Polypharmacy and potentially inappropriate prescribing in community dwelling people living with Alzheimer's dementia.

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Declaration

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Abstract

Older adults are the biggest consumers of medications worldwide[1], however they are underrepresented in the clinical literature. This is true also for people living with dementia who are often excluded from clinical trials of the medications frequently prescribed[2]. People living with dementia have higher levels of comorbidity than those without and significant polypharmacy associated with these co – morbidities [3,4]. They are particularly vulnerable to both the cognitive and non cognitive side effects of medication and require unique consideration when prescribing[5]. Chapter one of this thesis reviews the unique pharmacokinetics and pharmacodynamics associated with ageing and Dementia.

There are a number of existing prescribing tools available to guide prescribing in older people. Chapter two describes my systematic review exploring the existing prescribing tools for older people and their applicability for use in those living with dementia. This analysis was guided by an expert consensus group. We found significant heterogeneity among the prescribing tools included. There are few tools that are designed with consideration for people living with dementia. We support further research and the design of a single internationally accepted prescribing tool for older people to include specific considerations for people with dementia across the spectrum of the disease.

Following the extensive literature review, systematic review and expert opinion consensus I investigated prescribing practices in a cohort of people with mild to moderate Alzheimer's disease (AD). The cohort investigated were participants in a large,

investigator led, international randomised control trial 'Nilvadapine in mild to moderate Alzheimer disease' (NILVAD)[6,7] . This study and study population are described in detail in Chapter 3.

In Chapter 4, I describe analysis of this cohort of people with mild to moderate AD for potentially inappropriate prescriptions (PIM). Using the STOPP/START [8] prescribing tool I examined the prevalence and factors associated with ongoing PIM use, in addition to the effects of this at 18 months of PIM use. Overall, over half (55.8%; 250/448) of participants were using a potentially inappropriate medication. Of those prescribed a PIM over half were prescribed more than one PIM. The likelihood of being prescribed a PIM increased with total medication burden and was associated with both adverse events and serious adverse events, although not with worsening cognitive decline or dementia severity. PIM use was associated with unscheduled GP visits and hospitalisation.

In Chapter 5, I describe further analysis investigating a number medications associated with increased risk of adverse events when used in people living with dementia but frequently prescribed. Benzodiazepines (BDZR) were the most frequently prescribed PIM in our cohort. We examined benzodiazepine use for cognitive and non cognitive side effects in the group. There was no significant difference detected on cognitive scores at 18 month follow up for BDZR users compared to non users. There was however increased incidence of delirium and falls in BDZR users. Antipsychotics were also identified as a frequently prescribed PIM, they were also identified by the experts in the systematic review as requiring significant consideration when prescribing in dementia. We examined their use in our cohort. Ongoing use of antipsychotic medication was associated with greater cognitive decline at 12 and 18 months assessed by Alzheimer

Disease Assessment Scale - Cognitive Subsection (ADAS-Cog) score. There was also greater progression of AD on Clinical Dementia Rating – sum of boxes (CDR-sb)and Disability Assessment for Dementia (DAD) at 12 and 18 months.

Cholinergic burden is an important consideration in people with AD [9]. In chapter 6 we examine this in our cohort of people with mild to moderate AD. Over one quarter of participants were prescribed a medication with potential or definite anticholinergic properties at baseline (27.9%, n = 142). Higher ACB scores were significantly associated with greater Disability Assessment for Dementia (DAD) scores. The DAD score reflects functional ability, a relevant marker when considering adverse effects of medication.

Finally, I examined the use of statins in our cohort. Statins are one of the most frequently prescribed medications worldwide[10] and they were frequently prescribed in our cohort. The existing literature surrounding statin use in people living with AD is conflicting [11-13] both in their role in prevention but also their use in those with established cognitive impairment or dementia. This is further complicated by the FDA blackbox warning on temporary cognitive impairment associated with statins [14]. In our cohort the ongoing use of statins was not associated with cognitive decline or worsening of dementia. Furthermore, use of these medications was not associated with an increased risk of adverse events, serious adverse events or unscheduled healthcare utilisation.

Chapter 7, the final chapter describes conclusions, limitations, implications for future research and my own reflections on how this work will impact my work as a practicing Geriatrician.

Aims

- Review the existing literature surrounding medication management in people living with Alzheimer's dementia.
- Review the existing international prescribing tools for older people and their suitability for use in people living with Dementia.
- Investigate the clinical impact of potentially inappropriate prescriptions on people living with AD in a community dwelling setting with particular focus on the impact of inappropriate prescriptions on cognitive function, adverse events and serious adverse events in this group.
- Investigate the effect of statin use on cognitive function in people with dementia, an area where existing literature is conflicting.
- Investigate the clinical effects of particular high risk medications on people living with dementia including antipsychotics, benzodiazepines and medications with a high anticholinergic burden.

Hypothesis

- Older adults living with Alzheimer's Disease dementia are more vulnerable to the adverse effects of medication than older adults without dementia, particularly the effect of potentially inappropriate medications.
- The existing prescribing tools for older people are not tailored specifically for people with dementia and further consideration is required when prescribing for this group.

Research Outputs

Murphy C, Dyer A , Lawlor B , Kennelly S. " Potentially Inappropriate Medications (PIM) use in mild to moderate Alzheimer disease: prevalence, predictors and consequences"

- Murphy C, Dyer AH, Lawlor B, Kennelly SP; NILVAD Study Group. Potentially inappropriate medication use in older adults with mild-moderate Alzheimer's disease: prevalence and associations with adverse events. Age Ageing. 2020 Jul 1;49(4):580-587. doi: 10.1093/ageing/afaa067. PMID: 32474584.
- Oral presentation Irish Gerontological Society 67th Annual and scientific meeting 2019.
- Poster Presentation European Geriatric Medicine Society 2020

Murphy C, Dyer A , Lawlor B , Kennelly S. What is the Impact of Ongoing Statin Use on Cognitive Decline and Dementia Progression in Older Adults with Mild-Moderate Alzheimer's Disease?

- Murphy C, Dyer AH, Lawlor B, Kennelly SP; NILVAD study group. What is the impact of ongoing statin use on cognitive decline and dementia progression in older adults with mild-moderate Alzheimer disease? PLoS One. 2023 May 11;18(5):e0285529. doi: 10.1371/journal.pone.0285529. PMID: 37167234; PMCID: PMC10174559.

- Poster presentation at European Union Geriatric Medicine Society

2020 E Congress

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Associated Research output with co-authorship

Dyer AH, Murphy C, Segurado R, et al. Is Ongoing Anticholinergic Burden Associated with Greater Cognitive Decline & Dementia Severity in Mild to Moderate Alzheimer Disease ? The Journals of gerontology. Series A, Biological Sciences and Medical Sciences. 2019 Oct DOI: 10.1093/Gerona/glz244.

- Published October 2019 The journals of gerontology, Series A - PMID: 31613323
- Poster presentation Irish Gerontological Society 67th Annual and scientific meeting 2019

Dyer AH, Murphy C, Lawlor et al. Cognitive Outcomes of Long-Term Benzodiazepine and Related Drug (BDZR) Use in People Living with mild to Moderate Alzheimer Disease: Results from NILVAD. JAMDA 2020 Feb; 21 (2):194-200.

- Published JAMDA February 2020 - PMID: 31604674.
- Poster presentation Irish Gerontological Society 67th Annual and scientific meeting 2019.

Dyer AH, Murphy C, Lawlor B, Kennelly SP, For The Nilvad Study Group. 'Long-term antipsychotic use and cognitive decline in community-dwelling older adults with mild-moderate Alzheimer disease: Data from NILVAD' Int J Geriatr Psychiatry. 2021 Nov;36(11):1708-1721. doi: 10.1002/gps.5591. Epub 2021 Jul 1.

- Published 2021 International Journal Geriatric Psychiatry PMID: 34173272.

Abbreviations

AD	Alzheimer's Disease
ADAS-Cog	Alzheimer Disease Assessment Scale - Cognitive Subsection
ADCS-CGIC	Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change
ADR	Adverse Drug Reaction
ADL	Activities of daily living
AE	Adverse Event
ATC	Anatomic Therapeutic Classification
BBB	Blood Brian Barrier
BDZR and related drugs	Benzodiazepines
BMI	Body Mass Index
CDR-sb	Clinical Dementia Rating – sum of boxes
CI	Confidence interval
CSF	Cerebrospinal Fluid
CNS	Central Nervous system
DAD	Disability Assessment for Dementia
FDA	US Food and Drug Administration
GP	General Practitioner
ICD – 10	International Classification of Diseases
IMP	Investigational medicinal product
IQR	Interquartile range
LFTs	Liver Function Tests

PPI	Proton Pump Inhibitor
PIM	Potentially Inappropriate Medication
PIP	Potentially Inappropriate prescription
RCT	Randomised Control Trial
SAE	Serious Adverse Event
SD	Standard deviation
sMMSE	Standardised Mini-Mental State Examination
SSRI	Selective Serotonin reuptake Inhibitors
N	Total number
NSAID	Non Steroid Anti-inflammatory drugs
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's disease Criteria
NP	Neuropsychiatric inventory
OR	Odds ratio
WHO	World Health Organisation

Chapter 1

Pharmacokinetics and pharmacodynamics in people living with dementia

1:1 Background

There has been a significant increase in life expectancy globally in recent years with the number of older adults expected to have doubled by 2050. Importantly this increased life expectancy is also associated with improved disability free survival and quality of life , a marker of successful ageing [15]. However despite stable or declining disability levels there is an increased incidence of chronic disease, multi morbidity and increased healthcare utilisation in this population [16]. Increased incidence of chronic disease and multi-morbidity is associated with higher levels of polypharmacy among older adults [17]. This is true particularly for older adults with a diagnosis of dementia, a cohort increasing in number associated with the increase in longevity.

Dementia is an umbrella term used to describe the cognitive and functional decline associated with several neurodegenerative brain conditions. These conditions are associated with progressive loss of brain cells resulting in a clinical presentation characterised by disturbance of multiple higher cortical functions leading to impairment in daily function without the clouding of consciousness [18,19]. This encompasses a variety of aetiological subtypes with variable neuropathological and clinical characteristics the most common being Alzheimer's disease (AD) dementia accounting for at least 70% of dementia [20]. Other subtypes of dementia include but are not limited to Vascular dementia, Lewy Body dementia, Fronto- temporal dementia, Parkinson's Disease dementia and Mixed dementia. Ageing is the primary risk factor for developing dementia, incidence increases with age and is 1% per year. The prevalence of dementia at age 65years is 5% and increases to 40% at 90 years of age [21]. Dementia is one of the leading causes of disability and dependency worldwide affecting not only people living

with dementia but also families and caregivers[22]. Older adults both with and without dementia often have high levels of comorbidity. Higher levels of comorbidity are associated with greater cognitive decline in people with AD [23,24]. Multi-morbidity is associated with increased number of medications. Furthermore a diagnosis of dementia is an independent risk factor for polypharmacy with one study demonstrating an 11% increase in total medication use one year after diagnosis of AD [25].

Older people require consideration in relation to prescribing practices not only in relation to pharmacokinetics and pharmacodynamics which are altered in this group but also regarding adverse effects of medication and polypharmacy. Furthermore people living with dementia require further consideration due to increased incidence of adverse events[3,5] . This group have an increased cognitive vulnerability to side effects and are at increased risk of poor outcomes following hospitalisation. There may be challenges in drug delivery, variability in the spectrum of disease and changing goals of care for an individual. Despite being the biggest consumers of medications older adults are underrepresented in the clinical trials literature[2]. Historically age limits excluded this cohort from inclusion in clinical trials. Whilst there has been a significant effort and trend towards including older adults in clinical research over recent years the disease based exclusion criteria that are often present will disproportionally effect older adults [2]. This is true particularly for older adults living with dementia [26]. A diagnosis of dementia poses many challenges in clinical research including but not limited to; difficulties with consent, communication, retention, outcome measurement and ethical considerations. As a result many of our prescribing practices in this cohort are not based in evidence which poses questions of the efficacy and safety of frequently used medications in this group.

1:2 Pharmacokinetics

Pharmacokinetic and pharmacodynamic changes occur in ageing, which can effect drug absorption, distribution , metabolism and elimination and warrants consideration in this context . Physiological changes in the gastrointestinal tract include slower transit times and altered pH levels which may effect the bioavailability of orally delivered medication, however in practice few studies have shown significant effects of ageing on drug absorption [(27)]. The distribution of medication however has been shown to be effected by ageing processes primarily related to changes in body composition [(28)]. These changes include increased body fat and decreased total body water, plasma volume and extracellular body fluid [(29)]. The resultant effect on drug distribution include increased serum concentrations of hydrophilic drugs such as Gentamycin and Digoxin due to smaller volumes of distribution. Lipophilic medications such as diazepam and lignocaine demonstrate higher volumes of distribution prolonging the half life of such medications in older cohorts [(28)]. Drug metabolism is primarily through hepatic clearance along with intestinal metabolism. Changes associated with age include reduced hepatic blood flow and liver volume which ultimately effect hepatic drug clearance. Renal drug elimination is effected by reduced glomerular filtration rates in older adults which is particularly important when considering drugs with renal clearance or narrow therapeutic indices.

The literature examining pharmacokinetic changes in people living with dementia is sparse and similar to the evidence in ageing, the clinical effects have not been conclusively demonstrated. However, many of the physiological effects are the result of increased frailty and changes in body composition including weight loss, higher total

body fat, lower levels of albumin and reduced renal function, all of which have higher incidence in older adults with dementia than those without. Furthermore, co-morbidity and the use of concomitant medication influences pharmacokinetics and pharmacodynamics , which is more prevalent in older adults with dementia than those without.

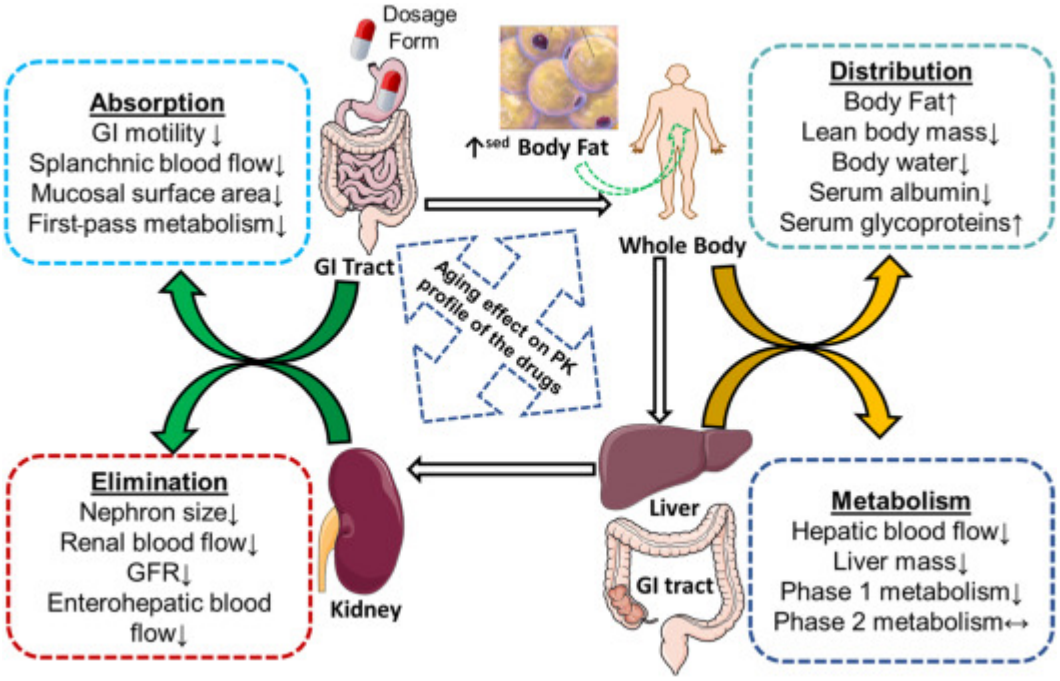

Figure 1 : Impact of ageing on the pharmacokinetics (PK) and pharmacodynamics of the drugs.[30]

1:3 Pharmacodynamics

Similarly to the pharmacokinetic changes in people with dementia, the pharmacodynamic changes are primarily related to ageing and frailty. This area however is difficult to research due to the individual drug dependent responses and as a result the literature on pharmacodynamics in ageing is limited. [28]

The blood brain barrier (BBB) is a cellular barrier that ensures proper neuronal function by controlling the microenvironment of the CNS [31]. Disruption in the BBB has been demonstrated as a result of normal ageing [32 , however it is also evident in many neurological Conditions. Increased permeability in people with dementia compared to those without [33] may account for some of the increased CNS adverse drug reactions of medications in older people with Dementia including delirium. [34]

A loss of cholinergic function has been demonstrated in people living with Alzheimer's Disease dementia [35] . It is unsurprising that this group have an increased vulnerability to experience both peripheral and central adverse effects from exposure to anticholinergic medication. In addition to this we know that long term use of medications with a high anticholinergic burden is associated with a diagnosis of dementia as demonstrated by Richardson et al [36]. Between 20-50% of people with a diagnosis of dementia take at least one anti cholinergic medication [37] again highlighting challenges in prescribing for this group.

1:4 Polypharmacy and potentially inappropriate prescribing in people living with dementia.

The co-morbidity associated with a diagnosis dementia often requires multiple medications. It is estimated people living with a diagnosis of dementia take between 5-10 medications per day. [38]. An increased total number of medications is associated with an increased number of potentially inappropriate medications (PIM), however we must be mindful of the underprescribing of appropriate medications in this group. Total medication burden but more importantly the PIMs are associated with increased risk of adverse events, serious adverse events, increased costs and morbidity and mortality. A

serious adverse event includes an event resulting in death or risk of death, disability or required intervention to prevent disability or an event requiring hospitalisation. While figures vary due to the heterogeneity of adverse drug reaction definitions, it is estimated that approximately 10% of admissions to acute hospitals in those over 65years of age are related to adverse drug reactions [39] . Furthermore many of these reactions are preventable, estimated internationally between 19-28% of presentations [40] . We know that hospital admission for a person living with dementia is associated with poor outcomes including functional and cognitive decline [41], delirium and increased mortality. Rates of hospital admission increases towards end of life in a person living with dementia [42] , hospitalisation can be distressing for patients and caregivers, an outcome we aim to avoid where possible.

In addition to potentially inappropriate prescriptions and inappropriate omissions, a diagnosis of dementia also increases the risk of prescribing cascades. A prescribing cascade is where a side effect of a medication is misinterpreted as a new medical condition and results in further prescription which may be inappropriate for that person. An example is anti-cholinergic medication prescribed for urinary incontinence in a person prescribed a cholinesterase inhibitor [43]. Prescribing cascades increase the risk of polypharmacy and therefore adverse events and adverse outcomes in older people [44].

The importance of appropriate prescribing internationally has been recognised by the World Health Organisation (WHO) who have selected medication safety as the third Global Patient Safety Challenge 'Medication without harm'[45]. A key focus of this patient safety initiative includes reducing inappropriate prescribing internationally across all patient groups. This highlights the morbidity, mortality and financial burden of

inappropriate prescribing across all patient groups where older people with Dementia are particularly vulnerable.

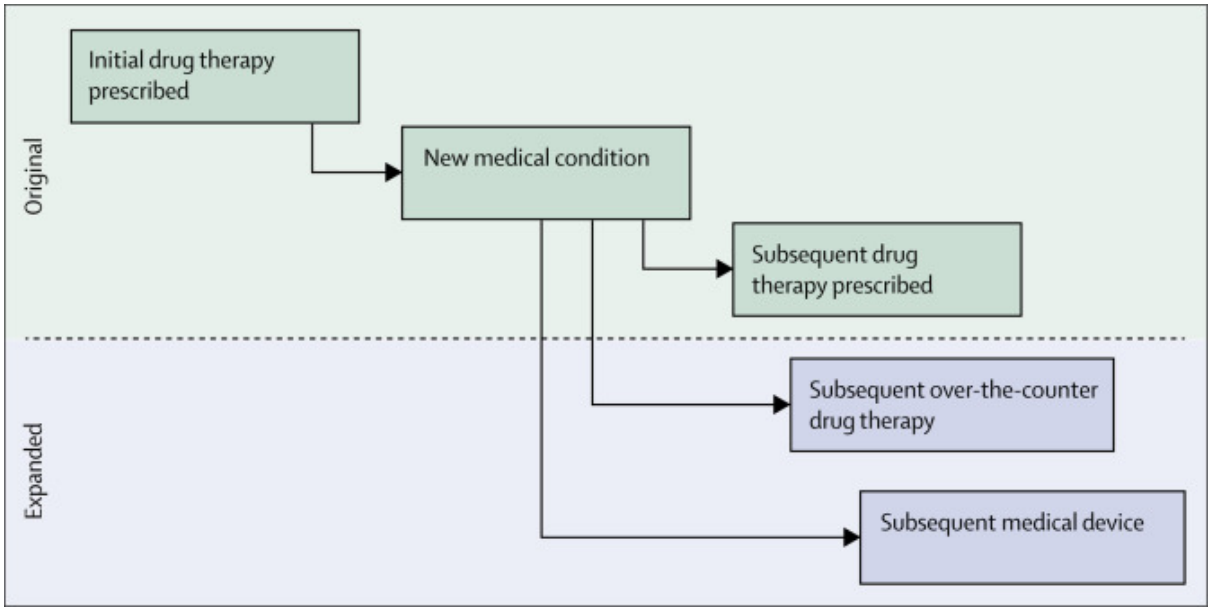

Figure 2 :Original prescribing cascade and expanded prescribing cascade. Adapted from Rochon and Gurwitz.[46]

1:5 Medication compliance

Another important consideration in prescribing for people with dementia is medication compliance. A diagnosis of dementia is associated with higher comorbidity and higher total medication use compared to those without. Complex medication regimes can reduce medication adherence in this group [37]. Reduced cognitive function and support can effect medication compliance [47]. Two systematic reviews investigating non-compliance with medication in dementia estimated the rate to be between 11% – 42% [48].

1:6 Challenges associated with the spectrum of disease in Dementia.

The spectrum of disease is a further important consideration when prescribing in dementia. The goals of care for an individual patient shift with disease progression. While preventative medications such as antihypertensives, statins and anticoagulation are likely to be entirely appropriate early in the disease course, with disease progression further considerations to therapy continuation arise. Some of these challenges include difficulty with drug delivery due to dysphagia, reduced tolerability to medications with increase adverse events and limited life expectancy requiring medication review. Prescribing for people living with dementia is complex and prescribing practices should reflect the variability in severity. Treatment goals requiring individualisation and frequent review.

1:7 Conclusion

A diagnosis of dementia is an independent risk factor of polypharmacy. As highlighted above medication management in this cohort is complex . Prescribing requires important considerations such as multimorbidity, increased incidence of adverse events , cognitive vulnerability to side effects and the poor outcomes associated with unscheduled medical care and hospitalisation. There are unique considerations also with the pharmacokinetics and pharmacodynamics of medications in this group, however despite these complexities people living with dementia are underrepresented in the clinical literature, often excluded from clinical trials. In this context many of our prescribing practices are without detailed evidence base in this cohort.

We aimed to evaluate prescribing practices in a cohort of older people living with AD. To investigate the current prescribing tools and to examine the effects of some high risk medications in this group.

Chapter 2

A systematic review of the existing prescribing tools for older people and their relevance and applicability to people living with dementia.

2:1 Background

Prescribing practices in older people have been internationally studied and with increased frequency over the past number of years. There have been a number of prescribing criteria or 'tools' developed to improve prescribing practices in this cohort. These can be explicit lists of drugs or diseases compiled through clinical evidence, expert opinion or consensus, implicit judgement based indicators which are patient centred or mixed explicit and implicit criteria. The most commonly used tools include the American BEERS criteria [49] and the European STOPP/START criteria [50] with many other countries adapting these criteria for their population or developing new criteria. There have been previous reviews examining the available prescribing tools for older people [51] and these tools have been used in people with dementia [52]. However to date the relevance and applicability of these tools for people with dementia is unexplored. We systematically reviewed the literature on existing prescribing tools for older people. We aimed to review the existing prescribing tools for older people with specific consideration to their use in people living with dementia guided by international expert consensus as to important considerations in design and implementation of the tool.

2:2 Methods

2:2:1 Search Strategy

Following an initial scoping literature search the systemic review was registered on PROSPERO (CRD42020202828). A systematic literature review was then performed searching databases MEDLINE, EMBASE, Web of Science core collection, The Cochrane database and Psychinfo to identify all prescribing tools for older people. The

search was performed from an earliest date of October 1980 to October 2020. Search terms used were ‘inappropriate prescribing’, ‘inappropriate prescriptions’, ‘potentially inappropriate’, ‘prescribing’, ‘prescriptions’ ‘older’, ‘elderly’, ‘over 65yrs’ , ‘tools’, ‘criteria’ or combinations thereof.

2:2:2 Inclusion/exclusion criteria

Only articles accessible in English were included. Articles describing prescribing tools for people aged 65 years or older were included (explicit, implicit or mixed tools). We included tools designed for community, residential or hospital settings. We did not include tools that were solely computer based tools, tools that were designed for specific drugs or diseases (other than dementia) or tools that were only education based tools and not designed for use in clinical practice. When compiling search terms we specifically did not include dementia as we wanted to analyse tools for all older people not only those for people with dementia. Initial search and screening was completed by the main author (CM) . Further detailed screening and analysis of the individual prescribing tools was completed in duplicate by two doctors specialising in geriatric medicine and any disputes were resolved by a consultant in geriatric medicine.

2:2:3 Selection of studies

A total of 4,416 articles were identified on the initial search. Articles that were not describing use of a prescribing tool for older people were excluded on initial screening, 251 articles were selected for further screening. We further excluded duplicates, articles that did not describe a new prescribing tool for older people and articles where the full article was not available in English , this resulted in 45 articles and prescribing tools

which were examined in detail. A further 8 prescribing tools were excluded as they did not meet the inclusion criteria, three articles were web based only and one was a teaching tool. One article was excluded as it was examining pain and inflammation only. Another article analysed only four medications so was also excluded. The final two were excluded as one was for use in palliative care only and the other was for a single research study only. Thirty seven articles were included in our analysis. See figure 3.

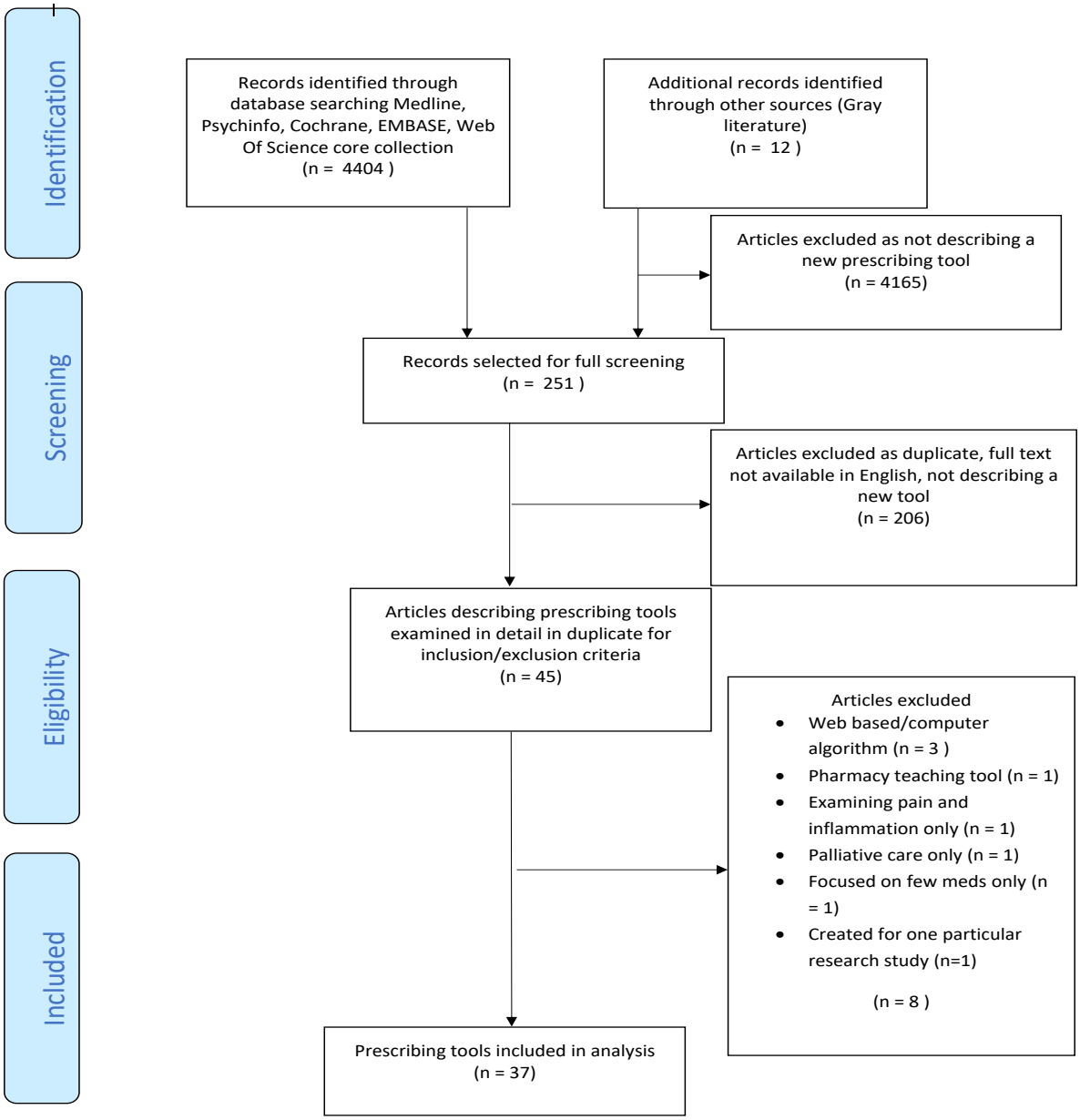

Figure 3 : PRISMA summary of literature search and selection.

2:2:4 Data Extraction

Data collected for analysis included descriptive study details including publication details, study funding, country of origin, aims/objectives , targeted patient cohort and setting, method of design including use of other existing tools and name of tool created. To further inform the data extraction process and ensure all relevant identifiers were examined in each tool we sought expert consensus from an international panel of geriatricians, psychiatrists of old age, physicians in general internal medicine and general practitioners. We sought representation and input from specialist professionals in geriatric medicine, psychiatry of later life, and primary care in Ireland and the United Kingdom. These practitioners were surveyed remotely as to what they feel were important considerations when considering a prescribing tool for people living with dementia. Based on the collected information each tool was analysed for its characteristics, inclusion of people with dementia in study design or recommendations, life expectancy mentioned in recommendations, deprescribing recommendations, initiation of medications for dementia and communication challenges in older people. We also reviewed whether consideration given to antipsychotic use in dementia or anticholinergic burden of medications. Finally we extracted data on type of specialist involved in the study particularly involvement of pharmacist, geriatrician or psychiatry of later life.

2:2:5 Quality and bias assessment

There a number of potential biases, primarily the clinical experience of the team involved in the design of the tool is likely to affect the outcome of the tool recommendations. The

environment and population that the tool is designed for will also effect the contents and design of the prescribing tool. The heterogeneity of the prescribing tools in design and function makes assessment of bias and quality difficult to objectively assess. No formal bias assessment was felt to be appropriate as a result of this.

2:3 Results

2:3:1 Expert consensus to guide data extraction

Eleven clinicians participated in the expert consensus , eight practicing in Ireland with three in the United Kingdom. 55% (n=6) were practicing geriatricians, 33% (n=4) in psychiatry of later life and 9% (n = 1) in general internal medicine. Just under half of clinicians 45.5% (n = 5) ranked themselves as somewhat familiar with prescribing tools in older people with 36% (n = 4) being very familiar. STOPP/START [50] was the most frequently used prescribing aid followed by BEERs criteria [30] , 36% (n = 4) reported not routinely using any prescribing aid in clinical practice. Most participants described themselves as being unsure if the existing prescribing tools were suitable for use in people living with dementia (63% n=7) with three feeling the current tools were applicable (27%) and one participant feeling they were not suitable for use in this cohort.

Seventy two percent of clinicians felt a prescribing tool for use specifically in people living with dementia would be useful with 27% of respondents being unsure. The consensus on whom may find such a prescribing aid beneficial was wide ranging to include clinicians specialising in the care of older people, pharmacists, general practitioners and clinicians not specialising in the care of older people. When asked if the

spectrum of dementia and variation in underlying pathology limits the development of a prescribing tool for this cohort almost half of clinicians (45% n = 5) felt it would, with 36% (n= 4) feeling it would not and two participants unsure. We asked participants to rank in order of importance what would be most important in a prescribing tool for people with dementia. This was done on ranking scale 1 – 5 , 1 being strongly disagree and 5 being strongly agree. The statement 'The inclusion of people with dementia in the initial design and pilot of the prescribing tool is important in creating a prescribing tool for people with dementia' was seen as the most important criteria. (See Table 1)

Table 1 – *Expert consensus on what would be most important consideration in a prescribing tool for people with dementia in descending order.*

Statement	**Ranked score**
The inclusion of people with dementia in the initial design and pilot of the prescribing tool is important in creating a prescribing tool for people with dementia	5.0
The inclusion of de-prescribing advice for potentially inappropriate medications specific to people living with dementia is important in the creation of a prescribing tool for people living with dementia.	4.90
Recommendations specific to pharmacological treatment for dementia such as cholinesterase inhibitors/memantine are important criteria in a prescribing tool for people living with dementia.	4.70
Consideration of an individuals anticipated life expectancy at the time of medication review is an important criteria when reviewing the utility of a prescribing tool for people living with dementia	4.09
The inclusion of medication recommendations specific to people living with dementia is important in a prescribing tool for older people	3.60
A prescribing tool to guide prescriptions for people living with dementia should include prescription advice reflecting the spectrum of dementia during an individuals life course	3.55

A prescribing tool designed specifically for people living with dementia should include guidelines on the avoidance of prescribing cascades in this group.	2.27

We also asked participants what they felt was the most important recommendation in a prescribing tool for people living with dementia. Avoidance of antipsychotics in people was considered the most important recommendation with minimising the use of medications with a high anticholinergic burden considered the second most important recommendation. (see table 2)

Table 2 – *Expert consensus on most important recommendations in a prescribing tool for people living with dementia in descending order.*

Statement on recommendation	**Score**
When prescribing for people living with dementia the use of antipsychotics should be avoided unless there is severe distress and the person is a risk to themselves or others	3.50
When prescribing for people with dementia it is important to minimise the use of medications with a high anticholinergic burden	2.64
When prescribing for people with dementia the use of benzodiazepines should be avoided for periods longer than 4 weeks.	2.45
Deprescribing of preventative medications such as statins is important in people living with advanced dementia	1.36

2:3:2 Prescribing tools analysis

The existing prescribing tools for use in older people are heterogeneous and varied. A mix of explicit, implicit and mixed tools were included in this study with explicit criteria accounting for the majority of prescribing tools studied. The development of most tools

was multidisciplinary with Geriatricians involved in 94.5% (n= 35), pharmacist involvement in 81% (n = 30) and psychiatry of later life involved in 24.3 % (n=9). Neurologists, general practitioners and physicians practicing in general internal medicine were also involved in the development of some tools. People living with dementia were included as a consideration in the design of 45.9 % (n=17) of studies included with 70.2 % (n=26) of the prescribing tools making recommendations for people living with dementia. Most tools, 81 % (n=30) mentioned the cholinergic burden of medications or anticholinergic side effects as cautions in their recommendations whereas fewer, 54 % (n=20) included guidance on the use of antipsychotics in people living with dementia. Just over a third (40.5 % n=15) of the prescribing tools mentioned life expectancy as a consideration in the prescribing tool and 27% (n=10) advised on the initiation of medications for dementia such as cholinesterase inhibitors.

Despite dementia being a common co-morbidity as one of the leading causes of death and disability in older adults [(53)], one third of existing prescribing tools for older people made no reference to people living with dementia in their recommendations. The Medication appropriateness tool for co morbid health conditions in dementia tool (MATCH D) [(54)] was identified by our study as the most comprehensive prescribing tool for people living with dementia. This consists of 67 statements that were agreed on by an expert panel using the Delphi method. It is an explicit tool advising on preventative medication, symptom management, disease progression, psychoactive medication, treatment goals, principles of medication use, side-effects and medication reviews. It is applicable for use in older people with dementia across the spectrum of the course of the disease giving clear guidelines in mild, moderate and advanced dementia. See Table 3 below for further details on each prescribing tool.

Table 3 – *Summary of existing prescribing tools for older people and their inclusion of people with dementia*

Prescribing Tool	Year	Aim of tool	Tool design	Dementia mentioned in tool design.	Dementia mentioned in recommendations	Specific deprescribing advice given	Initiating medication for dementia advised	Life expectancy included	Anticholinergic burden of medications discussed	Antipsychotic medication in dementia discussed	Pharmacist consulted	Geriatrician consulted	Psychiatry of later life consulted	Other
FORTA Japan	2020	To create a FORTA list relevant to JAPAN.	2 step Delphi process. 13 experts. Based on EURO forta Explicit tool	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	210 items in 24 indication groups.
Turkish Inappropriate use in the elderly (TIME criteria)	2020	To create an up to date screening tool originating from the two user friendly criterion sets: the STOPP/STARTv2 criteria and CRIME criteria.	STOPP/START V2 and CRIME criteria reviewed via Delphi consensus panel Explicit tool	No	Yes	Yes	Yes	Included in some criteria I.E statin and blood pressure not considered as a whole	Yes	Yes	Yes	Yes	Yes	153 TIME criteria, 112 TIME to STOP, 41 TIME – to – START.
The Systematic tool to reduce inappropriate prescribing (STRIP)	2017	Combine implicit tools POM/GIVE with explicit STOPP/START and shared decision making.	Review and development. Mixed Tool	No (patients condition to be considered including cognition)	No	Yes	Yes – Stopp/start	Yes	Yes – stop/start	Yes – Stopp/Start	Yes	Yes	No	5 step prescribing guide incorporating STOP/START
Prescribing optimisation method for improving prescribing in elderly patients receiving polypharmacy (POM)	2009	To evaluate the usefulness of the POM as a tool for improving appropriate prescribing of complex polypharmacy in the elderly	Created through application of case studies by general practitioners. Implicit Tool	Not specifically	Yes	Yes anticholinergics	No	Yes	Yes	Not specific to dementia	Yes	Yes	No	Six questions for prescribers covering - undertreatment, adherence, unnecessary medication, inappropriate, adverse effects, dose.
McLeod et al Canadian prescribing tool	1997	To develop a consensus-based list of inappropriate practices in pre-scribing for elderly people	Based on BEERS criteria, Drug interactions - quarterly expert review and the medical letter handbook of adverse drug	Yes	Yes – avoidance of long acting benzodiazepines in dementia. Avoidance of nylidrin, niacin or pentoxifylline to treat dementia.	Not specifically	No	No	Yes	Not specific to dementia	Yes	Yes	No	

Prescribing Tool	Year	Aim of tool	Tool design	Dementia mentioned in tool design.	Dementia mentioned in recommendations	Specific deprescribing advice given	Initiating medication for dementia advised	Life expectancy included	Anticholinergic burden of medications discussed	Antipsychotic medication in dementia discussed	Pharmacist consulted	Geriatrician consulted	Psychiatry of later life consulted	Other
			interactions. Modified Delphi. Explicit											
PRISCUS list (Holt et al)	2010	Design a PIMs in older people list suitable for the German population	Literature review, qualitative analysis and Delphi method. Explicit	Yes	Yes Neuroleptics advised, Pentoxifylline, naftidrofuryl, nicergoline, piracetam advised against Cognitive effects of anticholinergic highlighted.	No	Yes	No	Yes	Yes increased mortality	Yes	Yes	Yes	83 drugs in a total of 18 drug classes were rated as potentially inappropriate for elderly patients.
Korean elderly PIM list (Dong et al)	2010	To develop a list of potentially inappropriate drugs for the elderly in Korea using the Delphi technique.	Literature review – list compiled from BEERS, Canadian criteria and Zhan's criteria. Two round Delphi method. Explicit list.	Yes	Yes Pentoxifylline ineffective in dementia. Anticholinergics muscle relaxants , antispasmodics, barbiturates, methylphenidate , anticholinergics avoid in cognitive impairment.	Yes – concept of inappropriate prescribing throughout	No	No	yes	Not specifically related to dementia	Yes	Yes	Yes	57 PIM for the elderly Independent of diagnosis. 93 drugs were potentially inappropriate for the elderly with 29 diagnoses
BEERs Criteria	2012	Update the previous Beers Criteria analysing drug-related problems and adverse drug events (ADEs) in older adults.	Systematic review and Delphi Process. Explicit	Yes	Yes advised against Antipsychotics, anticholinergics, benzodiazepines, H2 receptor antagonists, Zolpidem in people with dementia.	Not specifically although concept includes	No	No – discusses end of life care but not life expectancy	Yes CNS side effects	Yes increased mortality	Yes	Yes	Yes	Fifty-three medications or classes divided into three categories: PIM ,classes to avoid in certain diseases a and medications to be used with caution.
PIM Taiwan (Chang et al)	2012	Develop PIM criteria speciifc to Taiwan.	Literature review, list based on BEERS, McLeod, Winiti Watjana, NORGEP, Laroche,Rancourt,	No	Yes Benzodiazepines and anti cholinergic medications advised against.	No	No	No	Yes	Not in relation to dementia	Yes	Yes	Yes	36 statements - 24 medication /medication classes to

Prescribing Tool	Year	Aim of tool	Tool design	Dementia mentioned in tool design.	Dementia mentioned in recommendations	Specific deprescribing advice given	Initiating medication for dementia advised	Life expectancy included	Anticholinergic burden of medications discussed	Antipsychotic medication in dementia discussed	Pharmacist consulted	Geriatrician consulted	Psychiatry of later life consulted	Other
			STOPP followed by Delphi process. Explicit Tool											be generally avoided in older adults, 12 chronic conditions with six medication classes that patients with these conditions should avoid
Austrian PIM list (Mann et al)	2012	To develop a consensus list of PIM for ge- riatric patients in Austria	Literature review, two round Delphi process. Explicit Tool	No	No Mentions cognitive side effects of some drugs listed i.e anticholinergics.	No	No	No	Yes	Cognitive side effects of antipsychotics mentioned not specifically in relation to dementia.	Yes	Yes	Yes	73 drugs to be avoided in older patients because of an unfavorable benefit/risk profile and/or un-proven effectiveness .Alternatives suggested.
OPTI-SCRIPT (Clyne et al)	2013	To apply the Medical Research Council framework to the development of an intervention to decrease PIP in Irish primary care.	Literature review, expert consensus, case study analysis with GPs Explicit tool.	No	No	Not specifically	No	No	Yes	No	Yes	Yes	No	
The EU 7 PIM list (Renom-Guiteras et al)	2015	To develop a European list of PIM for older people, to compare prescribing patterns across European countries and for clinical practice.	Literature review – list from German PRISCUS, French Laroche. American Beers, and Canadian McLeod. Two round Delphi process Explicit list.	Yes	Yes Antipsychotics in dementia Ginko Bolboa no efficacy.	Yes alternatives given	Yes	No	Yes	Yes	Yes	Yes	Yes	Experts reached a consensus that 282 chemical substances or drug classes from 34 therapeutic groups are PIM for

Prescribing Tool	Year	Aim of tool	Tool design	Dementia mentioned in tool design.	Dementia mentioned in recommendations	Specific deprescribing advice given	Initiating medication for dementia advised	Life expectancy included	Anticholinergic burden of medications discussed	Antipsychotic medication in dementia discussed	Pharmacist consulted	Geriatrician consulted	Psychiatry of later life consulted	Other
														older people; some PIM are restricted to a certain dose or duration of use.
The South Korean PIM list (Kim et al)	2015	The aims of this study were to generate a comprehensive potentially inappropriate medi-cation (PIM) list applicable for Korean elderly based on the international PIM lists	List compiled from BEERS, STOPP, PRISCUS. Two round Delphi process. Explicit list.	No	Yes TCAS, Benzodiazepines, Neuroleptics, antimuscarinics.	No	No	No	Not specifically	Yes	Yes	Yes	Yes	Twenty-six drug ingredients belonging to seven drug classes were selected for the PIM list.
STOPP/START version 2 (O'Mahony et al)	2015	To update version 1 of the 2008 STOPP/START criteria	Literature review and Delphi Process. Explicit list.	Yes	Yes Tricyclics, anticholinergics, neuroleptics and anti muscarinic's advised against.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	114 criteria, 80 STOPP criteria and 34 START criteria
Sri Lankin Modified STOPP/START (Samaranayake et al)	2019	we aimed to modify STOPP/START criteria (Version 2) to suit Sri Lanka.	Review of STOPP/START and Delphi process. Explicit List.	Not specifically but in stop/start recommendations	Tricyclics, anticholinergics, neuroleptics and anti muscarinic's advised against	Yes	No removed due to resource restriction,	No	Yes	Yes	Yes	Yes	No	The expert panel agreed on a list of 105 criteria, including 70STOPP and 35 START criteria, indicating an 8% reduction in criteria compared to the original version

Prescribing Tool	Year	Aim of tool	Tool design	Dementia mentioned in tool design.	Dementia mentioned in recommendations	Specific deprescribing advice given	Initiating medication for dementia advised	Life expectancy included	Anticholinergic burden of medications discussed	Antipsychotic medication in dementia discussed	Pharmacist consulted	Geriatrician consulted	Psychiatry of later life consulted	Other
Screening Tool for Older Persons' Appropriate Prescriptions for Japanese	2016	Revision of the 'Guidelines for medical treatment and its safety in the elderly 2005'	Systematic literature search and expert consensus. Explicit list.	Yes	Yes	Yes	No	Yes – life functions	Yes	Yes	Yes	Yes	Unclear	
STOPP Frail (Lavan et al)	2017	To validate STOPPFrail, a list of explicit criteria for potentially inappropriate medication (PIM) use in frail older adults with limited life expectancy	Literature review, three round Delphi process. Explicit list	Yes	Yes	Yes	No tool for advanced disease	Yes	Yes	Yes	Yes	Yes	Yes	27 criteria relating to medications that are potentially inappropriate in frail older patients with limited life expectancy
NORGEP – Norwegian general practice criteria. (Rogensted et al)	2009	To establish a clinically relevant list with explicit criteria for pharmacologically inappropriate prescriptions in general practice for elderly people ≥70 years.	Literature review encompassing criteria from BEERS. Three round Delphi Process. Explicit list	No	No	No	No	No	Anticholinergic effects ofindividual durgs mentioned not entire class	No	Yes	Yes	No	Clinically validated list of 36 explicit criteria for potentially inappropriate prescriptions to patients]70 years in general practice
GheOP3S - (Ghent Older People's Prescriptions community Pharmacy Screening Tool - Tommelein et al)	2013	To develop an explicit screening tool to detect relevant PIP that can be used in the typical community pharmacy practice, adapted to the European market.	Two-round RAND/UCLA (Research and Development/University of California, Los Angeles) process (includes literature review and 2 round Delphi process. Explicit.	No	Yes - Advises against Anticholinergics (e.g. antihistamines, antidepressants, antipsychotics and antispasmodics) with dementia or cognitive impairment	Some – Reassessment of antidepressants.	No – community pharmacy tool.	No – consciously excluded - community pharmacy setting.	Yes	Yes	Yes	Yes	No	83 criteria suitable for screening in community pharmacy setting.
Medication appropriateness tool for co morbid health conditions in dementia - MATCH D (Page et al)	2016	This study sought expert opinion to create a consensus list to define appropriate medication management of co-morbidities for people with dementia.	Delphi technique Explicit list	Yes	Yes	Yes	Yes	Yes	yes	yes	Yes	Yes	No	67 statements agreed on preventative medication, symptom management, disease progression, psy-

Prescribing Tool	Year	Aim of tool	Tool design	Dementia mentioned in tool design.	Dementia mentioned in recommendations	Specific deprescribing advice given	Initiating medication for dementia advised	Life expectancy included	Anticholinergic burden of medications discussed	Antipsychotic medication in dementia discussed	Pharmacist consulted	Geriatrician consulted	Psychiatry of later life consulted	Other
														choactive medication, treatment goals, principles of medication use, side-effects and medication reviews.
Norwegian general practice criteria in nursing home. NORGEP NH. Gunhild et al	2015	To develop a set of explicit criteria for pharmacologically inappropriate medication use in nursing homes.	Literature review, three round Delphi method. Explicit tool.	No	Yes Antipsychotics advised against for BPSD, Antidepresents limited effect for depression in dementia.	Yes	No	Yes	As side effects not class on there own	yes	Yes	Yes	No	34 explicit criteria for potentially inappropriate medication use in nursing homes
Fit fOR The Aged – FORTA (Khun thiel et al)	2014	To perform expert consensus validation of the FORTA (Fit fOR The Aged) List, a drug classification combining positive and negative labelling of drugs chronically prescribed to elderly patients.	Delphi process Explicit Tool	Yes	Yes Caution in antipsychotics in dementia. Antimuscarinics in dementia cautioned.	Not specifically but as a concept	Yes	No	Yes	Yes	No	Yes	Yes	Fit fOR The Aged – FORTA (Khun thiel et al)
Criteria to assess appropriate medication use among elderly complex patients. - CRIME criteria Graziano et al	2014	To produce recommendations to guide pharmacologic prescription in older complex patients with a limited life expectancy, functional and cognitive impairment, and geriatric syndromes, and providing physicians with a tool to improve the quality of prescribing, independent of setting and nationality.	Literature search and Delphi consensus. explicit	Yes – not one of key diseases examined but mentioned in glycaemic control	Yes	Yes	No	Yes	No	No mentioned in relation to BP not dementia.	No	Yes	No	CRI teria to assess appropriate medication use among elderly complex patients. - CRIME criteria Graziano et al
Prescribing indicators tool based on commonly occurring medications and	2012	To develop prescribing indicators for elderly (aged >65 years) Australians.	Literature review based on the most frequent medications	Yes	Yes – avoid anti cholinergic medications in Dementia, avoid	No	No	Yes	Yes	Not in relation to dementia	Yes	No	No	Prescribing indicators tool based on

Prescribing Tool	Year	Aim of tool	Tool design	Dementia mentioned in tool design.	Dementia mentioned in recommendations	Specific deprescribing advice given	Initiating medication for dementia advised	Life expectancy included	Anticholinergic burden of medications discussed	Antipsychotic medication in dementia discussed	Pharmacist consulted	Geriatrician consulted	Psychiatry of later life consulted	Other
medical conditions. Basger et al			prescribed to Australians and most common medical conditions among older Australians. Explicit list.		warfarin in unsupervised dementia.- falls.									commonly occurring medications and medical conditions. Basger et al
Concise consensus list of clinically important drug-disease interactions in older adults, (Linbald et al)	2006	To compile a list of clinically important drug-disease interactions in older adults, obtain the consensus of a multidisciplinary panel of geriatric health care professionals on these interactions	Literature review, 2 round Delphi process. Explicit list	Yes	Yes – evaluate for clinical importance in patients with dementia - Benzodiazepines Central nervous system stimulants (eg, - methylphenidate) older antiepileptics (eg, phenytoin, carbamazepine) Opioid analgesics Tricyclic antidepressant. Anticholinergic, Barbiturates	No – nature of tool	No	No	Yes	In relation to falls not dementia	Yes	Yes	No	No specific name - Concise consensus list of clinically important drug-disease interactions in older adults, (Linbald et al)
French list of potentially inappropriate medications. Laroche et al	2007	To establish a list of inappropriate medications for French elderly	Literature review criteria examined from BEERS, Canadian list of PIM , French practice criteria 2001, French medicine agency two round Delphi Process. Explicit list	No	Yes – avoid medication with anticholinergic	No – general concept	No	Yes – consideration to prognosis	Yes	Not specific to dementia	Yes	Yes	No	French list of potentially inappropriate medications. Laroche et al
Consensus recommendations for prescribing in palliation and dementia Holmes et al	2008	To develop consensus recommendations for appropriate prescribing for patients with advanced dementia in whom palliation of symptoms is the primary goal.	List compiled from chart review. Modified three round Delphi process. Explicit List.	Yes	Yes	Yes	No – severe dementia criteria deemed not appropriate.	Yes	No but a palliative care protocol	Yes mentions continuing in end of life care	No	Yes	No	Consensus reached on 170 drugs or drug classes
Criteria for high-risk medication use in Thai older patients (Winit-wajana et al)	2008	To develop explicit criteria for determining high-risk	Three round Delphi process.	No	No – Advice in effect of anticholinergics on cognition no dementia mentioned.	Not specifically	No	No	Yes	Not specifically for dementia	No	Yes	No	77 practice statements were

Prescribing Tool	Year	Aim of tool	Tool design	Dementia mentioned in tool design.	Dementia mentioned in recommendations	Specific deprescribing advice given	Initiating medication for dementia advised	Life expectancy included	Anticholinergic burden of medications discussed	Antipsychotic medication in dementia discussed	Pharmacist consulted	Geriatrician consulted	Psychiatry of later life consulted	Other
		medication use in Thai older patients.	Explicit criteria							mentioned in other contexts				agreed by the expert panel.
Reducing Inappropriate polypharmacy the process of deprescribing Scott et al	2015	Development of a deprescribing protocol	Systematic review and guideline proposal. Implicit criteria	Yes	Yes – antipsychotics in dementia, reconsider medications in severe dementia i.e bisphosphonates	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Clinical deprescribing protocol developed, aimed over 65 yrs but can be used in all prescriptions.
Assessing Care of Vulnerable Elders and quality indicators- ACOVE 3 (Shrank et al)	2007	To update quality indicators for medication use in elderly adults	Literature review, expert opinion. Explicit list.	Yes	No mentions cognitive SE of medications and risk of dementia with Benzodiaxapime however ACOVE also has Dementia document separate to medication section.	No - concept	No	No – ACOVE has separate guidelines to explore this.	Yes	Yes	Medical doctors with interest in pharmacology	Unclear	Unclear	24 consensus statements agreed.
Spanish list of potentially inappropriate drugs in the elderly (ES-PIA project) (Harmond et al)	2019	Create a Spanish potentially inappropriate drugs list which could be applicable in clinical practice.	Literature review and two round Delphi model. Explicit list	No	Yes – avoid anticholinergics in dementia. Clomipramine and imipramine should be avoided in people with dementia.	No	No – mentions caution of these drugs in cardiac disease	No	Yes	Yes	Yes	Yes	No	Consensus reached on 138 accepted statements.
Assess, Review, Minimize, Optimize, Reassess ARMOR tool (Haque et al)	2009	The ARMOR tool is an attempt to consolidate these recommendations into a functional and interactive tool.	Literature review, incorporates existing guidelines BEERS into Mixed prescribing Tool	Yes	Yes – reassess cognition after new medication	No	Yes	No – mentions function and quality of life but not expectancy	Yes (uses beers criteria)	Yes (uses Beers criteria)	Yes	Yes	No	
A geriatric medication algorithm (Newton et al)	1994	Create a geriatric medication evaluation algorithm designed to educate physicians in reducing PIM and to make this algorithm an effective and feasible tool in the primary care setting.	Tool design based on chart review and expert consensus. Mixed Tool	No	No	Yes – concept reducing/stopping drugs	No- 1994	No	Yes	No	No	Yes	No	Created algorithm and lists some drug/drug interactions, drugs with less toxic alternatives

Prescribing Tool	Year	Aim of tool	Tool design	Dementia mentioned in tool design.	Dementia mentioned in recommendations	Specific deprescribing advice given	Initiating medication for dementia advised	Life expectancy included	Anticholinergic burden of medications discussed	Antipsychotic medication in dementia discussed	Pharmacist consulted	Geriatrician consulted	Psychiatry of later life consulted	Other
														and drugs requiring dose reduction.
Potentially inappropriate prescriptions for older patients in long term care. (Rancourt et al)	2004	To assess the prevalence of PIPs in this long-term care setting using published explicit criteria adapted for this study.	Cross sectional chart review, literature review and Delphi Model. Explicit	No	No	No	No	Yes – Considered in relation to statins	No	No	Yes	Yes	No	111 Explicit criteria developed – primarily to review prescribing practices. Focuses on doses, duration and drug drug interaction
Zhan et al – no specific name.	2001	To determine the prevalence of PIM use in community-dwelling elderly, categorize inappropriate medication use according to explicit criteria.	Based on BEERS, choose 33 of them validated with two round Delphi technique. Explicit criteria	No	No	No	No	No	No – old criteria	No	Yes	Yes	No	33 explicit criteria created for purpose of review.
	1995	Create guidelines for physicians with recommendations to reduce polypharmacy.	To examine the hypothesises if physicians were asked to focus on patients with polypharmacy and given guidelines containing specific recommendations then a better outcome may occur. Implicit tool	Literature review, tool created by authors	No	Yes	No	No	Not specifically but drug disease interactions mentioned	Not specifically but drug disease interactions mentioned for consideration	Yes	Yes	No	5 implicit guidelines agreed.

2:4 Discussion

This systematic review is the first to explore the existing international prescribing tools for older people with specific consideration to their applicability to people living with dementia. We found significant heterogeneity among the prescribing tools included, this was due in part to variability in study designs and the international nature of the studies including authors identifying needs of their specific populations or aligning guidelines with existing health services and resources. The clinical experience of those designing the tools also leads to significant variability with a multidisciplinary team involving a broad range of specialists caring for older people likely to create a more balanced prescribing tool. The existing prescribing tools as a group are thoroughly designed , extensive and often easily applied in clinical practice however, despite dementia being a common co -morbidity as one of the leading causes of death and disability in older adults [53], one third of existing prescribing tools for older people made no reference to people living with dementia in their recommendations.

The expert consensus group identified appropriate use of antipsychotics in people with dementia as a key consideration when prescribing for this group. Whilst the use of an antipsychotic may be an appropriate medication in a person with dementia the literature is well established on the risks associated with their use in this group including increased risk of stroke, mortality, cognitive decline and falls, with non-pharmacological treatments recommended as first line treatment for behavioural and psychological symptoms of dementia. In studies investigating inappropriate prescribing in people with dementia the use of antipsychotics is frequently identified as an inappropriate prescription [55]. In our study just over half the prescribing tools made recommendations for the use of antipsychotics in people living with dementia highlighting an area for further development.

The anticholinergic burden of medications is an important consideration in older people, this is reflected in the prescribing tools reviewed with over 80% of tools mentioning this in the recommendations. The cognitive adverse effects of these drugs can be more pronounced in people with dementia with increased mortality [56] and furthermore can negate the effects of medications used in the treatment of dementia such as cholinesterase inhibitors [57]. In this context more detailed consideration may be required in people living with dementia when reviewing anticholinergic prescriptions compared to those without.

We know that people living with dementia require specific considerations for a number of reasons previously discussed including the increased risk of adverse events in this group. The variability in pathology, presentation and clinical stage of dementia creates challenges in applying many of the existing prescribing tools for older people and in creating a prescribing tool for this cohort as acknowledged by the expert group in our study. A change in prescribing attitude is required as the goals of care change during disease progression. In advanced dementia increased vulnerability to side effects, changes in appetite and difficulty in articulation of symptoms may make an individual at increased risk of prescribing cascades. Many of the existing instruments are reliant on reporting of side effects from an individual and/or their carer yet of the existing tools reviewed only three commented on communication difficulties that may be encountered in this group.

Prescribing for people with advanced dementia may require consideration of non-verbal instruments or tools for assessing side effects, pain and other clinical symptoms which effect prescriptions. Of the existing prescribing tools studied a small number were designed for use in people living with advanced dementia, nursing home populations or frailty and give clear and useful guidelines for clinical practice in these groups however most tools studied did not

mention life expectancy or quality of life as a consideration in their recommendations. Only one tool was identified for use across the spectrum of dementia The Australian MATCH – D criteria [54]. This was the most comprehensive prescribing tool identified in this study for the use in older people with dementia across the spectrum of the course of the disease giving clear guidelines in mild, moderate and advanced dementia.

People living with dementia whilst a unique cohort also meet the general prescribing needs of older people especially early in the disease presentation. The contents of the already existing extensive prescribing tools as outlined above also need to be considered in this group across the disease spectrum. From this study we identify that there is scope for an international consensus guideline on prescribing for older people with specific consideration given to people living with dementia throughout this tool to include the variety of disease presentation and changing goals of care throughout. An explicit tool of this nature to include the general prescribing principals for older people and specific guidelines for the spectrum of dementia would create consistency and give clear guidance to both specialists and non specialists in the context of dementia care without the need to navigate between the many existing tools.

There are some limitations to this review that require consideration. It is difficult to assess bias when assessing the selected prescribing tools. The use of an expert panel was an effort to reduce bias. The panel consisted of international experts but was small in number and future directions may include larger expert panels in an effort to eliminate bias and achieve a more representative consensus.

2:5 Conclusion

The existing prescribing tools for older people are for the most part extensive and detailed in their recommendations. There is however significant heterogeneity between the tools and when considering the specific needs of people living with dementia, a unique and particularly vulnerable group, there are few tools that are designed for this group. We support further research and the design of a single internationally accepted prescribing tool for older people to include specific considerations for people with dementia across the spectrum of the disease.

With detailed knowledge of the existing prescribing tools and their applicability to people living with dementia we aimed to further assess a cohort of participants with mild to moderate AD. Using a prescribing aid we assess for potentially inappropriate prescriptions in this cohort and the effects of this on cognitive function, adverse events, serious adverse events and hospitalisations. We also assessed some medications frequently described as high risk in older people and assess their effect in a cohort of patients with mild to moderate AD.

Chapter 3

The Nilvadapine Cohort and Methodology

3:1 Nilvadapine Participants

The cohort of participants used for this research are a group of participants from the investigator led clinical trial 'Nilvadapine in mild to moderate Alzheimer disease' (NILVAD)[6] . The NILVAD trial was an international placebo controlled, double blind randomised control trial that included twenty three academic centres in nine European countries. This phase three trial investigated the role of the dihydropyridine calcium channel blocker Nilvadapine in slowing cognitive decline in people with mild to moderate Alzheimer's disease dementia. Nilvadapine has been shown to reduce amyloid beta levels in the brain and therefore was the subject of study in Alzheimer's Disease. This trial was negative for its primary end point. The dataset of 511 participants with mild to moderate Alzheimer's disease dementia was the patient cohort studied for this research. [7,58]

Participants included in this trial met the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's disease Criteria (NINCDS-ADRDA) for a diagnosis of probable Alzheimer's disease, all participants had a Standardised Mini-Mental State Examination (SMMSE) score of ≥ 12 and ≤ 27. All participants were 50 years or older. They all had a caregiver available who was able to engage in the clinical trial. Participants were included if they were on Memantine or. Cholinesterase inhibitor but only if stable on the medications for 12 weeks or more.

3:2 Collected Data

The trial ran for an 82 week period. Participants were assessed at week 6,13,26,39,52,65 and 78. Detailed information was collected on each participant. Data collected included demographics, blood pressure monitoring, medical history, detailed medication history. Baseline serum was taken for all participants for haematological and biochemistry testing including: Full Blood Count, Sodium, Potassium, Urea, Creatinine, Liver Function Tests, Calcium. Cognitive scores were collected at week 0, 13, 52 and 78 and included Standardised Mini-Mental State Examination (SMMSE), The Alzheimer's Disease Assessment Scale – Cognitive Subscale 12(ADAS-Cog 12) and the Clinical Dementia Rating Scale sum of boxes (CDR-sb). Disability was assessed with the Disability Assessment for Dementia (DAD). All serious and adverse events were reported on by the participant and carer at follow up visits. A subset of participants also provided Cerebrospinal Fluid (CSF) and genetic data such as consenting to testing APOE4 allele carriers.

3:2:1 Assessment of Cognitive function

The co – primary outcome measurements were ADAS-Cog 12 and the CDR-sb. Disability associated with cognitive decline was measured using the Disability Assessment for Dementia (DAD). All outcomes were measured at baseline and weeks, 13, 52 and 78.

3:2:2 The Alzheimer's Disease Assessment Scale – Cognitive Subscale 12(ADAS-Cog 12)

The ADAS – Cog 12 is a test of cognitive function assessing a range of cognitive domains including memory, language and praxis. It includes 12 tasks across these domains comprising of subject completed tests and observer- based assessments [59]. The score ranges from 0-80.

The ADAS- Cog 12 has been demonstrated to be sensitive in mild to moderate AD and to discriminate between mild cognitive impairment (MCI) and AD [60]

3:2:3 The Clinical Dementia Rating Scale sum of boxes (CDR-sb)

The Clinical Dementia Rating Scale sum of boxes assesses dementia severity across six key cognitive domains with integrated cognitive and functional end points. Domains examined are memory, orientations, judgement and problem solving, community affairs, home and hobbies and personal care. It is scored from 0-18, with a higher score demonstrating greater dementia severity. [61]

3:2:4 The Disability Assessment for Dementia (DAD).

Participant's functional ability was assessed using The Disability Assessment for Dementia scale. This scale assesses ability to perform activities of daily living in individuals with cognitive impairment. This assesses various executive functions including initiation, planning, organisation and performance. The scale is validated in community dwelling adults. A 40 item scale is administered and scored 0-100, lower scores indicating greater disability associated with dementia.

There was no significant difference in the NILVAD trial between the placebo and treatment groups for baseline demographics or use of medication to treat Alzheimer disease. Vascular risk factors, hypertension, hypercholesterolemia and renal disease were similar in both groups, however some co- morbid conditions, particularly diabetes was more prevalent in the treatment group.

3:2:5 Reporting of Adverse Events

At each study visit during the NILVAD, trial participants (and caregivers as appropriate) were asked about recent adverse events or serious adverse events. This included any new symptoms or clinical incidents and specific questions regarding cognitive status and delirium. Participants were also asked regarding unscheduled GP visits and unscheduled hospital visits. This information was collected at weeks 0, 6, 13, 26, 39, 52, 65 and 78.

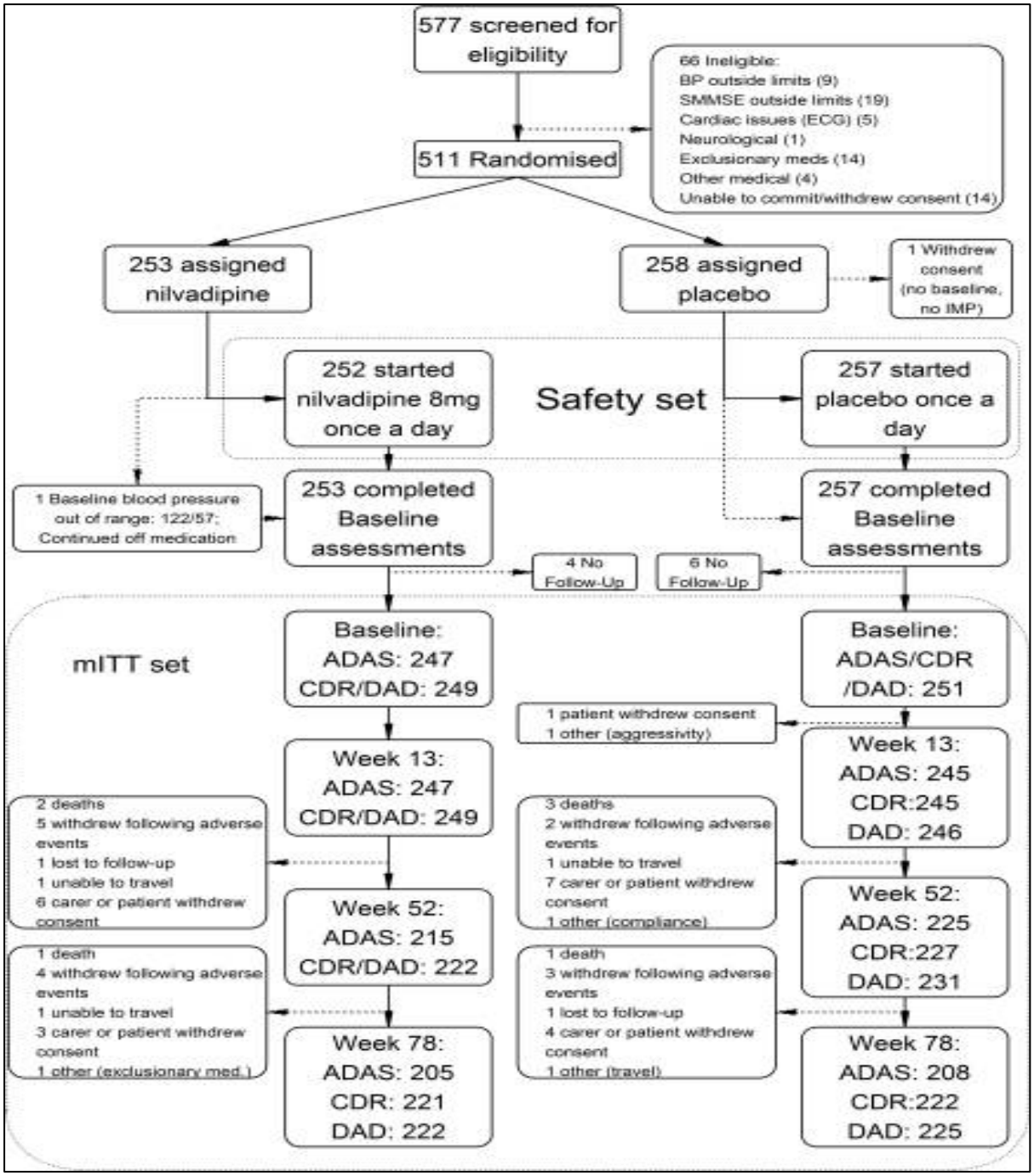

Figure 4 : Flowchart of the NILVAD study according to the consort guideline [6]

ADAS, Alzheimer's Disease Assessment Scale – Cognitive Subscale 12 Item; BP, blood pressure; CDR, clinical Dementia Rating Scale sum of boxes; DAD, disability Assessment for Dementia; ECG. Electrocardiogram; IMP investigational medicinal product; NILVAD, Nilvadapine in Alzheimer disease; SMMSE, standardised Mini mental State Examination.

3:3 Primary Results for NILVAD Trial

There was no treatment effect observed between the study group and the placebo group. There was no statistical difference detected in the primary end point ADAS-Cog 12 score or on the CDR-sb or DAD scores. There were no significant safety issues detected in the study drug. There was a median change in blood pressure of 5 mmHg over the 78 week study period but the reports of falls, dizziness or syncope were the same in both groups.

3:4 Methodology

For this study consent was sought from the lead principle investigator (Prof Brian Lawlor) and co-investigators of the NILVAD Consortium for access to the data from the Nilvadapine trial. The primary aim of this research was to review the prescribing practices and effects of inappropriate prescribing in people living with mild to moderate Alzheimer's Disease Dementia. It was acknowledged that the existing database had a significant amount of meticulously collected data under the conditions of a randomised control trial. This dataset was reviewed and re-organised for our purpose. A database with each participant was created to include all demographics, co-morbidities, adverse outcomes, serious adverse outcomes and prescriptions for that participant throughout the trial. All medications for each participant were assigned an Anatomical Therapeutic Chemical code (ATC code). This is an internationally accepted unique code assigned to a medicine according to mechanism of action and enabled organisation of the data. This ATC database is maintained by the World Health Organisation (WHO).

Chapter 4

Potentially Inappropriate Medication Usage in Older Adults with Mild-Moderate Alzheimer Disease: Prevalence and Associations with Adverse Events.

4:1 Background

A potentially inappropriate medication (PIM) is a medication prescribed without indication or where the net clinical benefit does not outweigh the risk associated with that medication and are associated with both increased adverse drug events (ADE) and adverse drug reactions (ADR) [62,63]. Older adults with dementia have a higher incidence of polypharmacy and PIM usage compared to those without dementia [64,65] which is consistent across both community dwelling adults and those resident in nursing homes [66]. The estimated prevalence varies between 14-74%, which varies based on the criteria used and population studied [67-69].
A body of literature has emerged demonstrating the association between polypharmacy , potentially inappropriate prescriptions and increased mortality in older adults [70]. Similarly, both PIMS and polypharmacy are associated with a reduced quality of life in patients with dementia living in nursing homes [71]. Furthermore, PIM usage has also been shown to increase the risk of malnutrition and depression in older adults amongst other adverse events [72,73]. As described in the literature PIM usage in older adults with dementia is associated with personal cost to the person with increased adverse events, hospitalisation and mortality, PIMs are also associated with significant financial cost [70]. Whilst the effects of PIM usage have been well studied in older adults in population based and longitudinal studies, the prevalence, associations and factors associated with ongoing PIMs in those with dementia, a group who may be particularly vulnerable to polypharmacy, is less well explored [74].

A recent study of PIM usage in community and nursing home adults with dementia across eight European countries [75] found a high prevalence of PIM usage in this population and higher risk of two or more PIMS in patients who were 80 + yrs, in residential care, high comorbidity and functionally impaired - overall a vulnerable group. However, whilst studies

such as these have reported a high prevalence of PIMs in those with a diagnosis of dementia, the impact of ongoing PIM usage are less well explored.

In the current study, we analysed data from NILVAD, a randomized controlled trial of the antihypertensive Nilvadapine in mild-to-moderate Alzheimer Disease which was negative for the primary endpoint of change in cognition/dementia severity at 18 months. As previously described there are a number of tools existing to aid with prescribing for older adults. We assessed the prevalence and risk factors associated with ongoing PIM use, in addition to the effects of PIM use at 18 months on those with mild-to-moderate AD using the STOPP/START prescribing tool.

4:2 Methods

4:2:1 Background and Setting

The current study reports analysis of data from the NILVAD trial (Clinicaltrials.gov NCT02017340; EudraCT number 2012-002764-27). NILVAD was a multicentre investigator-led phase-3 clinical trial which evaluated the potential efficacy of *Nilvadipine* in mild-to-moderate Alzheimer Disease (AD). For detailed information about the clinical trial in addition to the main results, readers are guided to the original trial protocol and main results paper [6,7]. Briefly, participants with mild-to-moderate AD were recruited from 23 academic centres in nine European countries (Ireland, United Kingdom, Italy, the Netherlands, France, Greece, Sweden, Germany and Hungary). Block randomization was used to assign patients to either Nilvadipine 8mg once daily or placebo for of 78 weeks. Ethical approval was granted from appropriate National Competent Authorities, Independent Ethics Committees and Institutional Review Boards for all study sites.

4:2:2 Participants

For detailed inclusion and exclusion criteria see the initial trial protocol [6,7]. In short, those who were included in the trial are as follows: community-dwelling, aged 50 years or older, diagnosed with AD as per the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's disease Criteria (NINCDS-ADRDA) with a Standardised Mini-Mental State Examination (sMMSE) score from 12-26. All participants were included in this analysis including 15.4% (N = 69/448) who were aged <65yrs. Baseline demographic information, AD associated risk factors and a comprehensive medical history were collected as part of the initial study visit.

4:2:3 Medication Records

A detailed medication history was obtained from patients and caregivers as part of the initial trial visit. Anatomical Therapeutic Classification (ATC) codes were applied to medication lists to ensure consistency. For the current study, the STOPP criteria v2.0
were applied to each patient's medication list taking into account their medical history and laboratory parameters. Medical history was available for the entire 18 month study duration . It was collected via interview with participants and caregivers in conjunction with medical records and all active medical conditions were coded using international classification diseases (ICD) codes. This validated tool provides criteria for inappropriate prescriptions in the STOPP criteria and inappropriate omissions in the STARTT criteria [50], As this current study is investigating inappropriate prescriptions not omissions the STOPP criteria only were used. STOPP criteria have demonstrated validity and utility in predicating adverse outcomes in older adults [76]. Short term prescriptions <4 weeks duration were excluded from the study. Given the extensive data available in this cohort it was possible to apply all STOPP criteria except the two criteria which required class of heart failure as this data was not available.

This was performed in duplicate by two physicians with a background in geriatric medicine with any disputes resolved by a consultant in geriatric medicine. A Potentially Inappropriate Medication (PIM) was defined as one meeting these criteria and a total number of PIMs per patient was calculated. A PIM vs one or more PIM was also computed for each participant. Further, we created an "appropriate medication" variable which represented the number of prescribed medications which did not meet the STOPP criteria (or total number of appropriate medications excluding PIMs. This was created in order to control for total medication burden and assess the effect of non-PIM medications on adverse events.

4:2:4 Adverse Events, Unscheduled GP Visits and Hospitalisations

Participants in the NILVAD trial attended follow up at weeks 0, 6, 13, 26, 39, 52, 65 and 78. At each visit, adverse events were reported and medication lists updated. Detailed description of adverse and serious adverse events can be found in the trial protocol [6] specifically adverse event included any untoward medical event that did not have a causal relationship to the treatment studied, it did not include adverse drug reactions. Adverse events and serious adverse events were based on clinical judgement. Further, participants/informants were asked at these visits whether the participant had experienced any unscheduled hospitalisations or GP visits. For the current analysis outcomes were selected based on the data available from the initial study protocol [6,7], we calculated the total number of adverse events, serious adverse events, unscheduled hospitalisations and unscheduled GP visits per participant. For each participant prescribed a PIM (as above), the adverse events log was reviewed and cross referenced to the prescribed PIMs in order to assess for a potential/definite link between the adverse event and a prescribed PIM. This was performed in duplicate by the physicians (as above). Adverse event-PIM links were categorised as follows: unrelated, potentially related or definitely related.

4:2:5 Cognitive and Dementia Severity Assessment

Cognition was measured at baseline using the Alzheimer Disease Assessment Scale - Cognitive Subsection (ADAS-Cog 12) [77], with greater scores indicating greater impairment. dementia severity was rated using the standard Clinical Dementia Rating – sub of boxes (CDR-sb). We examined the link between ongoing use of PIMs and change in ADAS-Cog and CDR-sb at 18 months to examine for an effect of PIMs on AD progression.

4:2:6 Statistical Analysis

This is a retrospective cohort analysis of a randomised control trial population. STATA V.15 (Stata Corp, College Station, Texas, USA) was used for all data analysis in the study. For all analyses, statistical significance was considered as $p<0.05$.

Descriptive statistics consisted of means (and standard deviations) as well as medians (Interquartile Ranges). For each patient, the total number of PIMs was calculated in addition to a binary PIM vs no-PIM variable and an "appropriate medication" variable, as described above. The total proportion of patients taking PIMs was expressed as a percentage of the overall study population. In order to analyse differences between countries in proportions, a chi-square test was used.

Between-group differences were assessed using t-tests, Wilcoxon rank sum tests in addition to chi-square tests as appropriate. Multivariate analysis of factors associated with PIM prescription were modelled using binary logistic regression with PIM vs no. PIM as the dependent variable. In analysing the effect of PIMs on adverse outcomes (adverse events, serious adverse events, unscheduled GP visits and unscheduled hospitalisations) over 18 months, Poisson regression was used with total number of PIMs as the independent variable

to model associations with adjustment for overall health (age, medications, comorbidities) and AD (diagnosis duration, AD severity and cognitive score, years of education) associated covariates. In order to check over dispersion in the Poisson models, analysis were re-run using negative binomial regression and the predictive value of models compared.

In order to assess for the impact of PIM use on cognitive function/dementia severity at 18 months, mixed effects linear regression models were used with country considered as a random effect and total PIMs used as a predictor of the change in either ADAS-Cog or CDR-sb scores at 18 months. In the first instance, associations were tested unadjusted (model 1). Further models were constructed to control for factors with a known impact on cognitive function or factors predictive of PIM prescription: model 2 controlled for age, sex baseline score (ADAS-Cog or CDR-sb), study group (nilvadipine or placebo) whilst model 3 included further adjustment for years of formal education and years since dementia diagnosis in addition to total number of appropriate medications and total number of comorbidities. Linear models were examined for multicollinearity and residual versus fit plots examined.

4:3 Results

4:3:1 Participant Characteristics

In total, 448 patients with mild to moderate AD (aged 72.56 ± 8.19 years; 62.28% female), randomized to receive either the study drug (Nilvadipine) or placebo had complete follow-up data available over 18 months. At baseline, the median number of prescribed medications were 5 (3-7) and the median number of comorbidities was 4 (2-5). Median years since AD diagnosis was 1.09 (IQR: 0.47-2.26) and median years since symptom onset as described by participant and caregiver was 3.7 (IQR: 2.45-5.42). Median years of education was 16 (IQR:

14-18). Concerning the severity of included patients, the median baseline ADAS-Cog was 32 (27-41) and the median dementia severity rated using the CDR-sb was 4 (3-6.5).

4:3:2 Prevalence of PIM Use

Overall, over half (55.8%; 250/448) of participants were using a potentially inappropriate medication as per the STOPP v2.0 criteria. Within those who were prescribed a PIM, just under half (46.0%; N = 115/250) were prescribed a single PIM, with over half (54%, N = 135/250) prescribed two or more potentially inappropriate medications. Of those prescribed a PIM, 24.8% (N = 62/250) were prescribed 3 or more PIMs.

The most frequent PIMs were benzodiazepine >4 weeks with no indication (11.6% N = 52/448), SSRI (selective serotonin reuptake inhibitors) without appropriate indication (11.1% N = 50/448), PPI (proton pump inhibitors) without appropriate indication (10.7% N = 48/448), antipsychotic medications without appropriate indication (8% N – 36/448) and regular NSAID (Nonsteroidal Anti-inflammatory Drugs) without PPI cover (4.2% N = 19/448). Notably, the prevalence of PIM usage significantly differed by country and ranged from 35% in Greece (N = 28/80) to 74% in France (N = 40/54) ($p<0.001$, $\chi^2 = 29.3$).

4:3:3 Factors associated with PIM Use

The characteristics of those patients prescribed a PIM in comparison with those not prescribed a PIM, in addition to appropriate univariate statistics, are included in **Table 4**. Of note, patients prescribed a potentially inappropriate medication at baseline were older, had a higher total number of appropriate medications, longer duration since symptom onset, and a longer duration since formal diagnosis (univariate analysis, all $p< 0.05$). On binary logistic

regression of all covariates, the association persisted for total number of (non-PIM) medications (OR 1.52, 1.34-1.70, p<0.001).

Table 4. Baseline characteristics between group differences in **t**hose with Mild to Moderate Alzheimer's Disease (AD) prescribed a PIM vs those not prescribed a PIM

Baseline Characteristic	**No PIM (N = 198)**	**1+ PIM (N = 250)**	**P-Value**
Age, mean years (SD)	71.67 (8.17)	73.09 (8.18)	**0.035**
Gender, % Female (N)	61.62% (122)	62.80% (157)	0.797
On Nilvadipine, % (N)	50.51% (100)	50.00% (125)	0.915
Years of Education, median (IQR)	16 (13-20)	16 (14-18)	0.850
No. Medications, median (IQR)	4 (2-5)	6 (4-8)	**<0.001**
No. Comorbidities, median (IQR)	4 (2-4)	4 (2-5)	0.054
Yrs Since Symptom Onset, median (IQR)	3.33 (2.05-4.73)	3.95 (2.61-5.81)	**0.004**
Yrs Since Diagnosis, med. (IQR)	0.82 (0.40-2.08)	1.32 (0.50-2.59)	**0.004**
Baseline CDR-sb Score, median (IQR)	4.4 (3-6)	4.5 (3.5-7)	0.096
Baseline ADAS-Cog Score, median (IQR)	32 (27-41)	32 (26-41)	0.758

Abbreviations : PIM, potentially inappropriate medication; SD, standard deviation; N, total number; IQR interquartile range, CDR-sb score, clinical dementia rating sum of boxes score; ADAS-Cog score, Alzheimer's disease assessment scare cognitive subscale**,** OR, Odds ratio; CI, confidence interval

Table 5. Multivariate analysis of between group differences in those with Mild to Moderate Alzheimer's Disease (AD) prescribed a PIM vs those not prescribed a PIM

Multivariate analysis		
Baseline Characteristic	**OR (95% CI)**	**P-Value**
Age	1.01 (0.98 - 1.03)	0.744
Gender	1.07 (0.69 - 1.68)	0.765
Study Group (Nilvadapine vs Placebo)	1.00 (0.65 - 1.52)	0.982
Years of Education	1.02 (0.96 - 1.08)	0.563
No. Medications	1.52 (1.36 - 1.71)	**<0.001**
No. Comorbidities	0.87 (0.77 - 0.97)	**0.010**
Years Since Symptom Onset	1.04 (0.95 - 1.15)	0.399
Years Since Diagnosis	1.03 (0.88 - 1.20)	0.723
Baseline CDR-sb Score	1.12 (1.00 - 1.24)	0.061
Baseline ADAS-Cog Score	0.98 (0.96 - 1.02)	0.339

Abbreviations : PIM, potentially inappropriate medication; SD, standard deviation; N, total number; IQR interquartile range, CDR-sb score, clinical dementia rating sum of boxes score; ADAS-Cog score, Alzheimer's disease assessment scare cognitive subscale**,** OR, Odds ratio; CI, confidence interval.

4:3:4 PIM Use and Adverse Events Over 18 Months

In total the median number of adverse events per patient involved in the study was 3 (IQR: 1-6), which did not differ by study group (Nilvadipine vs Placebo) (p = 0.387). Serious adverse events were reported for just under one-fifth of the study population (14.29%, N = 64). PIM usage was associated with both adverse events (IRR 1.14, 1.12-1.17, p<0.001) and serious adverse events (IRR 1.24, 1.16-1.32, p<0.001) in an unadjusted Poisson model. Both total PIMs (IRR 1.17, 1.13-1.19, p<0.001) and appropriate medications (total medications excluding PIMs) were associated with adverse events (IRR 1.08, 1.06-1.10, p<0.001) in fully adjusted models (See **Table 6**). On analysis of total number of serious adverse events using the fully adjusted model, similar associations were seen for both total PIMs (IRR 1.27; 1.17-1.37, p<0.001) and appropriate medications (IRR 1.23; 1.17-1.31, p<0.001) (See **Table 6**). Further, increasing age (IRR 1.02, 1.01-1.05, p = 0.044) and increasing ADAS-Cog severity at baseline (IRR 1.03, 1.01-1.06, p = 0.026) were associated with a greater risk of serious adverse events. Female gender (IRR 0.71, 0.51- 98, p = 0.039) was associated with a decreased risk. See **Table 6.** Mortality was not included as an end point as mortality rates were low in this cohort 1.37% (N=7)

Overall, 80 participants (17.9%; N = 80/448) had a potential/definite link between their potentially inappropriate medication and a subsequent adverse event. The most frequent

adverse events potentially caused by a PIM were falls (4.2%, N=19), increasing confusion (3.7%, N=17), over-sedation (2.4%, N = 11), and agitation (2.4%, N = 11).

4:3:5 PIM Use and Unscheduled Hospitalisations/GP Visits

In total, 16.3% (N = 73) patients had one or more unscheduled hospitalisations over the 18 month study period whilst 46% (N = 206) had an unscheduled visit to their general practitioner. Unadjusted, total number of PIMs was associated with a greater risk of both unscheduled hospitalisations (IRR: 1.18, 1.06-1.31, p = 0.003) and unscheduled GP visits (IRR: 1.18, 1.12-1.24, p<0.001). In the adjusted model, total number of PIMs was the only factor associated with total number of unscheduled hospitalisations (IRR 1.16, 1.03-1.30, p=0.016) and unscheduled GP visits (IRR 1.14 95% CI 1.05- 1.31, p<0.001) (See **Table 6**). Notably, appropriate medications were not associated with unscheduled GP visits or hospitalisations. Results of the adjusted models are presented in **Table 6.**

Table 6. Association between PIM use and adverse events, Serious adverse events, unscheduled GP visits and unscheduled hospitalisations

Baseline Characteristic	**IRR (95% CI)**	**P-Value**
Adverse Events		
Total PIM	1.17 (1.13 - 1.19)	**<0.001**
Appropriate Medications	1.08 (1.06 - 1.10)	**<0.001**
Age	1.00 (0.99 - 1.01)	0.761
Gender (Female)	1.08 (0.99 - 1.19)	0.077
Study group (Nilvadapine vs placebo)	0.95 (0.87 - 1.03)	0.201
Total No. of Comorbidities	1.01 (0.87 – 1.03)	0.345
Years Since Diagnosis	0.98 (0.95 - 1.01)	0.081
Baseline CDR-sb Score	0.99 (0.96 - 1.01)	0.209
Baseline ADAS-Cog Score	1.00 (0.99 - 1.01)	0.576
Serious Adverse Events		

Total PIM	1.27	(1.17 - 1.37)	**<0.001**
Appropriate Medications	1.23	(1.17 - 1.31)	**<0.001**
Age	1.02	(1.01 - 1.05)	**0.044**
Gender (Female)	0.71	(0.51 - 0.98)	**0.039**
Study group (Nilvadapine vs placebo)	0.97	(0.63 - 1.48)	0.870
Total No. of Comorbidities	1.02	(0.93 - 1.12)	0.646
Years Since Diagnosis	0.97	(0.79 - 1.04)	0.161
Baseline CDR-sb Score	1.03	(0.94 - 1.13)	0.456
Baseline ADAS-Cog Score	1.03	(1.01 - 1.06)	**0.026**
Unscheduled Hospitalisations			
Total PIM	1.16	(1.03 - 1.30)	**0.016**
Appropriate Medications	1.00	(0.91 - 1.11)	0.942
Age	1.03	(0.99 - 1.05)	0.149
Gender (Female)	0.82	(0.68 - 1.62)	0.840
Study group (Nilvadapine vs placebo)	0.79	(0.54 - 1.24)	0.339
Total No. of Comorbidities	1.06	(0.96 – 1.16)	0.255
Years Since Diagnosis	0.98	(0.87 - 1.11)	0.751
Baseline CDR-sb Score	1.05	(0.97 - 1.03)	0.386
Baseline ADAS-Cog Score	1.00	(0.98 - 1.06)	0.967
Unscheduled GP Visits			
Total PIM	1.22	(1.15 - 1.28)	**<0.001**
Appropriate Medications	1.05	(0.99 - 1.11)	0.086
Age	1.00	(0.98 - 1.02)	0.819
Gender (Female)	1.06	(0.82 - 1.39)	0.707
Study group (Nilvadapine vs placebo)	1.06	(0.97 - 1.38)	0.671
Total No. of Comorbidities	1.04	(0.90 – 1.10)	0.270
Years Since Diagnosis	0.98	(0.94 - 1.01)	0.582
Baseline CDR-sb Score	1.00	(0.98 - 1.06)	0.891
Baseline ADAS-Cog Score	1.01	(0.98 - 1.02)	0.666

Poisson regression analysis was used to assess the relationship between PIM use and adverse outcomes (total number). Results are reported as Incident Rate Ratios and approximate 95% confidence intervals. Abbreviations: IRR, incidence rate ratio; CI , confidence interval; PIM, potentially inappropriate prescription; CDR-sb score, clinical dementia rating sum of boxes score; ADAS-Cog score, Alzheimer's disease assessment scare cognitive subscale

4:3:6 PIM Use and Cognitive Decline/Dementia Severity at 18 months

In the cohort overall, the mean ADAS-Cog score increased indicating a greater cognitive decline (mean difference: +8.98 ± 9.18) as did the mean CDR-sb (mean difference: +3.48 ± 3.15), also indicating increased dementia severity. Under all three models there was no effect of total number of PIMs on cognitive decline or dementia severity at 18 months (See Table 6.). Further, analysis repeated using the binary PIM vs no PIM predictor yielded no significantly different results. Results of the regression analyses examining the link between PIM use, dementia severity and cognitive outcomes is included in table 7. Mixed-effects linear regression analysis was used to assess the relationship between PIM use and cognitive severity (ADAS-Cog)/Dementia Severity (CDR-sb) at 18 months. Results are reported as coefficients and approximate 95% confidence intervals.

Table 7 PIM Use and Predict Dementia Progression at 18 Months.

Change in ADAS-Cog	**Model 1**		**Model 2**		**Model 3**	
	β **-Coef (95% CI)**	***P***	***β*** **-Coef (95% CI)**	***P***	***β*** **Coef (95% CI)**	***P***
Total PIMs	-0.16 (-0.78 - 0.47)	0.612	0.08 (-0.524 - 4.71)	0.749	0.07 (-0.65 – 0.79)	0.850
Age			-0.26 (-0.37 - -0.16)	**<0.001**	-0.25 (-0.35, -0.13)	**<0.001**
Gender (Female)			-1.08 (-0.284 – 0.68)	0.230	-0.79 (-2.58, 1.00)	0.387
Baseline ADAS-Cog			0.18 (0.09, 0.27)	**<0.001**	0.21 (0.12, 0.31)	**<0.001**
Study group (Nilvadapine vs placebo)			-0.61(-2.30, 1.09)	0.484	-0.51 (-2.20, 1.18)	0.557
Education (Years)					0.18 (-0.06, 0.43)	0.159
Diagnosis (Years)					-0.57 (-1.08, -0.05)	0.033
Total Comorbidities					0.08 (-0.34, 0.50)	0.706

Appropriate medications					0.08 (-0.33, 0.48)	0.716
Change in CDR-Sb	**Model 1**		**Model 2**		**Model 3**	
	***β* -Coef (95% CI)**	***P***	***β* -Coef (95% CI)**	***P***	***β* Coef (95% CI)**	***P***
Total PIMs	0.08 (-0.12 – 0.27)	0.427	0.05 (-0.14 – 0.23)	0.641	0.05 (-0.14 – 0.23)	0.969
Age			-0.07 (-0.10 – -0.03)	<0.001	-0.07 (0.10 – 0.03)	0.001
Gender (Female)			-0.11 (-0.70 – 0.48)	0.712	-0.11(-0.70 – 0.48)	0.849
Baseline CDR-sb			0.22 (0.12 – 0.33)	<0.001	0.22 (-0.12 – 0.33)	<0.001
Study group (Nilvadapine vs placebo)			-0.19 (-0.78 – 0.32)	0.514	-0.19 (-0.76 – 0.38)	0.568
Education (Years)					-0.01(-0.09 – 0.03)	0.769
Diagnosis (Years)					-0.21 (-0.40 – 0.03)	0.024
Total Comorbidities					-0.05 (-0.20 – 0.09)	0.473
Appropriate medications					0.07 (-0.07 – 0.21)	0.308

Abbreviations: ADAS-Cog: Alzheimer's Disease Assessment Scale – Cognitive Subsection, CDR-sb: Clinical Dementia Rating Scale – Sum of Boxes; CI , confidence interval; PIM, potentially inappropriate prescription; CDR-sb score, clinical dementia rating sum of boxes score; ADAS-Cog score, Alzheimer's disease assessment scare cognitive subscale

4:4 Discussion

The current study reports frequent usage of PIMs in community-dwelling people living with mild-to-moderate AD. Of note, the majority of older adults with AD in the current study were prescribed at least one PIM. Particularly concerning is the number of patients prescribed

multiple inappropriate medications. The likelihood of being prescribed a PIM increased with total medication burden and was associated with both adverse events and serious adverse events over an 18 month period, although not with worsening cognitive decline or dementia severity. A possible explanation for the minimal effect of PIM on dementia severity score is the relatively short duration of the trial 18 month period. The total number of PIMs prescribed was a significant factor associated with unscheduled hospitalisations and GP visits over 18 month follow up. Whilst we acknowledge that unscheduled hospitalisations often have multiple precipitants our findings were independent of age, medical co-morbidity and other important co-variates. These findings have numerous important implications for de-prescribing and medication optimisation interventions.

The high percentage of PIM usage in this study population, with over 50% of patients on one or more PIM, is consistent with previous literature [68,69]. The number of patients prescribed three or more PIMS (>20%) is particularly concerning given the known association between PIMS and adverse events [75]. The most frequently encountered PIM was inappropriate prolonged use of benzodiazepines. Extensive literature exists highlighting the adverse effects associated with prolonged benzodiazepine use including dependency, falls fractures and cognitive decline [78-81]. On foot of this evidence base, the American Geriatric Society recommends avoiding the use of benzodiazepines in older adults particularly in those with dementia [82].

Proton Pump Inhibitors [PPIs] were also frequently inappropriately prescribed, consistent with previous cross sectional studies in similar cohorts studied [83]. Along with other PIM usage inappropriate prescriptions of PPIs can incur unnecessary healthcare costs but also side effects associated with achlorhydria and hypergastrinemia [84. The large number of patients

prescribed anti muscarinic medication is also concerning, given the evidence for anticholinergic burden and potential cognitive decline. The inappropriate use of antipsychotic medication is also something to be considered, and the adverse effects of antipsychotics in those living with dementia has been well documented [85,86]. These medications may represent particular targets for medication reviews and de-prescribing interventions in older adults with dementia. With the increasing availability of healthcare ICT applications, the role for e-prescribing and computerised decision support systems in reducing inappropriate prescriptions in this cohort is emerging and developing (87) .

Older people are more vulnerable to adverse drug reactions than younger people. This is also true for older adults with dementia and consistent across community dwelling, nursing home and hospital populations [88] . The current study found that PIMS and greater number of appropriate medications were both independently associated with adverse events in this population. There was a significant association with PIMs and unscheduled hospitalisations and GP visits identified in this study. Although with increasing frailty and co-morbidity GP visits have a clear role in management of older adults and chronic disease , hospital admission and unscheduled care has been shown to be associated with poor outcomes in patients with dementia [89]. Previous literature has demonstrated an increased frequency of hospitalisation with PIM use in older adults when applying STOPP criteria, [90] but this is less well studied in older adults with dementia. While not a noted outcome in this study, previous studies have reported that total medication burden is an independent risk factor for mortality in older adults with dementia (72). We did not find a positive association between PIM use and multimorbidity in this cohort. This study primarily investigated PIM prescriptions, however we have also demonstrated an increased incidence of serious adverse events associated with appropriate medications in this cohort. The need for appropriate polypharmacy in older

people and those with chronic conditions is increasingly acknowledged [91] and requires physician care, frequent review and healthcare professional education.

This study includes patients across nine European countries and under the care of a variety of specialists including geriatricians, neurologists and psychiatrists of older age. The international and multispecialty nature of this analysis is a strength of this study. The data collected in the NILVAD study and available for the current study included a detailed medical history, medication records and close follow up for adverse events and cognitive assessments. This was collected over an 18 month period and is a particular strength of this study in demonstrating the link between PIM use and adverse events. Clinical judgement is a key determinant for PIM identification and this will inevitably be a limitation in all studies investigating PIM use given variability in clinician practice, however by using the validated STOPP tool [92] and performing assessment in duplicate we have minimised this bias.

4:5 Conclusion and Implications

The current study demonstrates that over half of older adults with mild to moderate AD were on at least one potentially inappropriate medication, and many participants were on multiple PIMs. Of note, there was an increased rate of unscheduled hospitalisations and GP visits associated with PIMS. There was a concerning frequency towards inappropriate benzodiazepine prescriptions across all groups. Further efforts are needed in reviewing medications in older adults particularly those with dementia. De-prescribing interventions and optimal prescribing interventions are encouraged based on these results, and may produce benefit in those with AD, who may represent a particularly vulnerable group.

Chapter 5

Prevalence and complications associated with medications prescribed to manage non-cognitive symptoms of Alzheimer's disease in NILVAD cohort

5:1 Introduction

People living with dementia have a higher incidence of polypharmacy than those without. [93]The medications prescribed can be divided into three categories, medications aimed at slowing disease progression such as the cholinesterase inhibitors, medications aimed to treat the neuropsychiatric symptoms associated with dementia and medications prescribed for other co-morbid conditions. A number of medications were frequently prescribed in our cohort for neuropsychiatric symptoms of dementia. These medications are frequently deemed high risk in people with dementia so we further investigated the use of benzodiazepines (BDZR) and antipsychotics in our cohort. We also identified many medications prescribed for non-dementia related conditions. This was investigated by assessing the impact of the cholinergic burden of these medications on our population. Statins are commonly prescribed and not associated with dementia. The literature to date has been conflicting on statin use in dementia. The next two chapters describe this work. The research was performed in collaboration with my colleague AD (see acknowledgements), the work was completed and published together and is only for inclusion as part of this academic degree and none other. The cohort of participants used in this further sub analysis is the same NILVAD cohort previously described.

5:2 Background

People living with AD are often prescribed drugs acting on the central nervous system to treat symptoms associated with the disease, these include antidepressants, antipsychotics and sedative medications. In our research benzodiazepines were the most frequently prescribed PIM with antipsychotics and antidepressants also frequently prescribed as a PIM. The American Geriatric Society advise against the use of benzodiazepines in older adults, particularly older adults with cognitive impairment or dementia [(94)]. Despite this benzodiazepines are frequently prescribed in older people and in people living with dementia [(95,96)] . Similarly all clinical guidelines suggest only using antipsychotic medication once all non-pharmacological methods have been explored and with close monitoring throughout treatment [(97)] , however antipsychotic medications are commonly used to treat behavioural and psychological symptoms of dementia. (BPSD) [(98,99)].

Long term use of benzodiazepines is associated with cognitive decline and increased risk of dementia [(95,96)]. Benzodiazepines are also associated with falls, fractures, syncope and increased risk of delirium [(100-103)]. The long-term use of antipsychotic medication has been associated with increased risk of cerebrovascular events, cardiometabolic outcomes and mortality [(104,105)]. Furthermore long-term antipsychotic use has also been demonstrated to be associated with cognitive decline in dementia. The Clinical Antipsychotic Trials of Intervention Effectiveness Alzheimer's Disease (CATIE-AD) Study demonstrated accelerated decline in ADAS-Cog and MMSE consistent with 1 year's deterioration [(106)]. Cognitive decline has also been demonstrated in more recent meta-analysis with long term antipsychotic use [(105)]. Ellul et al [(107)] found an association with both benzodiazepine use and antipsychotic use and dementia progression in a population with AD, this population however

had greater disease severity than our cohort. Research is often focused on nursing home populations or those with advanced dementia. We assessed cognitive decline in our community dwelling population with mild to moderate AD taking long term Benzodiazepines and antipsychotics. We also investigated for associations between BDZR use and Delirium and falls. Full papers can be reviewed at reference 108,109.

5:3 Methodology

The NILVAD cohort as previously described were used for these studies. Medication lists were assessed in duplicate (AD, CM) for BDZR and antipsychotics using ATC classification codes. BDZR use was defined as use of one of more of these drugs for the entire 18 month study duration. Short term BDZR users were excluded. Antipsychotic usage was further subdivided into first and second generation antipsychotic agents. Long-term usage was those using antipsychotic medication for the entire study duration >18months. We also coded for definite anticholinergic burden score to ensure potential cognitive effects could be assessed independently to anticholinergic effects.

Cognitive assessment was performed using ADAS-Cog 12, CDR-sb and DAD at baseline and 18 month follow up. MMSE was assessed at baseline to assess Dementia Severity. For assessment of adverse events associated with BDZR use adverse event logs were assessed in duplicate (AD, CM). Delirium was assessed during the NILVAD study retrospectively by interview. An adapted version of the Family Confusion Assessment Method [(110)] was used.

Notably in the NILVAD study participants with any other significant neurological disorder were excluded including any AXIS 1 psychiatric disorder such as schizophrenia, bipolar or major depression. Also excluded were those with alcohol dependence one year preceding or

any behavioural and psychological symptoms of dementia (BPSD) symptoms that would limit study participation.

5:4 Cognitive outcomes of long-term Benzodiazepine and related drug (BDZR) use in people living with mild to moderate Alzheimer's disease: Results from NILVAD

5:4:1 Statistical Analysis

For univariate analysis of between-group differences comparing those with ongoing BDZR use to nonusers, we used t tests, Wilcoxon rank-sum, and chi-square tests as appropriate. In order to analyse the predictors of ongoing BDZR use, we used binary logistic regression and presented results as adjusted odds ratios (ORs) with 95% confidence intervals (CIs) and p values. We analysed the effect of ongoing BDZR use on ADAS-Cog score at 18 months using mixed effects linear regression models with country included as a random effect. In the first instance, we tested this association alone with BDZR use as the independent variable and ADAS-Cog score difference at 18 months as the dependent variable (model 1). This was followed by minimal adjustment for age, baseline ADAS-Cog score, gender, and study group (Nilvadipine vs placebo, to control for potential effects of study drug) (model 2). Following this, we adjusted for other AD (diagnosis duration, years of education) and general health covariates (total comorbidities and total number of medications) based on known impact on cognitive function (model 3). Analysis was repeated separately in those with mild and moderate AD (based on MMSE score classification) to assess if the effect of BDZR use on cognitive function varied with AD severity. Results of linear models were reported as co-efficients with 95% CIs and the associated p value.

In order to assess the relationship between BDZR use and adverse events, serious adverse events, falls, and delirium, we used multivariate Poisson regression. We first tested associations unadjusted (model 1). Following this, we adjusted for age, gender, study group, duration of AD, baseline cognition (ADAS-Cog score), and AD severity (CDR-sb score) (model 2). Finally, we adjusted for total number of medications (excluding BDZRs) and total number of medical comorbidities (model 3). Incidence rate ratios were calculated and 95% CIs reported. In each instance where Poisson regression was used, we carried out a negative binomial regression to compare model fit and assess for over dispersion.

5:4:2 Results

Of the 448 participants, 62 (13.84%) were prescribed an ongoing BDZR. Participants were more likely to be prescribed a BDZR with higher total number of medications. Alprazolam was the most frequently prescribed BDZR. No participant was prescribed multiple BDZRs. There was no significant difference detected on cognitive scores at 18 month follow up for BDZR users compared to non-users, this was consistent across all models. There was however increased incidence for delirium and falls in BDZR users compared to non-users. BDZR users had higher rates of incident delirium in the unadjusted model (IRR 2.44, 95% CI 1.56-3.81, P < .001) (model 1), which persisted under both adjusted models (IRR 2.45, 95% CI 1.55-3.89, P < .001, for model 2; IRR 2.31, 95% CI 1.45-3.68, P < .001, for model 3). Ongoing BDZR use was associated with incident falls using unadjusted Poisson regression (IRR 1.73, 1.08-2.78, P 1⁄4 .022) (model 1). This finding persisted on both minimal (IRR 1.66, 1.03-2.71, P 1⁄4 .037) (model 2) and robust adjustment for covariates (IRR 1.66, 1.02-2.65, P 1⁄4 .041) (model 3)

Table 8 Analysis of the Association Between Ongoing BDZR Use and Adverse Events, Serious Adverse Events, Delirium, and Falls Over 18 Months:

Predictor	**Model 1**		**Model 2**		**Model 3**	
	IRR (95% CI)	***P***	**IRR (95% CI)**	***P***	**IRR (95% CI)**	***P***
Adverse Events						
Ongoing BDZR Use	1.26 (1.12, 1.42)	**<0.001**	1.26 (1.12, 1.42)	**<0.001**	1.19 (1.05-1.34)	**0.006**
Age			1.01(0.99, 1.08)	0.11	1.00 (0.99, 1.01)	0.86
Gender			1.09 (0.99, 1.19)	0.06	1.07 (0.96, 1.17)	0.19
Study Group			0.92 (0.83, 1.00)	0.05	0.92 (0.83, 1.01)	0.06
AD Duration			1.01 (0.98, 1.04)	0.60	1.01(0.98, 1.03)	0.72
ADAS-Cog (Baseline)			1.00 (0.99-1.01)	0.21	1.00 (0.99, 1.01)	0.23
CDR-Sb (Baseline)			1.00 (0.98-1.02)	0.95	1.01 (0.98, 1.02)	0.92
Total Comorbidities					1.01 (0.99, 1.03)	0.30
Total Medications (Non-BDZR)					1.07 (1.05, 1.09)	**<0.001**
Serious Adverse Events						
Ongoing BDZR Use	1.14 (0.74,1.42)	0.566	1.24 (0.81,1.90)	0.34	1.13(0.73,1.74)	0.60
Age			***1.04(1.02,1.06)***	***<.001***	***1.03(1.01,1.06)***	*0.004*
Gender			0.71 (0.52,0.98)	0.04	0.66(0.48,0.91)	.01
Study Group			0.93 (0.84,1.01)	0.6	0.60 (0.43,1.04)	0.6
AD Duration			1.02(0.93,1.12)	0.64	1.03(0.94,1.12)	0.60
ADAS-Cog (Baseline)			0.99 (0.95,1.01)	0.18	0.99 (0.99, 1.01)	0.22
CDR-Sb (Baseline)			1.02 (0.94,1.10)	0.62	1.03(0.98,1.02)	0.51
Total Comorbidities					0.97(0.89,1.05)	0.44
Total Medications (Non-BDZR)					1.20(1.12,1.27)	**<0.001**
Delirium						
Ongoing BDZR Use	2.44(1.56, 3.81)	**<0.001**	2.45 (1.55, 3.88)	**<0.001**	2.30 (1.45-3.67)	**<0.001**
Age			1.01 (0.98, 1.03)	0.51	1.01 (0.98, 1.03)	0.72
Gender			0.71 (0.47, 1.08)	0.11	0.70 (0.98, 1.03)	0.09
Study Group			0.86 (0.57, 1.29)	0.46	0.86 (0.57, 1.30)	0.47
AD Duration			0.95 (0.84, 1.06)	0.32	0.95 (0.84, 1.06)	0.33
ADAS-Cog (Baseline)			1.00 (0.98-1.02)	0.98	1.00 (0.98, 1.02)	0.95
CDR-Sb (Baseline)			1.19 (1.09-1.31)	**<0.001**	1.20 (1.09, 1.32)	**<0.001**
Total Comorbidities					0.98 (0.88, 1.07)	0.61
Total Medications (Non-BDZR)					1.10 (1.01, 1.21)	**0.04**
Falls						
Ongoing BDZR Use	1.73(1.08, 2.78)	**0.022**	1.66 (1.03, 2.71)	**0.037**	1.66 (1.02, 2.65)	**0.041**

Age			1.06 (1.03, 1.09)	**<0.001**	1.06 (1.03, 1.09)	**<0.001**
Gender			1.82 (1.15, 2.88)	**0.01**	1.82 (1.15, 2.87)	**0.01**
Study Group			1.12 (0.75, 1.67)	0.57	1.12 (0.75, 1.66)	0.57
AD Duration			0.99 (0.87, 1.12)	0.89	0.99 (0.87, 1.12)	0.88
ADAS-Cog (Baseline)			0.97(0.94, 0.99)	**0.03**	0.97 (0.94, 0.99)	**0.03**
CDR-Sb (Baseline)			1.02(0.9, 1.13)	0.76	1.01 (0.92, 1.13)	0.77
Total Comorbidities					1.01 (0.92, 1.11)	0.83
Total Medications (Non-BDZR)					1.00 (0.92, 1.10)	0.95

AD = Alzheimer Disease, BMI = Body Mass Index, ADAS-Cog = Alzheimer's Disease Assessment Scale, Cognitive Subsection, CDR-Sb = Clinical Dementia Rating, Sum of Boxes, BPSD = Behavioural and Psychological Symptoms of Dementia, BDZR = benzodiazepine related drugs.

5:5 Long-term antipsychotic use and cognitive decline in community-dwelling older adults with mild-moderate Alzheimer disease: Data from NILVAD

5:5:1 Statistical analysis

In order to compare those with antipsychotic usage to those without, univariate statistics consisted of *t*-tests, chi-square tests and Wilcoxon rank-sum tests as appropriate. Multivariate Logistic Regression was used in order to model predictors of antipsychotic prescription in those with mild–moderate AD. ADAS-Cog, CDR-Sb and DAD assessments were performed at baseline, 12 and 18 months. In order to predict the change on the three assessments over time, we used mixed-effects linear regression with country as a random effect and change in ADAS-Cog/CDR-Sb/DAD as the dependent variable. In the first instance, we tested associations unadjusted. Then, we adjusted for important factors known to influence cognitive trajectories such as age, sex, BMI, years of formal education, duration since AD

diagnosis and baseline score (on ADAS-Cog/CDR-Sb/DAD) in addition to study group (Nilvadipine vs. placebo) and cholinesterase inhibitor usage (model 1). In further models, we also adjusted for total medication burden (excluding long-term antipsychotics) and total number of medical comorbidities (model 2). Finally, we adjusted for use of definite anticholinergic medication (in order to explore if potential effects were independent of anticholinergic effects) in addition to the presence of BPSD, in order to control for confounding by indication (model 3)

5:5:2 Results

We included 509 participants in our analysis. One tenth (54/509, 10.6%) were prescribed a regular antipsychotic medication. Quetiapine was the most frequently prescribed antipsychotic.(44.4%, 24/54), Risperidone (13% , 6/54), amisulpride (11.1%, 6/54) and haloperidol (7.4%, 4/54) were also commonly prescribed. Those prescribed an antipsychotic had greater AD severity at baseline, greater medication burden and fewer years of formal education compared to those not prescribed at all. Ongoing use of antipsychotic medication was associated with greater cognitive decline at 12 and 18 months assessed by ADAS-Cog score, this persisted under all adjusted models at 12 and 18 months. There was also greater progression of AD on CDR-sb and DAD at 12 and 18 months. (See Table 9)

Table 9 . Long Term Antipsychotic Use, Cognitive Decline and Dementia Progression.

	Model 1		***Model 2***		***Model 3***	
ADAS-Cog Change: 12 Months	**β Coef. (95% CI)**	**P-value**	**β Coef. (95% CI)**	**P-value**	**β Coef. (95% CI)**	**P-value**
Long-Term Antipsychotic Use	**3.46 (1.04, 5.89)**	**0.005**	**3.12 (0.64, 5.59)**	**0.014**	**3.53 (0.91, 6.17)**	**0.008**
Age	-0.18 (-0.27, -0.09)	<0.001	-0.19 (-0.28, -0.10)	<0.001	-0.18 (-0.27, 0.09)	<0.001
Gender (Female)	-0.43 (-1.95, 1.08)	0.574	-0.46 (-1.95, 1.04)	0.547	-0.55 (-2.04, 0.95)	0.474
Body Mass Index (BMI)	-0.20 (-0.37, -0.03)	0.020	-0.21 (-0.38, -0.04)	0.014	-0.19 (-0.36, -0.02)	0.031
Education (Years)	0.08 (-0.11, 0.28)	0.407	0.09 (-0.10, 0.28)	0.347	0.07 (-0.12, 0.27)	0.460
Baseline ADAS-Cog	0.07 (-0.01, 0.15)	0.050	0.08 (0.01, 0.15)	0.038	0.09 (0.02, 0.16)	0.018
Diagnosis Duration	-0.19 (-0.61, 0.23)	0.374	-0.22 (-0.64, 0.20)	0.307	-0.31 (0.74, 0.12)	0.153
Study Group (Nilvadipine)	0.67 (-0.79, 2.12)	0.361	0.70 (-0.73, 2.13)	0.337	0.72 (-0.70, 2.15)	0.322
Cholinesterase Inhibitor	-0.29 (-2.60, 2.03)	0.808	-0.43 (-2.72, 1.87)	0.716	-0.35 (-2.63, 1.94)	0.764
Total Medications			0.16 (-0.14, 0.45)	0.304	0.16 (-0.14, 0.46)	0.285
Total Comorbidities			-0.01 (-0.36, 0.33)	0.935	-0.16 (0.36, 0.32)	0.928
“Definite” Anticholinergic Use					-0.55 (-2.92, 1.82)	0.650
BPSD					-2.40 (-5.03, 0.28)	0.075
ADAS-Cog Change: 18 Months						
Long-Term Antipsychotic Use	**4.01 (-0.93, 7.09)**	**0.011**	**3.95 (0.81, 7.10)**	**0.014**	**3.81 (0.49, 7.14)**	**0.024**
Age	-0.24 (-0.34, -0.13)	<0.001	-0.25 (-0.36, -0.14)	<0.001	-0.25 (-0.36, -0.14)	<0.001
Gender (Female)	-0.43 (-2.18, 1.33)	0.635	-0.48 (-2.25, 1.28)	0.591	-0.53 (-2.29, 1.23)	0.555
Body Mass Index (BMI)	-0.30 (-0.49, -0.10)	0.003	-0.30 (-0.50, -0.11)	0.002	-0.30 (-0.49, 0.10)	0.003
Education (Years)	0.10 (-0.12, 0.28)	0.370	0.11 (-0.12, 0.33)	0.350	0.10 (0.13, 0.32)	0.387
Baseline ADAS-Cog	0.19 (-0.10, 0.28)	<0.001	0.19 (0.10, 0.28)	<0.001	0.20 (0.11, 0.29)	<0.001
Diagnosis Duration	-0.48 (-0.99, 0.02)	0.059	-0.49 (-1.00, 0.01)	0.055	-0.55 (-1.07, -0.03)	0.038
Study Group (Nilvadipine)	-0.15 (-1.82, 1.51)	0.860	-0.14 (-1.81, 1.53)	0.870	-0.08 (-1.75, 1.59)	0.921
Cholinesterase Inhibitor	0.43 (-2.21, 3.06)	0.751	0.36 (-2.30, 3.01)	0.793	0.36 (-2.29, 3.02)	0.789
Total Medications			0.01 (-0.33, 0.36)	0.935	0.00 (-0.35, 0.35)	0.995

Total Comorbidities			0.14 (-0.26, 0.53)	0.494	0.14 (-0.26, 0.54)	0.486
"Definite" Anticholinergic Use					0.90 (-1.86, 3.66)	0.533
BPSD					-1.32 (-4.35, 1.70)	0.391
CDR-Sb Change: 12 Months						
Long-Term Antipsychotic Use	**1.98 (1.18, 2.77)**	**<0.001**	**1.96 (1.15, 2.77)**	**<0.001**	**1.85 (-0.97, 2.73)**	**<0.001**
Age	-0.03 (-0.06, 0.00)	0.093	-0.03 (-0.06, 0.01)	0.104	-0.03 (-0.06, 0.00)	0.087
Gender (Female)	-0.01 (-0.51, 0.50)	0.978	-0.01 (-0.51, 0.50)	0.984	0.01 (-0.49, 0.51)	0.973
Body Mass Index (BMI)	-0.03 (-0.08, 0.03)	0.380	-0.03 (-0.08, 0.03)	0.383	-0.03 (-0.09, 0.03)	0.306
Education (Years)	-0.04 (-0.19, 0.11)	0.211	-0.04 (-0.11, 0.02)	0.217	-0.04 (-0.10, 0.03)	0.286
Baseline CDR-Sb	0.08 (-0.01, 0.18)	0.079	0.09 (-0.01, 0.18)	0.080	0.08 (-0.02, 0.18)	0.105
Diagnosis Duration	-0.04 (-0.19, 0.11)	0.577	-0.04 (-0.19, 0.10)	0.569	-0.02 (-0.17, 0.13)	0.770
Study Group (Nilvadipine)	0.24 (-0.24, 0.73)	0.328	0.24 (-0.24, 0.72)	0.325	0.24 (-0.24, 0.72)	0.333
Cholinesterase Inhibitor	-0.08 (-0.84, 0.69)	0.846	-0.08 (-0.85, 0.69)	0.838	-0.10 (-0.87, 0.67)	0.797
Total Medications			0.01 (-0.09, 0.11)	0.836	0.01 (-0.09, 0.11)	0.849
Total Comorbidities			-0.01 (-0.13, 0.11)	0.858	-0.01 (-0.13, 0.11)	0.864
"Definite" Anticholinergic Use					0.13 (-0.67, 0.93)	0.743
BPSD					0.50 (-0.38, 1.39)	0.266
CDR-Sb Change: 18 Months						
Long-Term Antipsychotic Use	**1.62 (0.49, 2.75)**	**0.005**	**1.50 (0.34, 2.65)**	**0.011**	**1.41 (0.16, 2.67)**	**0.027**
Age	-0.07 (-0.11, -0.03)	0.001	-0.08 (-0.12, -0.03)	<0.001	-0.08 (-0.12, -0.03)	<0.001
Gender (Female)	-0.28 (-0.99, 0.42)	0.430	-0.31 (-1.01, 0.40)	0.394	-0.29 (-0.99, 0.41)	0.414
Body Mass Index (BMI)	-0.02 (-0.09, 0.07)	0.733	-0.02 (-0.10, 0.06)	0.674	-0.02 (-0.10, 0.06)	0.610
Education (Years)	-0.02 (-0.11, 0.08)	0.693	-0.02 (-0.09, 0.06)	0.726	-0.01 (-0.10, 0.08)	0.808
Baseline CDR-Sb	0.25 (0.11, 0.38)	<0.001	0.25 (0.12, 0.39)	<0.001	0.25 (0.11, 0.38)	<0.001
Diagnosis Duration	0.13 (-0.35, 0.09)	0.248	-0.13 (-0.35, 0.09)	0.233	-0.11 (-0.34, 0.11)	0.330
Study Group (Nilvadipine)	0.08 (-0.59, 0.75)	0.815	0.08 (-0.59, 0.75)	0.810	0.07 (-0.60, 0.75)	0.831
Cholinesterase Inhibitor	-0.24 (-1.29, 0.81)	0.655	-0.29 (-1.34, 0.76)	0.591	-0.31 (-1.36, 0.75)	0.567

Total Medications			0.05 (-0.09, 0.18)	0.515	0.05 (-0.12, 0.20)	0.511
Total Comorbidities			0.05 (-0.12, 0.21)	0.591	0.05 (-0.12, 0.21)	0.572
"Definite" Anticholinergic Use					0.05 (-1.08, 1.17)	0.939
BPSD					0.48 (-0.73, 1.70)	0.435
DAD Change: 12 Months						
Long-Term Antipsychotic Use	**-3.73 (-5.75, -1.72)**	**<0.001**	**-3.87 (-5.93, 1.81)**	**<0.001**	**-3.33 (-5.56, -1.10)**	**0.003**
Age	0.12 (0.05, 0.20)	0.002	0.12 (0.04, 0.20)	0.004	0.12 (0.04, 0.20)	0.003
Gender (Female)	-0.17 (-1.45, 1.11)	0.795	-0.19 (-1.48, 1.09)	0.769	-0.20 (-1.49, 1.08)	0.758
Body Mass Index (BMI)	0.01 (-0.15, 0.14)	0.937	-0.01 (-0.16, 0.13)	0.865	-0.01 (-0.15, 0.14)	0.927
Education (Years)	0.14 (-0.03, 0.29)	0.102	0.14 (-0.02, 0.30)	0.093	0.13 (-0.04, 0.29)	0.130
Baseline DAD	-0.05 (0.13, 0.03)	0.232	-0.05 (-0.13, 0.03)	0.249	-0.05 (-0.14, 0.03)	0.219
Diagnosis Duration	-0.18 (-0.54, 0.18)	0.328	-0.19 (-0.56, 0.17)	0.301	-0.21 (-0.59, 0.16)	0.265
Study Group (Nilvadipine)	0.06 (-1.17, 1.29)	0.922	0.07 (-1.16, 1.30)	0.909	0.05 (-1.18, 1.28)	0.933
Cholinesterase Inhibitor	0.18 (-1.77, 2.13)	0.856	0.10 (-1.86, 2.06)	0.922	0.19 (-1.76, 1.28)	0.848
Total Medications			0.07 (-0.18, 0.33)	0.568	0.09 (-0.17, 0.34)	0.499
Total Comorbidities			0.04 (-0.26, 0.33)	0.794	0.05 (-0.25, 0.34)	0.753
"Definite" Anticholinergic Use					-1.25 (-3.30, 0.79)	0.231
BPSD					0.85 (-3.16, 1.46)	0.472
DAD Change: 18 Months						
Long-Term Antipsychotic Use	**-4.65 (-7.14, -2.14)**	**<0.001**	**-4.74 (-7.29, -2.18)**	**<0.001**	**-3.86 (-6.64, -1.08)**	**0.006**
Age	0.17 (0.08, 0.26)	<0.001	0.16 (-0.07, 0.26)	0.001	0.17 (0.07, 0.27)	0.001
Gender (Female)	-0.65 (-2.19, 0.90)	0.414	-0.67 (-2.22, 0.88)	0.398	-0.67 (-2.22, 0.87)	0.391
Body Mass Index (BMI)	-0.04 (-0.22, 0.13)	0.619	-0.05 (-0.22, 0.13)	0.573	-0.05 (-0.22, 0.13)	0.609
Education (Years)	0.05 (-0.15, 0.25)	0.650	0.05 (-0.15, 0.25)	0.627	0.04 (-0.13, 0.07)	0.717
Baseline DAD	-0.03 (-0.13, 0.07)	0.567	-0.03 (-0.13, 0.07)	0.585	-0.03 (-0.13, 0.07)	0.549
Diagnosis Duration	-0.16 (-0.63, 0.32)	0.516	-0.16 (-0.63, 0.32)	0.521	-0.17 (-0.66, 0.31)	0.485
Study Group (Nilvadipine)	0.62 (-0.86, 2.10)	0.412	0.63 (-0.85, 2.10)	0.405	0.62 (-0.85, 2.10)	0.406
Cholinesterase Inhibitor	0.62 (-1.69, 2.93)	0.598	0.57 (-1.75, 2.89)	0.633	0.69 (-1.63, 3.01)	0.561
Total Medications			0.05 (-0.26, 0.35)	0.766	0.07 (-0.24, 0.37)	0.665
Total Comorbidities			0.06 (-0.30, 0.42)	0.741	0.07 (-0.29, 0.43)	0.710

"Definite" Anticholinergic Use					-1.87 (-4.33, 0.59)	0.136
BPSD					-1.09 (-3.98, 1.80)	0.461

AD = Alzheimer Disease, BMI = Body Mass Index, ADAS-Cog = Alzheimer's Disease Assessment Scale, Cognitive Subsection, CDR-Sb = Clinical Dementia Rating, Sum of Boxes, BPSD = Behavioural and Psychological Symptoms of Dementia.

5:6 Conclusion

In our study long-term antipsychotic use was associated with greater cognitive decline and dementia progression in community-dwelling older adults with mild–moderate AD. We found no effect of ongoing BDZR use on cognitive scores in those with mild to moderate AD over 18 months. However, ongoing use of these medications was associated with an increased risk of adverse events, delirium, and falls. These findings are consistent with previous evidence encouraging cautious and careful consideration of risks versus benefits of antipsychotic usage and benzodiazepine usage in people with AD. It also highlights the importance of guidelines on antipsychotic usage and benzodiazepine usage in any prescribing tool used in people with dementia.

Chapter 6

The associations of overall anticholinergic burden and statin use on adverse outcomes in the NILVAD cohort

6:1 Background

Older people with AD have a higher number of co-morbidities than those without. Many medications prescribed to people with AD are prescribed to treat these conditions but may still effect cognitive function. The total number of medications, but also the type of medication prescribed, requires consideration when reviewing prescribing practices in this group. In particular the total anticholinergic burden of medication. It is well accepted that medications with a high anticholinergic burden increases the risk of cognitive impairment and subsequent dementia diagnosis in community dwelling older adults [9,36,111] . Despite this medications with a high anticholinergic burden are frequently prescribed for older people [112]. Existing literature investigating the effect of anticholinergic medication on people living with a diagnosis of dementia demonstrated increased risk of falls, stroke, unscheduled hospitalisation and mortality [113]. The literature on the effect of anticholinergic medications on the cognitive outcomes of patients with an existing diagnosis of dementia is less well studied. The most commonly prescribed medication to treat cognitive decline in patients with a diagnosis of Alzheimer's Disease dementia are cholinesterase inhibitors. The co-existent prescription of medication with a high anti-cholinergic burden in this group may interfere with the effect of the prescribed cholinesterase inhibitors. The existing literature investigating this cohort is conflicting but to date studies have failed to demonstrate a significant benefit in reducing the anticholinergic burden in this group [114].

The co-existence of neurodegenerative disease and cardiovascular disease is common in older adults. Alzheimer Dementia (AD) and vascular disease dementia are the two most common types of dementia. Increasingly, AD and vascular pathology have been recognised to co-occur often as mixed pathology in cases of dementia [115]. People with AD commonly have

co-morbid vascular conditions. In older adults, the use of statins for secondary prevention is well-established, with statin use associated with reduced incidence of cardiovascular disease, cardiovascular death, fatal and non-fatal stroke [116-118]. Their use in people with dementia is less well studied. There is a potential role for statins in the prevention and treatment in people living with AD however there is no consensus on the use of statins in this group. In fact a recent systematic review [119] demonstrated much of the research to date on statin use in older people excludes those with a diagnosis of dementia.

The existing literature surrounding statin use in people living with AD is conflicting both their role in prevention but also their use in those with established cognitive impairment or dementia [120—123]. Many retrospective observational studies have demonstrated a reduced incidence of dementia in statin users [121-124] with some studies specifically demonstrating a protective effect of statins in the development of AD [125]. However this was not confirmed in randomised controlled trials and an early Cochrane review in 2001[126] and subsequent reviews[127] failed to demonstrate a protective role of statins in the development of dementia. The effect of statin use on the cognition in those with established disease is less well studied but also debated. Some studies have suggested improved cognitive scores in statin users with others including a recent Cochrane review demonstrating no effect [128-130].

In addition to the inconsistencies in the evidence for their use in the prevention and treatment of dementia, more recently concerns over reversible cognitive impairment in statin users have resulted in the FDA issuing a black-box warning to healthcare professionals against reversible statin related cognitive impairment [14]. This evidence is primarily based on case reports and early randomised control trials [131] in people without an existing diagnosis of dementia.

We assessed the effect of medications with a high anticholinergic burden and statins on cognitive performance and for effects on adverse events in our population [132].

6:2 Methodology

The NILVAD dataset was used to assess both the effect of anticholinergic burden and investigate the use of statins in this cohort. We included medication taken for the entire study duration for this trial. Information on historical medication use was not available so excluded.

Anticholinergic Cognitive Burden scores (ACB score) were calculated for each participant's medication by two physicians (AD, CM). Each medication is assigned a score of between 0 - 3 with this system. Medications with a score of 1 have potential anticholinergic effects with a score of 3 demonstrating an evidence base that this drug may cause delirium. An ACB score was calculated for each participant at various time points throughout the 18 months study duration; week 0, 13, 52 and 78. Participants co-morbidities were reviewed in duplicate to control for 'confounding by indication' for anticholinergic use. This included the presence of urinary incontinence, anxiety disorders and behavioural and psychological symptoms of dementia. These variables were computed as binary indicator variables for regression analyses.

Statin use was defined as use of any agent with the ATC code "C10AA" (HMG-CoA Reductase Inhibitors). Only those using statins for the entire 18 month study duration were considered for inclusion. Non-users were those who had not used statins in the 18 months of study duration. Liver Function Tests (LFTs) included: albumin, total protein, alanine

aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma-glutamyl transferase. Abnormal LFTs were defined as any abnormal LFT at either 0 or 18 months.

6:3 Is ongoing anticholinergic burden associated with greater cognitive decline and dementia severity in mild to moderate Alzheimer's Disease?

6:3:1 Statistical analysis

Statistical analysis was carried out on anonymized data using STATA V.15 (Stata Corp, College Station, TX). Descriptive characteristics were reported as means with standard deviations and medians with interquartile range. Univariate analysis of between-group differences was conducted using T-tests, Chi-square tests and Wilcoxon Rank-Sum tests as appropriate.

In order to analyse the impact of anticholinergic prescription on outcomes, mixed-effects linear regression was used with change in ADAS-Cog/CDR-sb/DAD as the dependent variable and country considered as a random effect. The impact of ongoing anticholinergic burden (ACB Score) was assessed using an *ACB Score*Visit* interaction to assess the effect of ACB score on changes in the three outcomes over time.

In the first instance, this association was tested unadjusted. In Model 1, the association was tested with adjustment for demographic (age, gender, body mass index, years of education) and AD variables (baseline cognitive/severity score as appropriate, diagnosis duration) in addition to study group (*Nilvadipine* vs Placebo) and cholinesterase inhibitor prescription (due to direct pharmacological antagonism). In Model 2, further adjustment was made for total medication burden (polypharmacy) and medical comorbidities. Finally, in Model 3, benzodiazepine use, urinary incontinence, in addition to a history of mood/anxiety disorder or

of behavioural and psychological symptoms of dementia were assessed in order to control for confounding by indication. Results are reported as β coefficients with 95% Confidence Intervals (CIs) and corresponding *p*-values.

In order to carry out sensitivity analysis, we repeated all of the above analyses, excluding participants with an ACB score of 1, representing potential anticholinergics, consistent with previous studies showing associations only for strong/definite anticholinergics (3). Further, in order to classify which medications were contributing to any observed effects, we repeated analysis for antipsychotics, antidepressants, and bladder antimuscarinics separately.

6:3:2 Results

Over one quarter of participants were prescribed a medication with potential or definite anticholinergic properties at baseline (27.9%, n = 142). Definite anticholinergic prescriptions accounted for 13.96% (n = 71) of medications and 13.75 % (n = 70) had potential anticholinergic properties. When analysed by total ACB score 11.98% (n = 61) had a score of 1, 1.96% (n = 10) had a score of 2 and 8.06% (n = 41) had a score of 3. The most frequently prescribed anticholinergic medications with definite anticholinergic properties in this group were Quetiapine, Oxybutynin, Paroxetine and Amitriptyline. The most common medications with potential anticholinergic properties were Trazadone, Venlafaxine, Alprazolam, Furosemide and Risperidone.

Participants prescribed an anticholinergic medication had an increased incidence of polypharmacy and a higher co-morbidity index than those without. The ADAS-Cog 12 and CDR-sb scores were analysed using adjusted mixed linear regression. Adjustment was made for polypharmacy (5 or more medications), medical co -morbidities, benzodiazepine use,

urinary incontinence , history of depression or anxiety and behavioural and psychological symptoms of Dementia. There was no significant difference in cognitive scores between groups using The ADAS-Cog 12 and CDR-sb. Higher ACB scores were significantly associated with greater DAD scores.

Table 10.

Effect of Anticholinergic Cognitive Burden (ACB) Score on Change in ADAS-Cog at 18 Months

	Model 1		Model 2		Model 3	
	β Coef. (95% CI)	*p*-value	β Coef. (95% CI)	*p*-value	β Coef. (95% CI)	*p*-value
ACB Score*Visit	0.28 (−0.94 to 0.64)	.144	0.28 (−0.93 to 0.65)	.143	0.28 (−0.94 to 0.64)	.144
Age	−0.12 (−0.17 to −0.07)	.001	−0.13 (−0.18 to −0.07)	.001	−0.12 (−0.17 to −0.06)	.001
Gender (female)	−0.38 (−1.23 to 0.47)	.378	−0.40 (−1.26 to 0.45)	.354	−0.48 (−1.34 to 0.38)	.271
Body mass index (BMI)	−0.19 (−0.29 to −0.09)	.001	−0.20 (−0.29 to −0.10)	.001	−0.20 (−0.30 to −0.10)	.001
Education (years)	0.05 (−0.06 to 0.16)	.374	0.05 (−0.06 to 0.17)	.356	0.07 (−0.04 to 0.19)	.202
Basline ADAS-Cog	0.06 (0.01 to 0.10)	.009	0.06 (0.02 to 0.11)	.008	0.06 (0.02 to 0.10)	.006
Diagnosis duration	−0.32 (0.57 to −0.07)	.012	−0.32 (0.57 to −0.07)	.012	−0.34 (0.59 to −0.09)	.008
Study group (Nilvadipine)	0.19 (−0.62 to 1.00)	.644	0.19 (−0.62 to 1.00)	.640	0.14 (−0.67 to 0.93)	.640
Cholinesterase inhibitor	−0.39 (−1.68 to 0.91)	.557	−0.40 (−1.70 to 0.89)	.539	−0.27 (−1.57 to 1.03)	.730
Polypharmacy			−0.03 (−0.97 to 0.90)	.948	−0.09 (−1.05 to 0.86)	.681
Total comorbidities			−0.07 (0.12 to 0.25)	.496	−0.05 (0.13 to 0.24)	.845
Urinary incontinence					−0.48 (−2.5 to 1.44)	.566
Benzodiazepine use					0.74 (−0.52 to 2.00)	.250
Mood/anxiety disorder					0.94 (−0.15 to 2.02)	.092
BPSD					−0.57 (−2.13 to 0.99)	.475

AD = Alzheimer Disease, BMI = Body Mass Index, ADAS-Cog = Alzheimer's Disease Assessment Scale, Cognitive Subsection, CDR-Sb = Clinical Dementia Rating, Sum of Boxes, BPSD = Behavioural and Psychological Symptoms of Dementia, CI = confidence interval

Table 11

Effect of Anticholinergic Cognitive Burden (ACB) Score on Change in CDR-sb and DAD at 18 Months

Change in CDR-sb	Model 1		Model 2		Model 3	
	β Coef. (95% CI)	*p*-value	β Coef. (95% CI)	*p*-value	β Coef. (95% CI)	*p*-value
ACB Score*Visit	0.10 (−0.03 to 0.23)	.145	0.10 (−0.03 to 0.22)	.142	0.10 (−0.03 to 0.22)	.138
Age	−0.03 (−0.05 to −0.01)	.001	−0.03 (−0.05 to −0.02)	.001	−0.03 (−0.05 to −0.01)	.001
Gender (female)	−0.17 (−0.47 to 0.13)	.264	−0.18 (−0.48 to 0.13)	.253	−0.18 (−0.48 to 0.13)	.251
Body mass index (BMI)	−0.02 (−0.06 to −0.01)	.238	−0.02 (−0.06 to −0.01)	.209	−0.03 (−0.06 to −0.01)	.143
Education (years)	−0.01 (−0.05 to 0.03)	.545	−0.01 (−0.05 to 0.03)	.659	−0.01 (−0.04 to 0.04)	.955
Baseline CDR-sb	0.12 (0.06 to 0.17)	.001	0.12 (0.06 to 0.17)	.001	0.11 (0.05 to 0.16)	.001
Diagnosis duration	−0.07 (−0.16 to −0.02)	.141	−0.07 (−0.16 to −0.02)	.122	−0.06 (−0.15 to −0.04)	.225
Study group (Nilvadipine)	0.08 (−0.21 to 0.37)	.589	0.08 (−0.21 to 0.37)	.595	0.05 (−0.24 to 0.34)	.735
Cholinesterase inhibitor	−0.11 (−0.56 to 0.34)	.632	−0.13 (−0.58 to 0.33)	.587	−0.18 (−0.58 to 0.33)	.589
Polypharmacy			0.23 (−0.10 to 0.56)	.179	0.23 (−0.16 to 0.52)	.293
Total comorbidities			−0.00 (−0.07 to 0.06)	.976	−0.00 (−0.06 to 0.07)	.988
Urinary incontinence					−0.40 (−1.08 to 0.29)	.260
Benzodiazepine use					0.14 (−0.30 to 0.57)	.544
Mood/anxiety disorder					0.24 (−0.14 to 0.62)	.218
BPSD					0.62 (0.08 to 1.15)	.024
Change in DAD						
ACB Score*Visit	−1.52 (−2.83 to 0.21)	.023	−1.51 (−2.83 to 0.21)	.023	−1.53 (−2.83 to 0.23)	.021

Age	0.24 (−0.06 to −0.43)	.010	0.23 (−0.04 to −0.42)	.017	0.19 (−0.01 to −0.38)	.060
Gender (female)	1.08 (−2.00 to 4.16)	.492	1.02 (−2.07 to 4.11)	.517	0.88 (−2.20 to 3.96)	.576
Body mass index (BMI)	0.02 (−0.53 to 0.17)	.310	−0.20 (−0.54 to 0.16)	.282	−0.17 (−0.52 to 0.19)	.356
Education (years)	0.16 (−0.23 to 0.55)	.416	0.17 (−0.22 to 0.56)	.392	0.14 (−0.26 to 0.54)	.486
Baseline DAD	−0.04 (−0.24 to 0.53)	.702	−0.04 (−0.23 to 0.16)	.719	−0.08 (−0.28 to 0.12)	.447
Diagnosis duration	−0.37 (1.27 to −0.52)	.420	−0.38 (−1.27 to −0.52)	.414	−0.28 (−1.20 to −0.66)	.562
Study group (Nilvadipine)	0.78 (−3.73 to 2.17)	.605	0.78 (−3.72 to 2.17)	.604	0.68 (−3.64 to 2.27)	.650
Cholinesterase inhibitor	−0.39 (−3.21 to 6.07)	.546	1.33 (−3.32 to 5.98)	.574	1.21 (−3.44 to 5.86)	.611
Polypharmacy			0.54 (−2.83 to 3.92)	.752	0.47 (−2.98 to 3.92)	.788
Total comorbidities			0.14 (−0.14 to 0.34)	.681	0.19 (−0.48 to 0.85)	.579
Urinary incontinence					−0.69 (−8.01 to 10.95)	.796
Benzodiazepine use					−0.37 (−4.83 to 4.10)	.872
Mood/anxiety disorder					−0.69 (−4.61 to 3.23)	.731
BPSD					−2.17 (−7.72 to 18.10)	.441

AD = Alzheimer Disease, BMI = Body Mass Index, ADAS-Cog = Alzheimer's Disease Assessment Scale, Cognitive Subsection, CDR-Sb = Clinical Dementia Rating, Sum of Boxes, BPSD = Behavioural and Psychological Symptoms of Dementia, CI = confidence interval.

6:4 What is the Impact of Ongoing Statin Use on Cognitive Decline and Dementia Progression in Older Adults with Mild- Moderate Alzheimer Disease ?

6:4:1 Statistical analysis

STATA V.15 (Stata Corp, College Station, Texas, USA) was used for all data analysis in the study with $p<0.05$ considered statistically significant. Between group univariate analysis was conducted using T Tests, Wilcoxon rank sum tests and chi-squared tests as appropriate. Descriptive statistics are reported as means (standard deviations), medians (interquartile ranges) and proportions (percentages).In ^order to analyse the association of ongoing statin use on change in ADAS-Cog/CDR-Sb/DAD over 18 months, mixed effects linear regression was used, with study site as a random effect. The association between statin use and the dependent variable was modelled using a statin time interaction term. This was tested unadjusted (Model 1) in the first instance, followed by adjustment for age, gender, baseline score (ADAS-Cog/CDR-Sb/DAD as appropriate), study group (Nilvadipine vs placebo) and years of formal education (Model 2). Model 3 made further adjustment for blood pressure, diabetes mellitus and polypharmacy.

In order to examine the association between ongoing statin use and incident adverse events/serious adverse events over the study duration, Poisson regression was used, again unadjusted in the first instance (Model 1) followed by further adjustment for age, gender body mass index, education and study group (Model 2). In model 3, adjustment was made for baseline ADAS-Cog and CDR-Sb in addition to medical co-morbidity (no. of medical co-morbidities) and polypharmacy. To assess potential associations between statin use and

deranged Liver Function Tests (LFTs) and incident falls, we used logistic regression with the same model adjustment as the Poisson models.

6:4:2 Results

Of 510 participants included in the NILVAD Study (mean age: 72.9 years; 61.9% female), 34.9% (178/510) were prescribed a statin for the 18 month study duration. Statin users vs non-users did not differ significantly in age, gender, blood pressure category, educational attainment, history of diabetes or BMI . There was a significantly greater burden of polypharmacy and medical co-morbidity in statin users vs. non-users ($\chi^2 = 40.2$, $p<0.001$, $z = -6.4$, $p<0.001$ respectively).

On longitudinal analysis, there was no association between ongoing statin use and the rate of either cognitive decline (ADAS-Cog) under any of the three models specified above (See Table 11. A trend for a slower rate of dementia progression was observed on the CDR-Sb with statin use, although results were not statistically significant (β: -0.34, -0.71-0.02, p = 0.07 unadjusted; -0.37, -0.74-0.01, p = 0.05 for model 1; -0.37, -0.76-0.02, p = 0.06 for model 2). Similarly, there was no association between ongoing statin use and change in scores on the DAD.

Table 12. Statin Use, Cognitive Decline and Dementia Progression over 18 Months

	Model 1		**Model 2**		**Model 3**	
Predictor	***β* -Coef (95% CI)**	***P***	***β* -Coef (95% CI)**	***P Value***	***β* Coef (95% CI)**	***p***
Change in ADAS-Cog						
Statin Use* Visit	-0.67 (-1.71, 0.36)	0.20	-0.74 (-1.77, 0.29)	0.16	-0.77 (-1.86, 0.33)	0.17
Age			-0.12 (-0.17, -0.07)	<0.001	-0.14 (-0.19, -0.08)	<0.001

Gender (Female)			-0.34 (-1.19, 0.51)	0.43	-0.60 (-1.51, 0.32)	0.20
Baseline ADAS-Cog			0.05 (0.00, 0.09)	0.03	0.04 (-0.01, 0.08)	0.09
Group (Nilvadipine)			0.14 (-0.67, 0.95)	0.73	-0.09 (-0.98, 0.80)	0.83
BMI, mg/kg^2			-0.17 (-0.26, -0.07)	0.001	-0.17 (-0.27, -0.07)	0.001
Years of Formal Education			0.02 (-0.09, 0.13)	0.68	0.07 (-0.05, 0.19)	0.26
Blood Pressure (Category) *Low* *Normal* *High*					1. (Ref) 0.61 (-0.63, 1.85) 0.09 (-1.16, 1.35)	 0.34 0.88
Diabetes Mellitus					0.57 (-2.27, 1.13)	0.51
Total Comorbidities					0.13 (-0.07, 0.33)	0.19
Polypharmacy					0.90 (-0.12, 1.91)	0.08
Change in CDR-Sb						
Statin Use* Visit	-0.34 (-0.71, 0.02)	0.07	-0.37 (-0.74, 0.01)	0.05	-0.37 (-0.76, 0.02)	0.06
Age			-0.03 (-0.05, -0.01)	0.002*	-0.03 (-0.05, -0.01)	0.001*
Gender (Female)			-0.16 (0.46, -0.14)	0.29	-0.19 (-0.51, 0.13)	0.25
Baseline CDR-Sb			0.10 (0.05, 0.16)	<0.001*	0.09 (-0.03, 0.15)	0.003*
Group (Nilvadipine)			0.06 (-0.23, 0.35)	0.70	-0.04 (0.35, 0.29)	0.82
BMI, mg/kg^2			-0.01 (-0.05, 0.02)	0.47	-0.01 (-0.05, 0.02)	0.47
Years of Formal Education			-0.02 (-0.06, 0.02)	0.83	-0.01 (-0.05, 0.04)	0.81

Blood Pressure (Category) *Low* *Normal* *High*					1. (Ref) 0.26 (-0.18, 0.70) 0.15 (-0.29, 0.59)	 0.24 0.51
Diabetes Mellitus					0.12 (-0.49, 0.72)	0.72
Total Comorbidities					-0.01 (-0.07, 0.07)	0.71
Polypharmacy					0.48 (0.12, 0.83)	0.01
Change in DAD						
Statin Use* Visit	-2.00 (-5.70, 1.70)	0.29	-1.91 (-5.65, 1.82)	0.31	-2.44 (-6.57, 1.69)	0.25
Age			0.22 (0.04, 0.41)	0.02	0.26 (0.05, 0.48)	0.02
Gender (Female)			0.81 (-2.26, 3.89)	0.60	1.45 (-1.98, 4.88)	0.41
Baseline DAD			-0.04 (-0.23, 0.15)	0.71	-0.06 (0.27, 0.16)	0.61
Group (Nilvadipine)			-0.78 (-3.73, 2.16)	0.60	-1.06 (-4.41, 2.30)	0.54
BMI, mg/kg^2			-0.21 (-0.55, 0.14)	0.24	-0.21 (-0.60, 0.17)	0.28
Years of Formal Education			0.16 (-0.22, 0.54)	0.40	0.23 (-0.21, 0.67)	0.31
Blood Pressure (Category) *Low* *Normal* *High*					1. (Ref) 1.32 (-3.33, 5.96) 0.39 (-4.34, 5.12)	 0.58 0.87
Diabetes Mellitus					-3.47 (-9.87, 2.93)	0.29
Total Comorbidities					0.06 (-0.67, 0.79)	0.87
Polypharmacy					-0.51 (-4.33, 3.31)	0.79

BMI = Body Mass Index, ADAS-Cog = Alzheimer's Disease Assessment Scale Cognitive Subsection; CDR-Sb: Clinical Dementia Rating Score, Sum of Boxes; DAD: Disability Assessment for Dementia

A similar number in both groups experienced a serious adverse event (61/333; 18.3% for non-users vs 30/178; 16.9% for statin users). Ongoing statin use was not associated with incident adverse events or serious adverse events under either unadjusted or fully adjusted models. Further, there was no association between ongoing statin use and incident unscheduled GP visits or unscheduled hospitalisations. (See Table 13) . Overall, 181 (37.9%) participants had at least one abnormal LFT at either 0 or 18 months. There was no association between statin use and abnormal LFTs. Further, whilst 88 individuals (17.9%) experienced at least one fall over the study period, there was no significant association between statin use and incident falls.

Table 13 -Statin use and association with adverse events, serious adverse events, unscheduled hospitalisations and unscheduled GP visits over 18 months

	IRR (95% CI)	**P Value**	**IRR (95% CI)**	**P Value**	**IRR (95% CI)**	**P Value**
Adverse Event						
Statin Use	1.09 (0.99, 1.18)	0.07	1.09 (0.99, 1.18)	0.08	0.93 (0.85, 1.02)	0.13
Age, years			1.00 (1.00, 1.01)	0.004*	1.00 (0.99, 1.01)	0.35
Gender (Female)			1.14 (1.04, 1.25)	0.05	1.10 (1.00, 1.20)	0.04*
Group (Nilvadipine)			0.92 (0.84, 1.01)	0.08	0.92 (0.85, 1.00)	0.07
Education, years			1.03 (1.02, 1.04)	<0.001**	1.03 (1.02, 1.05)	<0.001**
BMI, mg/kg^2			0.99 (0.98, 1.00)	0.16	0.99 (0.98, 1.00)	0.03*
Baseline ADAS-Cog					1.00 (0.99, 1.01)	0.76
Baseline CDR-Sb					1.00 (0.97, 1.02)	0.64

Total No. Comorbidities					1.03 (1.01, 1.05)	0.004*
Polypharmacy					1.58 (1.43, 1.73)	<0.001**
Serious Adverse Event						
Statin Use	0.93 (0.70, 1.22)	0.57	1.02 (0.77, 1.35)	0.90	0.77 (0.57, 1.03)	0.08
Age, years			1.05 (1.03, 1.08)	<0.001	1.04 (1.03, 1.06)	<0.001
Gender (Female)			0.82 (0.62, 1.07)	0.15	0.73 (0.55, 0.97)	0.03
Group (Nilvadipine)			0.67 (0.50, 0.87)	0.003	0.66 (0.51, 0.87)	0.003
Education, years			1.05 (1.02, 1.08)	0.001	1.07 (1.04, 1.10)	<0.001
BMI, mg/kg^2			0.96 (0.93, 0.99)	0.03	0.96 (0.93, 0.99)	0.01
Baseline ADAS-Cog					1.00 (0.98, 1.02)	0.97
Baseline CDR-Sb					1.07 (1.00, 1.14)	0.05
Total No. Comorbidities					1.04 (0.99, 1.09)	0.15
Polypharmacy					2.62 (1.93, 3.55)	<0.001
Unscheduled GP Visits						
Statin Use	1.33 (1.08, 1.64)	0.008	1.28 (1.04, 1.59)	002	1.01 (0.80, 1.27)	0.93
Age, years			1.00 (0.99, 1.02)	0.58	1.00 (0.98, 1.01)	0.62
Gender (Female)			1.12 (0.90, 1.40)	0.32	1.05 (0.84, 1.32)	0.64
Group (Nilvadipine)			0.94 (0.76, 1.15)	0.53	0.94 (0.76, 1.16)	0.56
Education, years			1.01 (0.99, 1.04)	0.32	1.02 (0.00, 1.05)	0.08
BMI, mg/kg^2			1.02 (0.99, 1.04)	0.12	1.01 (0.99, 1.04)	0.32
Baseline ADAS-Cog					1.01 (0.99, 1.02)	0.17
Baseline CDR-Sb					0.98 (0.93, 1.03)	0.47
Total No. Comorbidities					1.05 (1.01, 1.10)	0.04
Polypharmacy					1.98 (1.56, 2.51)	<0.001
Unscheduled Hospitalisations						
Statin Use	0.91 (0.59, 1.41)	0.67	0.93 (0.60, 1.46)	0.77	0.81 (0.51, 1.29)	0.37
Age, years			1.03 (1.00, 1.06)	0.03	1.02 (0.99, 1.05)	0.12
Gender (Female)			1.05 (0.68, 1.61)	0.84	1.00 (0.65, 1.55)	0.99

Group (Nilvadipine)			0.78 (0.52, 1.19)	0.25	0.80 (0.53, 1.21)	0.29
Education, years			1.04 (0.99, 1.09)	0.16	1.04 (0.99, 1.10)	0.10
BMI, mg/kg^2			0.99 (0.94, 1.04)	0.57	0.98 (0.93, 1.03)	0.46
Baseline ADAS-Cog					0.99 (0.96, 1.02)	0.56
Baseline CDR-Sb					1.06 (0.96, 1.18)	0.26
Total No. Comorbidities					1.03 (0.95, 1.13)	0.44
Polypharmacy					1.64 (1.04, 2.58)	0.04

BMI = Body Mass Index, ADAS-Cog = Alzheimer's Disease Assessment Scale Cognitive Subsection; CDR-Sb: Clinical Dementia Rating Score, Sum of Boxes

6:5 Conclusion

Ongoing use of anticholinergic medication was associated with greater dementia progression on the DAD, but not the CDR-sb. Further attention to medication reviews in patients with AD is warranted, in particular, to stop anticholinergic medications which may no longer be needed, or where needed, switch to an agent of the same class which lacks anticholinergic properties. This is particularly pertinent where patients are on more than one anticholinergic medication. Such intervention may produce cognitive benefits in this vulnerable cohort.

We support the continued use of statins in their role to reduce the risk of atherosclerotic cardiovascular disease in people with dementia. There was no adverse effect on cognition associated with their use demonstrated. The use of statins has been shown to be safe with no increased risk of adverse events and we would recommend their use where indicated for cardiovascular health in people with mild to moderate Alzheimer's disease.

Whilst these findings demonstrated no effect of statin use in the rate of cognitive decline or dementia progression in mild-moderate AD, it is possible that statin use in earlier years (for

instance in midlife) may have beneficial cognitive effects not observed here but reported elsewhere [133,134]. There may also be a role in those with early mild cognitive impairment as suggested by Kemp et al [135] which warrants further study. The use of a cohort with established cognitive impairment is noteworthy given the lack of studies addressing this population, but it must be noted that we cannot deduce conclusions on the role of statins in dementia prevention in the first instance, only on the rate of decline in those with established disease.

Again we highlight the need for considered prescribing in this group and the need for specific prescribing tools for people living with dementia.

Chapter 7

Conclusions, implications of research and areas for future study

7:1 Conclusions and Implications

Polypharmacy and potentially inappropriate prescribing in older people has been increasingly recognised and researched over the past decade. A number of prescribing tools have been developed and are routinely used in clinical practice to improve prescribing in this cohort. More recently there has been increasing interest in older people living with dementia recognising that this group are particularly vulnerable to adverse events from inappropriate prescriptions. This research paper provides a comprehensive review of prescribing practices in this community dwelling cohort of people living with mild to moderate Alzheimer's Disease dementia. We have studied the effects of PIM use in this group overall and focused on the effects particular high risk medications that are frequently prescribed as a PIM. This study is unique in its analysis of the existing prescribing tools for older people and their applicability to people living with dementia.

We have demonstrated a significant burden of inappropriate prescribing in our cohort with over half the cohort prescribed at least one PIM and with 24% of people being prescribed three or more PIMs. The existing literature estimates PIM use in people living with dementia to be between 11% and 74%, our study is consistent with this. Our study is also consistent with existing literature highlighting the medication groups most frequently prescribed a PIM. Benzodiazepines, SSRIs and other medications with a high anti cholinergic burden were most frequently prescribed. We have demonstrated that those who were older, longer since diagnosis of dementia and with a higher number of total medications were at greatest risk of being prescribed a potentially inappropriate medication. Identification of these risk factors can guide us in clinical practice.

A particular strength of our study is the analysis of the effect of potentially inappropriate prescribing in people with mild to moderate dementia. We demonstrated that those who were prescribed a PIM had increased incidence of adverse events, serious adverse events and unscheduled attendance with GPs and admissions to hospital compared to those without a PIM. We know unscheduled admission to hospital in those living with dementia can be associated with adverse outcomes including the loss of functional independence. Identifying PIMs as an independent risk factor for unscheduled care highlights the importance of improving prescribing practice in this cohort. We have assessed the most frequently prescribed PIMs and the effects of these high risk groups on our participants with dementia. We demonstrated that higher anticholinergic burden scores (ACB scores) were associated with greater Disability Assessment for dementia scores. We have also demonstrated greater cognitive decline in those prescribed long term antipsychotics which was sustained across an 18 month study duration. Benzodiazepines were associated with increased incidence of delirium, falls and adverse events. Through analysing the effects of individual medication groups as well as PIM use overall in people living with dementia, we add to the literature highlighting the importance of individualised and considered prescribing in this group.

We know that not all those prescribing for people living with dementia are experts in dementia care. The complexity of prescribing in this group has been demonstrated through our findings. This highlights the role for education and prescribing guidance for those prescribing for people living with dementia. Our study is novel in its assessment of the existing prescribing tools and their application to people with dementia. Hukins et al [136] carried out a detailed systematic review of the use of existing prescribing tools in people living with dementia. They demonstrated the use of these tools in research and clinical practice. However to our knowledge no study has previously analysed the applicability of

these prescribing tools for this cohort despite their frequent use. Through detailed literature review and consultation with an expert panel we have assessed the prescribing tools in this light.

We have found that there is significant heterogeneity in the existing prescribing tools and variability in which tools are applied clinically. We found that key considerations such as the use of antipsychotics and anticholinergic burden were absent from some tools. There was variability also in the interdisciplinary team members involved in tool design. We support further research and the design of a single internationally accepted prescribing tool for older people to include specific considerations for people with dementia across the spectrum of the disease.

7:2 Limitations

This research has some limitations to consider. Firstly the literature review and early part of this research including the systematic review was performed in 2020. As with all things in medicine the research is constantly evolving and there will have been further developments from the beginning of this project to now.

Our NILVAD cohort provided a unique opportunity to investigate a controlled group of people living with mild to moderate AD. Whilst there were many benefits associated with the strict nature of recruitment into a randomised control trial we must also accept the limitations. The participants in NILVAD met specific criteria (such as absence of neurological disease for instance), this may effect the generalisability of the findings as it may result in a highly selected cohort of individuals with dementia.

Although the NILVAD trial was a very well conducted clinical trial, data on adverse events, medications, clinical co-morbidities etc were collected via clinical interview from the participant or caregiver. There is always a possibility of missing data or inconsistencies with this. This is true also for the analysis of co-morbidities and medication lists by myself and colleagues. We performed this in duplicate to try to remove any possibility of error but there is a possibility that potential diagnoses were missed in certain instances, thus inadequately controlling for such comorbidities.

This research is performed on a cohort of people with mild to moderate Alzheimer's disease. This is a strength of our study as much of the research to date investigating prescribing practices is in moderate or advanced disease. However as newer disease modifying therapies come on stream for dementia there is a need to focus even earlier in the disease such as mild cognitive impairment, an area for future consideration.

7:3 How will this research effect my clinical practice as a Geriatrician?

Undertaking this research has reinforced to me the challenges for people living with a diagnosis of dementia and those caring for them. It has also highlighted to me the challenges we face when treating people living with dementia and the many important considerations with each treatment decision. The disease has many stages and clinical presentations, we constantly must adjust treatment plans and review goals of care with patients and carers. One of the most challenging treatment decisions for patients, carers and physicians alike is the weighing up of treatment for responsive behaviours in dementia and the effects of these

medications on cognition, falls, fractures, cardiovascular risks and even mortality. The balance of avoiding distressing symptoms for patients and avoiding over-sedation often takes time, multiple medication changes or dose adjustments and frequent review. The importance of advocating for the clinical resources to provide this care is highlighted to me. Whilst much of the research above highlights the risk of prescribing medications such as antipsychotics, anticholinergics and benzodiazepines we must not forget that these medications often also provide symptomatic relief for patients when used correctly.

This research has reminded me the importance of appropriate deprescribing in this cohort, particularly at the moderate and severe stages of dementia. I am armed with a huge wealth of knowledge of prescribing in older people having completed this research and I will use this daily in my clinical prescribing. However people with dementia are often cared for by a number of other specialists to manage co-morbid conditions or general practitioners. This highlights to me the role of education and training , the role of a prescribing tool to aid non experts and my own role in teaching colleagues and junior doctors the important considerations when prescribing for this group.

Finally this has reminded me that as geriatricians we have the privilege of caring for people at their most vulnerable, the effect of each treatment decision is highlighted by this research and reminds me of the huge reasonability associated with prescribing privileges. I will continue to put the patient at the centre of all decisions, take time to explain the risks and benefits to patients and carers and treat the person in their entirety.

7:4 Future directions

A strength of our study is the wealth of information gathered on each participant. The participant being part of a tightly controlled randomised control trail minimised bias and ensured accuracy of information recorded. In future I would like to compare our findings to a group of community dwelling participants whom are not part of a randomised control trial to ensure applicability across all community populations with mild to moderate dementia. I would like to analyse prescribing cascades in this group and in particular the association between prescribing cascades and adverse outcomes such as hospitalisation and unscheduled care.

Our research provides a comprehensive overview of inappropriate prescribing for people living with dementia. This research can be used to provide education to non-experts in dementia care whom are routinely prescribing to older people living with dementia. We have identified the need for international consensus on prescribing in people living with dementia and the risks of inappropriate prescribing in this group. We encourage the development of a prescribing tool that has application across the entire duration of the illness to be used in all prescribing in people with dementia to ensure uniformity and best practice in all settings. Separately we encourage increased inclusion of people living with dementia in clinical trials to address the gap in the literature and knowledge of medication effects in this particular group. This will inform prescribing in this cohort and ensure all practice is evidence based.

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