: Inappropriate prescribing in the older person – the voice of the community pharmacist.

Dear Professor Byrne

The Chairman approved the following:

- Cover Letter dated received 8th August 2018
- Amendment Application Form signed 3rd August 2018
- Participant Information Letter for General Practitioners Version 3.0 dated August 2018.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospital

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authonsed by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Topic guide – Interview study - version 4.0

Study title: "Deprescribing in the older person - the views of community pharmacists and general practitioners"

Part 1 - Description of the study

Thank you for agreeing to participate in this interview. Just before we start, I want to make sure that you are happy for this interview to be recorded? I also want to stress that everything you say in this interview is completely confidential, and I will anonymize all transcripts of this interview, and your name or the name of others will not appear on any documents or recordings. If you want to withdraw from this study, you can stop this interview at any time.

These interviews with pharmacists are part of my PhD which is looking at how we can prevent inappropriate prescribing in older people (65 years and older) and how we can involve the community pharmacists more in the process of deprescribing. We hope to use these interviews to get an insight into your views about the potential role of the community pharmacist in deprescribing inappropriate medications and what future changes that could be made to involve pharmacists more.

There are no right or no wrong answers to these questions, we just want your views and opinions and maybe some of your experiences, so just give as much detail as you can and would like to. The interview will probably last about 15-20 minutes.

I will let you do most of the talking and only ask you questions.

Does all that sound okay? Do you have any questions before we begin?

Deprescribing

We know from previous studies that a major difficulty for GPs is that many prescriptions are initiated by many different prescribers but repeat prescribing occurs mainly in the GP practice. Optimising drug regimens is a key component of care, especially in the multimorbid older patients using many medications daily and to achieve this regular drug reviews are required.

Deprescribing is the systematic process of identifying and reducing and/or discontinuing drugs in patients for which existing and potential harms outweigh the benefits in a safe and rational manner. The deprescribing process includes some or all of the following elements: a review of current medications, identification of medications to be reduced or discontinued, a discontinuation regimen, involvement of patients, and a review with follow-up.

Close collaboration between pharmacists and doctors seems to be the most sensible approach for this patient group and we wish to explore your views and opinions about how we can improve collaboration and encourage more deprescribing in primary care.

1) How beneficial do you think it is for older patients to have inappropriate medicines deprescribed?
2) What do you think are the potential benefits of deprescribing for multimorbid patients exposed to polypharmacy?
3) How would you describe your current role in deprescribing?
4) What are your current responsibilities in deprescribing?
5) How would you describe the current role of the community pharmacist/GP in deprescribing?
6) Can you describe the responsibilities of the GP/community pharmacist in deprescribing?
7) How well-defined do you think the roles are in deprescribing? Are there any overlaps?
8) How well-described you think it is of who does what and when in deprescribing?
9) How would more well-defined roles of the GP and of the pharmacist help you in your daily work?
10) How often do you interact with a GP/pharmacist?
11) What is a typical interaction you have with the GP/pharmacist about?
12) How often do you interact with a GP/pharmacist about deprescribing?
13) Can you describe a situation where you suggested/decided to deprescribe and tell me what you did?
14) How would you describe your current interaction with community pharmacists/GPs about deprescribing?
15) How do you find your communication with the GP/pharmacist about deprescribing?
16) What are your expectations to the GP/pharmacist when you interact with them about deprescribing?
17) So, if you were to sit down with the GP/pharmacist to work on deprescribing for a patient, what do you think your responsibilities would be in that collaboration?
18) In the collaboration about deprescribing what would you expect the GP/pharmacist to do?
19) What would you suggest to improve your collaboration with community pharmacists/GPs about deprescribing?
20) How would more collaboration with community pharmacists/GPs help you in your daily work?
21) What are the challenges to get more collaboration?
22) How important is it that we involve the patient in the deprescribing process?
23) What role do you think the patient has in deprescribing?
24) How do you find your contact with patients about deprescribing?
25) How can you as a GP/pharmacist involve the patient in deprescribing?
26) Say in an ideal world where we would all have time to review medicines in what way do you think a pharmacist could best support you? /How could you as a pharmacist best support the GP?
27) What information would you like to get from the GP/pharmacists in order for you to suggest deprescribing/deprescribe?
28) What do you think would be the best way for you to deliver (community pharmacist) or receive (GP) deprescribing recommendations to the GP/from the community pharmacist?
29) In the years to come what role do you think the community pharmacist could have in deprescribing? What would you like to see?
30) What are the challenges, as you see it, to get more pharmacist involvement in the deprescribing process?
31) What are the key factors that will facilitate more deprescribing in primary care?
32) What in your view is the ideal way of introducing more deprescribing?
33) What can we do to be more proactive about deprescribing and reducing inappropriate medicines?
34) How realistic do you think it is to involve pharmacists more in deprescribing in primary care?
35) Can you propose one or more essential things that you think would address deprescribing medicines in older people? (barriers and facilitators)
36) Is there anything else you would like to add or to expand further on?

- Gender:
- Can I ask you how old you are?
- How many years have you worked as a community pharmacist/GP?

Thank you for your time