Deprescribing of Acetylcholinesterase Inhibitors in Older Adult Nursing Home Residents with Severe Dementia

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Joshua Niznik, PharmD, PhD

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This thesis/dissertation was presented

by

Joshua Niznik, PharmD, PhD

It was defended on

May 14, 2019

and approved by

Joshua M. Thorpe, PhD, MPH, Division of Pharmaceutical Outcomes and Policy, University of North Carolina

Inmaculada Hernandez, PharmD, PhD, Assistant Professor, Department of Pharmacy and Therapeutics, University of Pittsburgh

Joseph T. Hanlon, PharmD, MS, Professor, Department of Medicine – Geriatric Division, University of Pittsburgh

Samuel Poloyac, PharmD, PhD, Professor, Department of Pharmaceutical Sciences, University of Pittsburgh

Thesis Advisor/Dissertation Director:
Carolyn T. Thorpe, PhD, MPH, Division of Pharmaceutical Outcomes and Policy, University of North Carolina

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Clinical guidelines and expert opinion suggest that deprescribing or discontinuing AChEIs may be an appropriate strategy to reduce medication burden and risk for adverse events, given the lack of evidence to support their effectiveness in patients with severe dementia. There have been few well-designed studies with adequate sample size that have evaluated the effects of deprescribing AChEIs on outcomes. The findings of this dissertation address a critical gap in the literature by examining the epidemiology and outcomes associated with deprescribing AChEIs.

The first study examined the epidemiology of deprescribing AChEIs and found that deprescribing was more likely in older residents who exhibited signs of declining clinical status. By contrast, regional rurality and non-geriatric prescriber specialty was associated with reduced likelihood of deprescribing. In the second study, we evaluated the association of deprescribing AChEIs with behavioral outcomes including depression severity and aggressive behaviors. The overall prevalence of behavioral symptoms in this population was low and deprescribing AChEIs was not found to be associated with a significant change in depressive symptoms or aggressive behaviors. Finally, we examined the downstream impact of deprescribing AChEIs on the use of other medications. Deprescribing AChEIs was associated with a general reduction in the total number of other non-AChEI medications prescribed, including a reduced likelihood of receiving new antipsychotic prescriptions. Deprescribing was not associated with an increased likelihood of discontinuing strong anticholinergic medications that may have originally been prescribed as part of the cholinergic prescribing cascade.

The findings presented in this dissertation suggest that deprescribing AChEIs may be a safe approach to reduce medication burden without worsening behavioral symptoms in older nursing home residents with severe dementia. Targeted educational interventions aimed at non-geriatric prescribers in rural nursing facilities may help to improve the dissemination and implementation of deprescribing in clinical practice.

Table of Contents

Preface xiii

1.0 INTRODUCTION 1

1.1 BACKGROUND ON DEMENTIA 2

1.2 PHARMACOTHERAPY FOR THE TREATMENT OF DEMENTIA 3

1.2.1 Overview 3

1.2.2 Properties of Individual Acetylcholinesterase Inhibitors 5

1.2.3 NMDA Receptor Antagonists 6

1.2.4 Efficacy of Pharmacologic Therapies 7

1.2.5 Safety of Pharmacological Therapies 10

1.2.6 Summary 12

2.0 LIMITED LIFE EXPECTANCY AND DEPRESCRIBING ACHEIS 13

2.1 LIMITED LIFE EXPECTANCY AND DEPRESCRIBING 13

2.2 LITERATURE REVIEW OF EVIDENCE ON DEPRESCRIBING ACHEIS 16

2.2.1 Methods 16

2.2.2 Results and Synthesis 17

2.2.2.1 Qualitative Studies in Patients with Severe Dementia. 17

2.2.2.2 Quantitative Studies in Patients with Severe Dementia. 19

2.2.2.3 Quantitative Studies in Patients with Moderate to Severe Dementia. 20

2.2.3 Discussion 23

2.3 SUMMARY 25

3.0 RESEARCH SUMMARY 27

3.1 OVERVIEW AND SPECIFIC AIMS 27

3.2 CONCEPTUAL MODEL 28

4.0 FACTORS ASSOCIATED WITH DEPRESCRIBING ACHEIS IN OLDER NURSING HOME RESIDENTS WITH SEVERE DEMENTIA 31

4.1 ABSTRACT 31

4.2 INTRODUCTION 32

4.3 METHODS 34

4.3.1 Design & Data Sources 34

4.3.2 Sample 35

4.3.3 Dependent Variable 40

4.3.4 Independent Variables 41

4.3.5 Statistical Analyses 43

4.4 Results 47

4.4.1 Sample Characteristics 47

4.4.2 Primary Analysis 51

4.4.3 Sensitivity Analyses 58

4.5 Discussion 70

4.6 Conclusions 73

5.0 THE IMPACT OF DEPRESCRIBING ACHEIS ON BEHAVIORAL OUTCOMES IN SEVERE DEMENTIA 74

5.1 ABSTRACT 74

5.2 INTRODUCTION 75

5.3 METHODS **77**

5.3.1 Design and Data Sources **77**

5.3.2 Sample **78**

5.3.3 Dependent Variables **80**

5.3.4 Independent Variables **81**

5.3.5 Statistical Analysis **85**

5.4 RESULTS **92**

5.4.1 Sample Characteristics. **92**

5.4.2 Secondary Analysis **101**

5.4.3 Sensitivity Analyses **103**

5.5 DISCUSSION **105**

5.6 Conclusions **109**

6.0 THE IMPACT OF DEPRESCRIBING ACHEIS ON MEDICATION-RELATED OUTCOMES **111**

6.1 ABSTRACT **111**

6.2 INTRODUCTION **112**

6.3 METHODS **114**

6.3.1 Design and Data Sources **114**

6.3.2 Sample construction **115**

6.3.3 Dependent Variables **116**

6.3.4 Independent Variables **118**

6.3.5 Statistical Analyses **119**

6.4 RESULTS **121**

6.4.1 Sample Characteristics 121

6.4.2 Impact of Deprescribing AChEIs on Incident Antipsychotic Prescriptions 124

6.4.3 Impact of Deprescribing AChEIs on Discontinuation of Strong Anticholinergic Medications 126

6.4.4 Sensitivity Analyses 130

6.5 DISCUSSION 134

6.6 CONCLUSIONS 138

7.0 CONCLUSIONS AND FUTURE DIRECTIONS 139

7.1 OVERVIEW OF SCOPE OF STUDY 139

7.2 SUMMARY OF FINDINGS 140

7.3 IMPLICATIONS 142

7.4 STRENGTHS AND WEAKNESSES 144

7.5 FUTRE DIRECTIONS 146

Appendix A 147

Appendix B 150

Appendix C 161

Bibliography 168

List of Tables

Table 1-1 Pharmacokinetic and pharmacodynamic properties of AChEIs 6

Table 4-1 - Characteristics of Elderly Nursing Home Residents with Severe Dementia Receiving AChEIs 48

Table 4-2 - Unadjusted and Adjusted Hazards Ratios from Primary Analysis 55

Table 4-3 - Sample Characteristics for Sub-group Analysis by Limited Prognosis Status at Index Assessment 59

Table 4-4 - Adjusted Hazards Ratios for Sub-group Analysis by Limited Prognosis Status 62

Table 4-5 - Unadjusted and Adjusted Hazards Ratios for Sensitivity Analysis using 60-day gap 67

Table 5-1 - Aim 2 Model Descriptions 91

Table 5-2 – Unweighted Assessment-level Characteristics for Aim 2 Analyses 93

Table 5-3 - Inverse Propensity-Weighted Assessment-level Characteristics for Aim 2 Analyses 95

Table 5-4 - Assessment-level Distribution of Behavioral Outcomes 98

Table 5-5 - Model Results for Association of Deprescribing with Depression Severity 99

Table 5-6 - Model Results for Association of Deprescribing with Aggressive Behaviors 100

Table 5-7 - Assessment Level Distribution of total Number of Prescribed Medications 102

Table 5-8 - Model Results for Effect of Deprescribing on Total Number of Medications 102

Table 5-9 - Results of Per-protocol Analysis for Association of Deprescribing with Depression Severity 104

Table 5-10 - Results of Per-protocol Analysis for Association of Deprescribing with Aggressive Behaviors 104

Table 5-11 - Results of Per-protocol Analysis for Association of Deprescribing with Total Number of Medications 104

Table 6-1 - Sample Characteristics for Chapter 6 Analyses (Episode-level and Assessment-level) 122

Table 6-2- Frequency of Incident Antipsychotic Prescribing in Sample..... 125

Table 6-3 - Model Results for Effect of Deprescribing on Incident Antipsychotic Use 125

Table 6-4 – Frequency of Anticholinergic Discontinuation in Sample 127

Table 6-5 - Model Results for Effect of Deprescribing on Anticholinergic Discontinuation 129

Table 6-6 - Results of Per-Protocol Analysis for Effect of Deprescribing on Incident Antispsychotic Prescriptions..... 131

Table 6-7 - Results of Per-Protocol Analysis for Effect of Deprescribing on Anticholinergic Discontinuation 131

Table 6-8 - Model Results for Effect of Deprescribing on Antimuscarinic Anticholinergic Discontinuation 133

List of Figures

Figure 3-1 - Conceptual Model 30

Figure 4-1 – Sample Construction for Aim 1 Analyses 37

Figure 4-2 - Cumulative Incidence of Deprescribing During Observation Period 52

Figure 4-3 - Cumulative Incidence of Deprescribing AChEIs Stratified by Limited Prognosis Designation 65

Figure 5-1 - Sample Construction for Aim 2 Analyses 79

Figure 5-2 - Data Structure and Coding for Chapter 5 Analyses 83

Figure 5-3 – Directed Acyclic Graph of Time-dependent Confounding 86

Figure 5-4 - Derivation of Inverse Propensity Treatment Weights for Chapter 5 Analyses 87

Figure 6-1 Data Structure and Coding for Chapter 6 Analysses 117

Figure 6-2 Derivation of Inverse Propensity Treatment Weights for Chapter 6 Analyses 120

Figure 6-3 - Proportion of Anticholinergic Classes Prescribed and Discontinued 128

Preface

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1.0 INTRODUCTION

Dementia is a life-limiting illness affecting over 5 million Americans[1] and more than 46 million world-wide.[2] The clinical progression of dementia is characterized by a gradual decrease in cognitive function, eventually leading to overall functional decline. Dementia represents an estimated economic burden of over $800 billion attributable to the advanced care needs for these patients including comorbidity burden, medications, assistance from formal or informal caregivers, frequent hospitalizations and emergency visits, and ultimately nursing home placement.[1,2] Interventions to reduce costs and improve the efficiency, safety, and quality of care in this population are needed, particularly in the nursing home, where between 50-80% of residents have dementia.[1,3,4]

One major area that can be targeted in this population is the use of medications. Due to the high level of comorbidity burden that often accompanies dementia in older adults, most patients in this population receive five to ten medications on a daily basis.[5,6] While many of these medications are appropriate for management of chronic conditions, it is estimated that up to 86% of medications prescribed to dementia patients may be seen as potentially inappropriate due to their potential for adverse effects as patients near the end of life.[5,7-9] Given the complex medication needs and increasing vulnerability to medication-related adverse effects associated with advanced age, interventions to improve the safety and effectiveness of medication use have the potential to be particularly impactful in improving the efficiency of patient care provided in this population.

1.1 BACKGROUND ON DEMENTIA

Dementia is defined as a decline in one or more cognitive domains (memory, language, and executive function) to a degree that is disruptive to normal functioning.[10,11] Older age is the most common risk factor for dementia, with most cases being diagnosed in individuals over the age of 65.[1] Dementia is diagnosed through history-taking from the patient and the use of objective cognitive evaluations to identify impairment in: short-term memory, reasoning and handling complex tasks, visuospatial abilities, language functions, and changes in personality or behavior.[10,12,13] The differentiation that sets apart dementia from mild cognitive impairment is the inability to function in daily activities.

Dementia can be characterized into one of several types depending on the underlying neurodegenerative cause including Alzheimer's disease, vascular dementia, and Lewy body dementia.[14] Alzheimer's disease is by far the most common underlying cause of dementia, representing up to 70% of cases.[15] The primary pathologic feature of Alzheimer's disease is the presence of neuritic plaques and neurofibrillary tangles in the cortical and medial temporal areas of the brain, which is accompanied by degeneration of neurons and synapses and cortical atrophy.[16] The presence of these plaques also causes changes in the synthesis and degradation of acetylcholine and impaired cholinergic signaling. In addition, Alzheimer's disease also leads to disrupted signaling along NMDA pathways that eventually leads to neuronal toxicity mediated by glutamate.[15] Vascular dementia is induced by some type of cerebrovascular event that causes damage to various areas of the brain. While different in mechanism, the inflammation and atrophy associated with these cerebrovascular events ultimately leads to similar deficits in neurotransmission seen in Alzheimer's disease.[17] Lewy body dementia is often diagnosed closely with Parkinson's disease and is characterized by the presence of Lewy bodies, or protein

aggregates found within neurons, that induce neurodegeneration and impaired neurotransmission, similar to the other dementias described above.[18]

The exact mechanism by which the pathological features of the various types of dementia arise is not well understood. However, it is generally accepted that the cognitive decline associated with dementia is caused primarily by the neuronal destruction that results from the various pathologies described above. The initial treatment goal for individuals diagnosed with dementia is to slow or delay the rapid decline in cognition associated with this disease. However, as dementia progresses to advanced stages, treatment goals may shift towards management of behavioral and psychological symptoms of dementia (BPSD), which include agitation, depression, and aggression.

1.2 PHARMACOTHERAPY FOR THE TREATMENT OF DEMENTIA

1.2.1 Overview

Due to the general lack of understanding of how the various pathological changes associated with dementia arise, the goal of current pharmacologic treatment strategies is not to reverse the degenerative processes leading to loss of cognitive function, but instead to preserve cognitive function by maintaining neurotransmission in remaining healthy neurons.[14,19] This is achieved by two different mechanisms, both of which are related to regulation of neurotransmitters. The first seeks to enhance neurotransmission across the healthy neurons that remain by increasing the availability of the neurotransmitter acetylcholine (Ach).[20] The second

mechanism seeks to reduce overstimulation of neurons and the resulting neurotoxicity that is caused by dysfunction of pathways that regulate synaptic concentrations of glutamate.

Acetylcholinesterase inhibitors (AChEIs) were the first class of medications approved for the treatment of dementia and include tacrine, donepezil, rivastigmine, and galantamine. Although tacrine was the first AChEI approved by the FDA, it has since been discontinued due to its elevated risk for hepatotoxicity.[21] AChEIs enhance neurotransmission along cholinergic pathways by inhibiting degradation of Ach by acetylcholinesterase. The cholinergic system is one of the primary neurotransmitter systems in the brain and is responsible for regulating executive functions and memory, which are affected by dementia.[15] Acetylcholine is the main neurotransmitter of this system with receptors on both pre- and post-synaptic membranes. The neurodegeneration associated with dementia results in decreased levels of acetylcholine and thus reduced signaling along these pathways.[22] AChEIs reversibly inhibit the enzyme acetylcholinesterase in the brain thus increasing the degree and duration of neurotransmission by Ach. This enhanced neurotransmission in the frontal regions of the brain provides a means to compensate for the overall decreased cholinergic activity due to the loss of neurons that accompanies the progression of dementia.[23] All three currently available medications are approved by the FDA for the treatment of mild to moderate dementia.[10] Donepezil, rivastigmine, and galantamine share the same primary mechanism of action, however there are a few differences between them with respect to their individual pharmacologic properties.[14,22] **Table 1-1** provides information on the pharmacokinetic and pharmacodynamics properties of each individual medication.

1.2.2 Properties of Individual Acetylcholinesterase Inhibitors

Donepezil is a selective, reversible inhibitor of acetylcholinesterase and the only medication in this class approved for the treatment of all stages of dementia (mild, moderate, and severe).[24] In addition to its primary mechanism of action, donepezil has also been shown to independently induce allosteric modulation of neuronal Ach receptors that may further enhance neuronal signaling.[25] Donepezil has the best bioavailability of the AChEIs, is available via oral dosage forms and requires only once daily dosing, which makes it an attractive option from the patient perspective.

Rivastigmine is a pseudo-irreversible inhibitor of acetylcholinesterase, meaning that reversibility at the binding site is slower compared to a readily reversible chemical entity.[23] Unlike donepezil, rivastigmine is only approved for the treatment of mild or moderate dementia and requires twice daily dosing.[26] However, it is the only medication in this class that is available as a non-oral dosage form, via a transdermal patch.[27] The transdermal formulation of rivastigmine is also approved for the treatment of mild or moderate dementia and offers the advantage of fewer reported adverse effects than its oral counterpart.[28]

Galantamine is a selective, reversible inhibitor of acetylcholinesterase that is approved for the treatment of mild or moderate dementia.[29] Much like donepezil, it also induces allosteric modulation of neuronal Ach receptors thereby potentially enhancing efficiency of neurotransmission.[23] Galantamine requires twice daily dosing, which may be less advantageous from the patient perspective.

Table 1-1 Pharmacokinetic and pharmacodynamic properties of AChEIs

Medication	Typical Dosage Range	Bioavail.	Metabolism	Clearance	Half-Life
Donepezil (oral)	5mg-23mg once daily	100%	Hepatic (CYP2D6, CYP3A4)	Urine (57%); Feces (15%)	70hrs
Galantamine (oral)	4mg-12mg twice daily	90%	Hepatic (CYP2D6)	Urine (20%)	7hrs
Rivsatigmine (oral)	1.5mg-6mg twice daily	36%	Cholinesterase-mediated hydrolysis in brain; minimal hepatic	Urine (97%); Feces (0.4%)	1.5hrs
Rivastigmine (transdermal)	4.6mg-13.3mg once daily	40%	Cholinesterase-mediated hydrolysis in brain; minimal hepatic	Urine (97%); Feces (0.4%)	3hrs

Among the currently approved AChEIs, donepezil is the most commonly prescribed, followed by rivastigmine and galantamine which are prescribed at similar rates.[30,31]

1.2.3 NMDA Receptor Antagonists

An additional and complementary mechanism for slowing the cognitive decline associated with dementia involves inhibition of NMDA receptors on neurons. In patients with dementia, decreased activity along cholinergic pathways results in excess concentrations of extracellular glutamate that is free to continue to bind with NMDA receptors. This excess of glutamate leads to a continuous background level of stimulation along the neuron, making true physiological signals more difficult to detect.[22] Blocking this background level of stimulation with NMDA receptor antagonist enhances the ability of the cholinergic system to transmit signals along these pathways because they are easier to distinguish.

Memantine is the only NMDA receptor antagonist that is FDA approved, and only for the treatment of severe dementia.[10,32,33] It is a non-competitive, voltage-dependent NMDA receptor antagonist, meaning that it is effectively blocks the background-level stimulation caused by excess

glutamate, but will dissociate and allow neurotransmission to proceed in the presence of true physiologic signals.[22] Memantine is most often added as combination therapy in patients already being treated with AChEIs when dementia symptoms progress in severity. Memantine is available as an immediate release formulation that is dosed twice daily or an extended release formulation that is dosed once daily.[34] Only one combination product exists that includes both an AChEI and NMDA receptor antagonist. Namzaric (memantine HCl extended-release + donepezil HCl) is a product that contains a fixed dose of donepezil (AChEI) and memantine (NMDA antagonist) and was approved for the treatment of moderate or severe dementia by the FDA in 2014.[35]

About half of all older adults with dementia receive pharmacologic agents (AChEIs, memantine, or both) to treat the progression of dementia.[36,37] A recent analysis studying treatment patterns of dementia in Medicare beneficiaries found that among treated patients, approximately 47% received AChEIs only, 41% received combination therapy, and only 12% received memantine alone. In addition, the analysis found that community-dwelling older adults had a higher overall treatment rates than patients residing in nursing homes (65% vs. 35%), but the distribution of individual therapies is relatively consistent in both settings.[36]

1.2.4 Efficacy of Pharmacologic Therapies

The primary outcome in evaluating efficacy in the treatment of dementia is change in cognitive function, which can be measured in a number of ways using standardized clinical assessment tools. The most common methods employed for measuring cognitive function in studies of dementia are the MMSE[38] and the ADAS-cog[39]. The MMSE is a short evaluation that is often used in clinical practice to evaluate cognitive function in elderly individuals across several domains including orientation, attention, memory, language, and visual-spatial skills. The ADAS-

cog evaluates similar domains, but was developed instead considering features of cognitive decline specific to Alzheimer's disease and thus may have enhanced ability to classify severity of cognitive impairment than the MMSE.[40]

Meta-analyses of randomized or placebo-controlled studies have shown that the individual AChEIs have comparable efficacy in managing cognitive decline in dementia[41-47], suggesting that the slight pharmacologic differences described here do not actually confer significant additional contributions to their overall therapeutic efficacy.[14] Systematic reviews of randomized controlled trials consistently report that all three medications in this class have comparable efficacy in treating dementia, exhibiting an overall positive effect on cognitive function compared to placebo.[14,45,48,49] However, although the differences in change in cognitive function scores between treatment and placebo often reach statistical significance, these estimates do not often reach a level that is clinically meaningful. For example, pooled estimates of change in cognitive function across types of dementia range from 0.8-1.6 points for the MMSE and 1.4-2.7 points for the ADAS-cog, but a clinically significant change on either scale is defined as a difference of 3 points for the MMSE or 4 points for the ADAS-cog.[14,49]

Another important point that must be taken into account is that nearly all randomized trials of AChEIs have been conducted exclusively in patients with mild to moderate dementia, limiting generalizability of the efficacy of these agents to patients with more advanced disease.[14] The few studies that have included patients with severe dementia or moderate-severe dementia either report findings that had minor clinical significance or were inconclusive.[50-57] There are currently no studies examining efficacy that have been conducted in populations specifically with end-stage dementia.[14]

There is also little evidence to support the long-term use of these agents (i.e. 1 year or longer).[58] Randomized controlled trials evaluating effectiveness tend to be shorter in duration, with most only evaluating outcomes after 3-6 months of use and few evaluating outcomes longer than 1-year.[45] Randomized studies of longer duration are plagued with problems related to internal validity including high drop-out rates or methods to addressing missing observations that have questionable validity.[58] Most observational studies that have evaluated long-term clinical outcomes report that long-term use of AChEIs is not associated with significant risks[58,59], but multiple clinical guidelines suggest there is not strong evidence to suggest that the cognitive benefits of these drugs are sustained in the long-term.[45,60] In fact, randomized studies conducted over longer durations provide evidence to suggest that although some improvement is still seen when compared to placebo, this difference declines over time and with progressive cognitive impairment.[61-64] Additional studies are greatly needed to determine the cognitive trajectories associated with long-term use of these agents, considering the potential for unnecessary exposure to adverse effects.

In addition to cognitive function, studies of efficacy also address behavioral symptoms and quality of life as secondary outcomes, but provide only modest support for use of AChEIs for these indications. For BPSD, a systematic review of studies that have examined the effect of AChEIs on BPSD found that there is limited evidence to support efficacy.[65] The majority of studies evaluated outcomes using the Neuropsychiatric Inventory questionnaire and only three of fourteen studies included found significant, but modest, improvement compared to placebo. Among the fourteen studies that were identified, only four actually examined BPSD as the primary outcome, suggesting that the majority of studies may be underpowered to evaluate these outcomes. However, given the significant risks associated with other pharmacologic categories that may be

used to treat BPSD, mainly antipsychotics, use of AChEIs may still be justified. Evidence for use of AChEIs to improve quality of life is also lacking. A systematic review of the effectiveness of the impact of various pharmacological interventions, including AChEIs and memantine, found that neither donepezil nor memantine has a significant impact on improving quality of life in patients with dementia and the effects of galantamine and rivastigmine on quality of life have not been studied.[66]

1.2.5 Safety of Pharmacological Therapies

The use of AChEIs in the treatment of dementia is not without risks. Adverse effects of AChEIs are likely a significant contributor to treatment non-persistence in older adults. Many of the adverse effects associated with AChEIs are a result of their primary mechanism of action that leads to increased levels of cholinergic activity. Increased levels of the neurotransmitter Ach are beneficial for cognition in the brain, but can be problematic in other pathways. Neurons that rely on Ach for signaling are present in numerous systems including the central nervous system, the autonomic sympathetic nervous system, and skeletal muscle.[14,23] Therefore, the excess of Ach may have adverse consequences for neurotransmission along other pathways potentially inducing cardiovascular events, muscle weakness, or gastrointestinal irregularity.

The most commonly reported adverse effects of AChEIs, according to an analysis of pharmacovigilance databases in the United States and Canada, included nausea/vomiting, falls, neurological dysfunction, and diarrhea.[67] This is also supported by evidence from systematic reviews of RCTs and observational studies, in which the rate of gastrointestinal adverse effects was increased by 2 to 5 times and the rate of any adverse event was increased by 2.5 times in patients receiving AChEIs compared to placebo.[14,48,68] Other clinically significant adverse effects

that have been reported include bradycardia and urinary incontinence.[14,58,69] By contrast, a recently published network meta-analysis examining the potential risks associated with AChEIs across both RCTs and observational studies found that among all potential adverse events that have been reported, only gastrointestinal effects and headache were significantly increased among patients compared to placebo.[68] Although the statistical significance of the adverse effects associated with AChEIs is somewhat inconsistent across studies, this should not diminish the clinical significance and severity of adverse effects from the patient perspective. Pooled trial data suggests that the adverse effects of AChEIs are a significant contributor to trial withdrawal rates, increased by more than twofold compared to patients receiving placebo.[14]

One clinically significant adverse effect not studied in the referenced systematic review was the potential for urinary incontinence, which may be induced by increased cholinergic activity in the autonomic nervous system. Incontinence is sometimes seen as a part of the progression of dementia and so this adverse effect is often unrecognized as being medication-induced. Instead of addressing the reversible adverse effect caused by AChEIs, physicians will often prescribe an anticholinergic medication to treat urge incontinence in a phenomenon known as a "prescribing cascade".[70,71] The use of anticholinergic medications in older adults is not without risk, as they have been shown to increase the likelihood for falls[72,73], functional decline[74,75], cognitive decline[73,75,76], and delirium[77,78]. In addition, the concurrent usage of anticholinergics and AChEIs is particularly problematic because the opposing mechanisms of action likely cancel out their respective therapeutic benefits, leading to suboptimal efficacy of both medications.

1.2.6 Summary

To summarize, AChEIs exhibit modest efficacy in slowing the cognitive decline associated with dementia in older adults. While statistically significant, the clinical significance of the effect of these medications is questionable and there is little evidence to support long-term efficacy of these agents, despite the fact that many patients remain on therapy for an indefinite duration of treatment. The use of AChEIs in older adults is not without risk for negative outcomes. Prescribers and patients should be cognizant of adverse effects that can result in increased potential for potentially inappropriate prescribing and substantially increased risk for adverse drug events that may ultimately result in hospitalization. Additional evidence is needed to understand the balance between the safety and efficacy of AChEIs, particularly in patients with advanced age and severe dementia that are infrequently included in currently published studies.

2.0 LIMITED LIFE EXPECTANCY AND DEPRESCRIBING ACHEIS

2.1 LIMITED LIFE EXPECTANCY AND DEPRESCRIBING

As many as 90% of patients with dementia will be admitted to a nursing home at some point before their death and over two-thirds of these patients will die in this setting.[79] Thus, the nursing home setting is an ideal setting for implementing strategies to improve care for patients with dementia. Patients with severe dementia have an elevated risk for death, with 6-month mortality rates ranging from 20% to as high as 70% in the nursing home.[80-84] Despite evidence of the high risk for mortality in this population, studies have unfortunately found that patients with severe dementia receive suboptimal end of life care. This is likely due to the fact that severe dementia is not often treated as a life-limiting illness leading to lower utilization of hospice and palliative care compared to other populations with limited prognosis such as patients with metastatic cancer.[80,85,86]

As older adults with dementia progress to more severe stages of the disease, the combination of declining quality of life and the prospect of limited life expectancy should drive prescribers to reconsider goals of care when making treatment decisions. This may include limiting the use of invasive procedures, cancer screenings, and life-saving measures, among others, as goals shift from treatment to palliation. Several articles in the literature have proposed frameworks for individualizing different types of preventive interventions in older adults by weighing associated risks and benefits in the context of time to benefit and anticipated remaining life expectancy.[87-89] These frameworks conclude that for older individuals with a life expectancy of less than 6 months to 1 year, many interventions routinely recommended for prevention of long-

term complications of disease likely do not produce adequate benefits relative to their associated short-term risks.

The use of medications for prevention or treatment of chronic diseases is one such intervention. Reconsidering the appropriateness of medications used is an excellent opportunity to increase quality of life and minimize avoidable risks, particularly in nursing home patients with severe dementia. Polypharmacy is highly prevalent in this population and unfortunately, medications that contribute to polypharmacy are often inappropriate for use in older adults, either due to increased risk for adverse events or limited benefit. Studies have found that among nursing home residents with severe dementia, the prevalence of use of potentially inappropriate medications ranges from 35% to up to 86%, with statins and AChEIs reported as some of the most frequently prescribed. [5,7,90-92] AChEIs are considered to be potentially inappropriate due to their modest efficacy in improving cognitive function, lack of evidence to support long-term efficacy in severe dementia, and potential for numerous adverse effects, as discussed in Chapter 1.

Deprescribing is defined as the discontinuation or gradual withdrawal of medications when the anticipated therapeutic benefits no longer outweigh the risks of adverse events associated with treatment.[93,94] A model developed by Holmes et al.[88] proposes that medications in the elderly should be re-evaluated for appropriateness based on four primary factors: treatment targets, goals of care, time until benefit, and remaining life expectancy. AChEIs are frequently identified by prescribers as being a potential target for deprescribing[92,95,96] for the reasons noted above. However, some prescribers report hesitation due to the general lack of uncertainty of downstream effects associated with deprescribing.[95,96]

In addition to delaying the cognitive decline associated with dementia, AChEIs have been shown in some studies to also reduce the incidence and severity many of the behavioral symptoms

that often accompany dementia.[97-100] Individual studies of deprescribing AChEIs have reported that withdrawing treatment may result in worsening of aggressive behaviors, hallucinations, anxiety, apathy, sleep or appetite changes, and depression.[97,101,102] However, these studies report inconsistent results as to which behaviors are most affected, making the clinical relevance of their findings uncertain. Another important consideration is the potential positive and negative impact on the prescribing of other medications. Since patients may experience a worsening of behavioral symptoms after discontinuing AChEIs, as described above, deprescribing AChEIs has the potential to lead to a subsequent increase in the usage of high-risk antipsychotic medications to manage these symptoms.[103,104] Conversely, deprescribing of AChEIs may also initiate a chain of events that leads to an overall reduction in polypharmacy, specifically the usage of potentially inappropriate anticholinergic medications. Use of AChEIs is associated with increased usage of potentially inappropriate anticholinergic medications due to the increased levels of cholinergic activity caused by AChEIs, inducing adverse effects including urinary incontinence, gastrointestinal upset, and others. Unrecognized as being drug-induced, these adverse effects are subsequently treated with anticholinergic medications in a phenomenon known as a "prescribing cascade".[70] The concurrent usage of these medications with AChEIs is particularly problematic because their opposing mechanisms of action likely cancel out the therapeutic benefits of either drug, leading to suboptimal efficacy. Unfortunately, the effect of deprescribing AChEIs on medication-related outcomes has not been studied extensively in the literature so we can only speculate the potential impact on the overall quality of prescribing.

Previously published reviews of the implications associated with deprescribing AChEIs have limited clinical utility due to limited generalizability to patients with severe dementia. Studies of deprescribing tend to include populations with a range of dementia severities, with

majority being those with mild to moderate dementia, creating the potential for bias due to inherent differences in treatment decisions by dementia severity. There is stronger evidence to suggest that patients with mild to moderate dementia will have a positive response to treatment with AChEIs as opposed to those with more severe dementia.[14] The questionable probability of continued clinical efficacy and higher likelihood for mortality in the setting of end stage disease makes patients with severe dementia the most appropriate candidate population for deprescribing AChEIs. To date, there has been no systematic review of the literature focusing specifically on patients with severe dementia.

2.2 LITERATURE REVIEW OF EVIDENCE ON DEPRESCRIBING ACHEIS

A literature review was conducted to identify studies of deprescribing of AChEIs, focusing specifically on older adults with severe dementia. Studies were included that evaluated either outcomes associated with deprescribing or prescriber, patient, and caregiver perceptions of deprescribing.

2.2.1 Methods

A literature search was conducted using Medline, Ovid, and Google Scholar. Searches were conducted with combinations of several MeSH terms and key words for acetylcholinesterase inhibitors (cholinesterase inhibitor, ChEI, AChEI, antidementia, dementia drug therapy, Alzheimer's disease drug therapy) used in combination with "deprescribe" or "discontinue medication". References from systematic reviews and meta-analyses were also reviewed to

identify individual studies. The results from the combined searches were screened by reviewing abstracts to identify studies in which the objectives explicitly mentioned discontinuing or withdrawing AChEIs. This subset of results was then reviewed using full text to characterize the dementia severity of patients included. Six studies were identified that focused specifically on patients with severe dementia, three of which were qualitative studies. In order to provide a more comprehensive review of the literature, we also reviewed several studies that included patients with moderate or severe dementia with the caveat that their generalizability to patients with severe dementia may be limited.

2.2.2 Results and Synthesis

The combined searches initially yielded 724 total results. Review of abstracts from these studies found 64 studies that explicitly mentioned discontinuing or withdrawing AChEIs in their objectives. Within this group, there was a significant amount of heterogeneity in terms of the dementia severity of patients included. The majority (n=42) were non-specific and were conducted among patients with any severity of dementia. The remainder were limited to specific severities of dementia and included the following: mild only (n=1), mild to moderate (n=10), moderate to severe (n=4), or severe only (n=6).

2.2.2.1 Qualitative Studies in Patients with Severe Dementia.

Three qualitative studies focused specifically on patients with severe dementia evaluated prescriber perceptions and experiences with deprescribing AChEIs. Prescribers were either interviewed or completed surveys and included neurologists, psychiatrists, geriatricians, and hospice medical directors. Interviewees were asked to comment on the effectiveness of AChEIs

in severe dementia, when and why they would consider deprescribing these medications, or potential barriers to deprescribing.

Only one study asked prescribers to estimate the prevalence of prescribing of AChEIs for their patients with severe dementia. Shega et al. reported that the treatment rate among hospice patients with severe dementia was over 20% in the majority of practices.[96] Across studies, most prescribers agreed that AChEIs had limited efficacy and could be safely deprescribed in patients with severe dementia, but that this decision should be primarily based on patient or caregiver preferences and presence of adverse effects. There was less agreement over what constituted a decline significant enough to warrant discontinuation, however. In one study[95], prescribers expressed difficulty providing a time frame after which they would feel comfortable deprescribing and also what would constitute decline significant enough to recommend deprescribing, either based on MMSE scores, emergence of BPSE, or ADLs. In both cases, this was primarily attributable to a combination of variability in the perceived clinical significance of different evaluations for cognitive function and the general lack of available evidence to support long-term efficacy of AChEIs. This sentiment was echoed in a study by Ray et al.[105] where less than half of prescribers said that a "significant decline" in physical function would justify deprescribing and even less (40%) based on an MMSE score < 10. Other clinical characteristics mentioned that may trigger prescribers to consider discontinuation included significant clinical deterioration as measured by the Global Deterioration Scale (GDS), swallowing difficulties, weight loss, worsening BPSD, and initiation of palliative care.[95]

The most significant barrier to discontinuing AChEIs reported was family preference, with 72% of prescribers in one study having encountered resistance when this was recommended to families.[96] Prescribers reported that about half of patients ultimately discontinued therapy when

recommended.[96] In terms of prescribers' perceptions of the impact of deprescribing AChEIs based on practice experience, the study by Shega et al. reported that approximately 30% of prescribers reported observing accelerated cognitive and functional decline and also emergence of challenging patient behaviors.[96]

2.2.2.2 Quantitative Studies in Patients with Severe Dementia.

Three small studies were identified that examined the impact of discontinuing AChEIs in older adults with severe dementia. The first study by Burns et al.[106] was a prospective clinical study that was conducted in a sample of 42 nursing home residents with advanced dementia based on cognitive assessments within the MDS. Prescribers and surrogate decision-makers were asked to volunteer to have AChEIs withdrawn. Residents were followed every 3 months for a total of 18 months during the study. The following outcomes were measured at each visit: (ADLs), the cognitive performance scale (CPS), weight, functional ability, and neuropsychiatric inventory (NPI). At the end of the 18 months of follow up, no significant differences were observed between those who continued on therapy and those who had AChEIs withdrawn.

The second study by Simpson et al.[107] was a 12-week prospective audit of patients enrolled in the Alzheimer's Medication Service, a treatment monitoring service for dementia patients in the UK. A total of 25 patients were recommended to discontinue treatment based on low MMSE scores indicating severe dementia (MMSE<12) based on guidelines from the National Institute for Clinical Excellence. In this small group, 68% of individuals experienced a negative event (5 deaths and 12 global deteriorations). However, there was no identifiable comparator group in this study and all results for the impact of deprescribing were purely descriptive with no formal statistical analysis.

The third study by Suzuki et al.[108] was an open-label trial of 44 inpatient or nursing home residents with severe dementia. Subjects in the discontinuation group (n=22) included older adults with severe dementia who had been receiving a stable dose of donepezil for at least 3 years, whereas the control group consisted of patients with severe dementia who were not currently receiving AChEIs (n=22). Neuropsychiatric symptoms and cognitive function were evaluated using the NPI and MMSE respectively. The investigators also examined changes in the use of psychotropic medications over time, including benzodiazepines, antidepressants, and antipsychotics. After 16 weeks of follow-up, no significant changes in NPI or MMSE scores and no significant changes in the use of psychotropic medications were noted between groups.

Taken together, these three small studies[106-108] suggest that discontinuing AChEIs does not result in significant worsening of neuropsychiatric symptoms in patients with severe dementia. While informative for exploratory purposes, it should be noted these studies are severely limited by their small sample sizes, inadequate control groups, lack of adjustment for potential confounders, and questionable generalizability. Well-designed studies with larger samples and adequate adjustment for potential confounders are needed to further explore the impact of deprescribing AChEIs specifically in patients with severe dementia in order to inform clinical decision-making.

2.2.2.3 Quantitative Studies in Patients with Moderate to Severe Dementia.

Due to the small number of studies focusing specifically on severe dementia and the fact that all were qualitative in design, we also evaluated four studies that were limited to patients with moderate or severe dementia patients. In this group, there were three randomized studies and one observational study.

Among randomized studies, there was heterogeneity in terms of the populations studied and outcomes evaluated. Two of three randomized studies were conducted in community-dwelling older adults with Alzheimer's disease.[102,109] These actually utilized the same study population with the first being the primary analysis of the DOMINO-AD trial.[110] The primary analysis sought to compare the effect of donepezil monotherapy, donepezil discontinuation, monotherapy with memantine, and dual therapy with donepezil and memantine on cognitive function and ADLs.[102] The second study was a post-hoc secondary analysis comparing the effect of each on nursing home placement.[109] In the DOMINO-AD trial, patients treated with donepezil for at least 3 months were randomized to one of the following: continue donepezil, discontinue donepezil, discontinue donepezil and start memantine, continue donepezil and start memantine. For patients who discontinued donepezil, the initial dose was reduced by half for four weeks prior to being stopped completely. In the first study, outcomes were evaluated over a period of 52 weeks, whereas in the second study, patients were followed for up to 4 years following randomization.

The third randomized study by Herrmann et al.[111] was conducted in long-term care residents with Alzheimer's disease with a primary outcome of change in Clinician Global Impression of Change (CGI-C) and secondary outcomes evaluating safety, efficacy, and tolerability. In this study, patients were required to have been treated with any AChEI for at least 2 years and on a stable dose for 3 months prior to randomization. On study entry, patients were subsequently randomized to either continue treatment or receive placebo following a 2 week taper, but were only followed for 8 weeks.

The two DOMINO-AD studies[102,109] found statistically significant associations between donepezil discontinuation and cognitive function, ADLs, and nursing home placement. The original analysis of the DOMINO-AD trial[102] found an average difference of +1.9 points in MMSE

(superior cognition) and -3.0 points in ADLs (superior physical function) between groups, the difference favoring continuation of donepezil at 52 weeks. It should be noted, however, that only the difference in MMSE scores reached a threshold considered to be a clinically significant difference. The post-hoc analysis[109] found that withdrawal of donepezil significantly increased the risk for nursing home placement by 2-fold in the first year after stopping treatment, but this was not significant at time points beyond 1 year. By contrast, the study by Herrmann et al.[111] conducted in nursing home patients found no significant worsening in overall global status between those that continued on therapy and those that discontinued at 8 weeks, nor were there any significant differences in secondary outcomes related to safety, efficacy, or tolerability.

The only observational study of deprescribing AChEIs in patients with moderate or severe dementia was a descriptive pilot study conducted in French nursing home residents that sought to describe reasons for deprescribing, safety of sudden discontinuation, and changes in cognition, BPSD, and use of psychotropic medications over 6 months.[112] Thirty-three patients were enrolled to have their antidementia therapy (AChEIs or memantine) reviewed by a multidisciplinary for potential discontinuation and in 22 cases, therapy was deprescribed. Reasons for recommending discontinuation, as reported by the multidisciplinary group included severe dementia, lack of therapeutic benefit, and high usage of concomitant psychotropic medications. Sudden discontinuation without a taper was well-tolerated as no adverse events were observed. Differences in the change in MMSE scores by 6 months between discontinuation and continuation groups were minimal and not clinically significant[113] (-1.8 points and -2.2 points, respectively). No worsening of BPSD was observed with discontinuation and interestingly, a reduction in the number of psychotropic drugs was seen.

All of the randomized studies had low risk for bias when evaluated using the Cochrane Risk of Bias Tool. However, it is worth noting that the study by Herrmann et al.[111] had a significantly smaller sample size than either of the studies by Howard et al.[102,109] and thus may have been underpowered to detect differences between groups. The observational pilot study[112] by contrast has high potential for bias as it was purely descriptive in nature, had a small sample size, and no formal statistical analyses were conducted. In addition, selection bias may have been a problem as patients were not randomized to discontinue therapy, but rather were selected by a multidisciplinary team based on clinical evaluation which may have been biased towards more clinically stable patients.

2.2.3 Discussion

There is a paucity of evidence evaluating the implications of deprescribing AChEIs in patients with severe dementia. Only three quantitative studies have been conducted in patients with severe dementia. Although these studies suggest no significant worsening of behavioral symptoms, their interpretation is severely limited due to small sample sizes, questionable generalizability, and inadequate control groups. Qualitative studies related to patients with severe dementia found that most prescribers believe that AChEIs can be safely discontinued in patients with severe dementia, but that it may result in negative consequences. The general lack of evidence to when deprescribing is appropriate combined with family resistance were noted as major barriers to deprescribing. Extending our inclusion criteria to include studies of patients with moderate or severe dementia yielded four additional articles. Two of three randomized studies found statistically significant associations between deprescribing and negative outcomes including cognitive function, functional ability, and nursing home placement. Although statistically

significant, changes in cognition and functioning seen did not reach levels considered to be clinically significant. In an observational pilot study, changes in cognition over time were minimal between patients who discontinued therapy and those who continued on treatment and no changes in BPSD or use of antipsychotic medications were observed.

The heterogeneity of findings seen among the four studies evaluating outcomes associated with deprescribing in patients with moderate or severe dementia may be explained by differences in study design. The two randomized studies by Howard et al. that did find statistically significant associations between deprescribing and outcomes had larger sample sizes compared to the studies by Herrman and Pyero. Here, larger sample size translates to greater statistical power in these analyses to detect differences between groups. We also noted above that while the three randomized studies had limited potential for bias, the pilot study had high potential for bias due to its descriptive nature and lack of rigorous design. Another factor that has implications for the interpretation of findings is the variation in length of follow-up for evaluating outcomes across studies. The studies by Howard et al. followed patients for 52 weeks for evaluating cognitive and functional outcomes and 1-3 years for nursing home placement. By contrast, the studies by Herrmann et al. and Pyero et al. only followed patients for 8 weeks and 6 months after discontinuation, respectively. Again, only the studies with longer follow-up were able to find statistically significant associations between deprescribing and outcomes. This suggests that for patients with moderate to severe dementia, the implications of deprescribing may only be relevant in the long-term, which may be less relevant for patients with limited life expectancy due to severe dementia, as opposed to short-term.

We must acknowledge the potentially limited generalizability of the four studies evaluating outcomes to patients with severe dementia, as the studies also included patients with moderate

dementia. As mentioned above, there is stronger evidence to support efficacy of AChEIs in treating mild or moderate dementia, but limited evidence for severe dementia. It is likely that there is a ceiling effect in terms of the improvement that AChEIs can provide that is dependent on the dementia severity. In patients who have already progressed to severe dementia, the actual improvement in cognition from use of AChEIs may be reduced to a point where discontinuing therapy would result in less of an impact than it would for patients with moderate dementia. We also acknowledge that long-term risks associated with deprescribing, such as those observed in the two studies by Howard et al., may not be as relevant for patients with severe dementia who have already been admitted to the nursing home, given the high risk for 6-month mortality in this population. Finally, we must consider that only one of the four studies was conducted specifically in patients in the nursing home setting and thus generalizability may be limited only to community-dwelling older adults with dementia.

2.3 SUMMARY

A limited number of studies have evaluated the impact of deprescribing of AChEIs on outcomes in patients with severe dementia, despite the fact that these patients are the most likely to be targeted for deprescribing. Qualitative studies conducted among prescribers revealed that most believe that AChEIs can be safely deprescribed in patients with severe dementia. However, the general lack of evidence to support deprescribing combined with resistance from patients and families creates uncertainty over when and how to stop these medications. The few quantitative studies that have been conducted in patients with severe dementia suggest that deprescribing may

be safe, but these are severely limited by small sample sizes, inadequate control groups, and questionable generalizability. Studies evaluating outcomes in patients with moderate to severe dementia were few in number and presented inconsistent findings that may be dependent on sample size and whether outcomes are evaluated in the short-term versus long-term. Well-designed studies with larger sample sizes are needed in order to adequately assess the impact of deprescribing AChEIs on clinically relevant outcomes in patients with severe dementia and subsequently inform clinical practice.

3.0 RESEARCH SUMMARY

3.1 OVERVIEW AND SPECIFIC AIMS

The goal of this dissertation, which is structured around 3 independent studies, was to identify factors associated with deprescribing of AChEIs among older adult nursing home patients with severe dementia and subsequently characterize related outcomes. Using administrative data from the MDS and Medicare Parts A, B, and D, we conducted an analysis to identify patient-level, facility-level, and physician-level characteristics that are associated with deprescribing. We then identified downstream effects of deprescribing of AChEIs, including behavioral outcomes and use of potentially inappropriate medications. Specific aims and related hypotheses evaluated in this work included:

Aim 1. Identify factors associated with deprescribing of AChEIs in older adult nursing home patients with dementia, considering patient, provider, and facility characteristics.

Approach: Patient-level factors, provider characteristics, and facility characteristics measured at baseline will be assessed for their association with deprescribing of AChEIs after admission to the nursing home.

Hypothesis 1: Given the lack of evidence surrounding discontinuing AChEIs, a combination of patient, provider, and facility-level factors will be associated with deprescribing AChEIs.

Aim 2. Examine the effect of deprescribing of AchEIs on changes to behavioral outcomes.

Approach: Aggressive and depressive symptoms will be measured to determine whether deprescribing is associated with worsening symptoms over time.

Hypothesis 2: Those who stop using AchEIs will experience modest worsening of behavioral outcomes over time.

Aim 3. Examine the effect of deprescribing of AchEIs on changes in the use of potentially inappropriate antipsychotic or anticholinergic medications.

Approach: We will examine the impact of deprescribing AChEIs on the likelihood of receiving incident antipsychotic prescriptions as well as the likelihood of discontinuing strong anticholinergic medications.

Hypothesis 3: Deprescribing AchEIs will be associated with an increase in the use of antipsychotic medications will increase to manage potential worsening of behavioral symptoms, while strongly anticholinergic medications that are being used concomitantly will be discontinued.

3.2 CONCEPTUAL MODEL

The conceptual model shown in Figure 1 was used to guide variable selection and outline each aim of this project. The model was developed based on a literature review of previous investigations that have studied factors influencing prescribing and represents a synthesis of several applications of behavioral theory applied to deprescribing.[88,114-120]

Four primary categories of factors were identified that likely influence the relationship between AchEI deprescribing and outcomes, they include: demographics, clinical assessment, environment of care, and prescriber knowledge/skills. Demographics include age, race/ethnicity,

sex, marital status, and location prior to admission. Clinical assessment represents factors related to the potential risks associated with deprescribing based on patients' past medical histories and factors related to quality of life based on the patients' current clinical state. Environment of care represents facility-specific factors of nursing homes that enable or restrict prescriber decisions to optimize quality of care. Finally, prescriber knowledge and skills represents the variation in decision-making that may be due to differences in clinical experience and practice specialty.

The studies outlined in the conceptual model provide insight into the factors that influence decisions to deprescribe AChEIs in the setting of advanced dementia as well as the potential downstream effects. The relationship between these factors and deprescribing and outcomes is demonstrated by the arrows connecting portions of the model. Each of the four primary categories of factors act independently to influence the prescriber behavior "deprescribing of AChEIs". In Chapter 4, both individual factors are examined to determine their association with the decision of whether or not to deprescribe AChEIs (Aim 1). Deprescribing subsequently induces downstream effects including changes to behavioral outcomes and medication-related outcomes over time. In Chapter 5, behavioral symptoms, including aggressive symptoms and depression severity, are measured to determine whether or not there is a significant difference in how these change over time between patients who are deprescribed versus those who continue on therapy (Aim 2). In Chapter 6, changes to medication related outcomes are also measured to determine how deprescribing affects: 1) the use of antipsychotic medications that may be added to manage behavioral and psychological symptoms of dementia (BPSD) and 2) the use of medications that may be used to treat adverse effects of AChEIs (strong anticholinergics) (Aim 3).

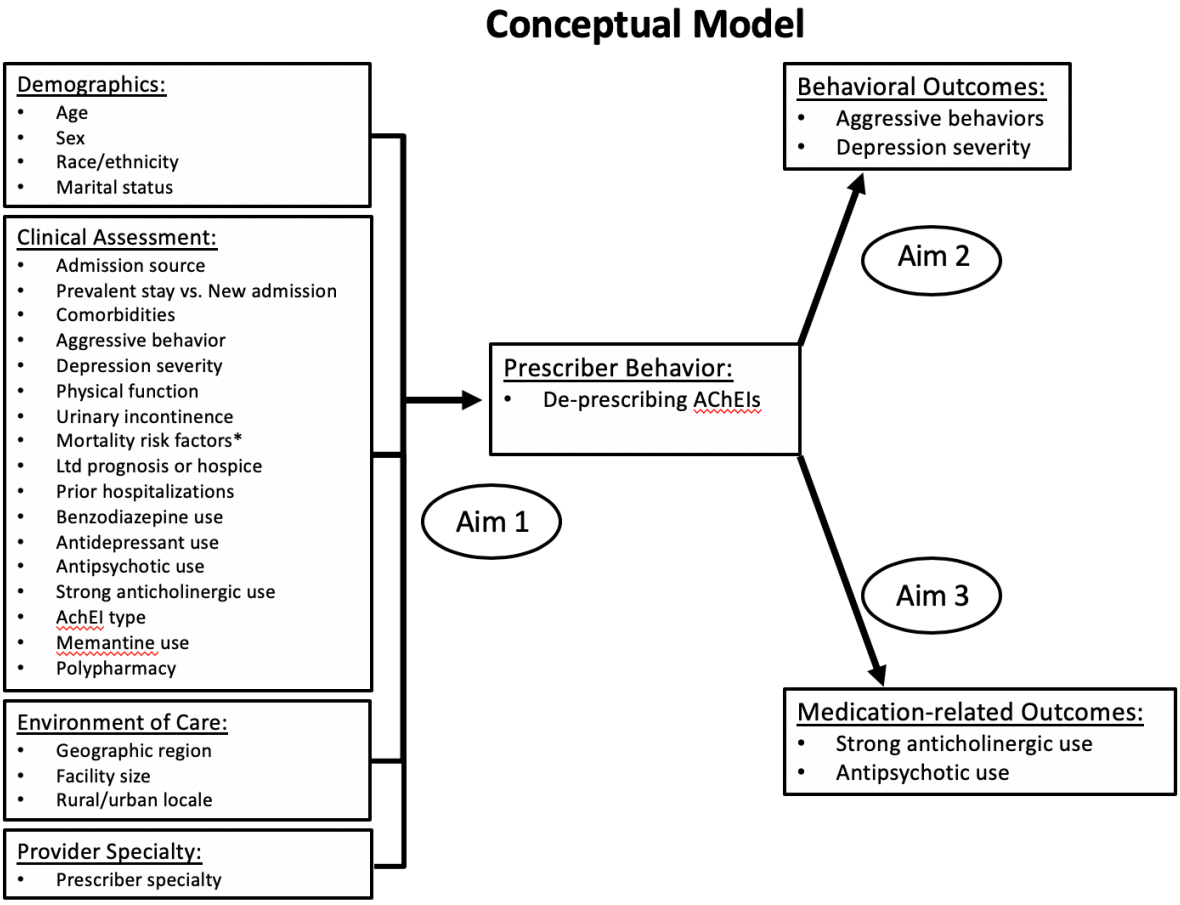


Figure 3-1 - Conceptual Model

4.0 FACTORS ASSOCIATED WITH DEPRESCRIBING ACHEIS IN OLDER NURSING HOME RESIDENTS WITH SEVERE DEMENTIA

4.1 ABSTRACT

Uncertainty regarding benefits and risks associated with acetylcholinesterase inhibitors (AChEIs) in severe dementia means providers do not know if and when to deprescribe. We sought to identify which patient, provider, and system-level characteristics are associated with deprescribing.

This was an analysis of 2015-16 data from Medicare claims, Part D prescriptions, Minimum Data Set v3.0, Area Health Resource File, and Nursing Home Compare for Medicare Nursing Home residents. Cox-proportional hazards models with time-varying covariates were used to identify patient, provider, and system-level factors associated with deprescribing (≥30-day gap in AChEI supply), accounting for censoring due to death, discharge, and end of data.

We included non-skilled NH residents aged 65+ with severe dementia receiving AChEIs within the first 14 days of an MDS assessment in 2016 (n=37,106). The sample was primarily white (78.7%), female (75.5%), and ≥80 years old (77.4%). The most commonly prescribed AChEIs were donepezil (77.8%), followed by transdermal rivastigmine (14.6%). The cumulative incidence of deprescribing was 29.7% at the end of follow-up (330 days), with mean follow-up times of 194 days for continuous users of AChEIs and 105 days for those who were deprescribed. Factors associated with increased likelihood of deprescribing were new admission, older age, difficulty being understood, aggressive behavior, poor appetite, weight loss, mechanically altered diet, limited prognosis designation, hospitalization in 90 days prior, and northeastern region.

Factors associated with decreased likelihood of deprescribing included memantine, use of strong anticholinergics, polypharmacy, rurality, and primary care prescriber vs. geriatric specialist.

Among nursing home residents with severe dementia being treated with AChEIs, the cumulative incidence of deprescribing was just under 30% at 1-year of follow-up. Our findings provide insight into potential drivers of deprescribing AChEIs, identify system-level barriers to deprescribing, and help to inform covariates that are needed to address potential confounding in studies evaluating the potential risks and benefits associated with deprescribing.

4.2 INTRODUCTION

The use of acetylcholinesterase inhibitors (AChEIs) in severe dementia is controversial. Although there are numerous studies of the efficacy of these agents, only a limited number include patients with severe dementia, and these present variable findings.[50-56] Whereas most studies show minor improvements in cognition[50-54,56], few have demonstrated any benefit for activities of daily living (ADLs) or behavioral and psychological symptoms of dementia (BPSD).[53,65,66] There is also uncertainty regarding the long-term efficacy of AChEIs, as most clinical trials were ≤6 months duration, and only a handful longer than a year.[48]

In the absence of data on the effects of continued use versus discontinuation of AChEIs in the context of severe dementia, it is not surprising that a recent systematic review of clinical practice guidelines found a great degree of inconsistency in recommendations for whether and when to discontinue AChEIs.[60] Only three of 16 guidelines addressing the use of AChEIs for dementia recommended discontinuation specifically in the context of severe dementia, with most other guidelines deferring to individual physician clinical judgement and patient and family

preferences.[60] Qualitative interviews with prescribers echo the uncertainty associated with deprescribing, with most citing family preference as the primary barrier to deprescribing.[95,96,105]

Quantitative studies of patients with varying dementia severity suggest that variation in non-persistence with AChEIs is driven by a combination of individual-level and system-level factors.[30,31,121-138] Individual-level factors that have been found to be significantly associated with increased likelihood of discontinuation include female sex[31,121,122], older age[31,121,123,127,134], behavioral disturbances[135,137], hospice enrollment[126], longer length of stay[126] (if in a long-term care facility), use of anticholinergic medications[131], use of medications that impair cognition[125], low BMI[135], falls[135], syncope[137], and frailty[137]. By contrast, individuals with longer duration of AChEI use[137], frequent physician visits[122,130], higher comorbidity burden[122,138], heart failure[123], diabetes[123], and antidepressant use[127] have been shown to be less likely to discontinue AChEIs. System-level factors noted to have an association with deprescribing were related to characteristics of the care setting and the prescriber, including insurance type and medication costs[122,123], care setting (community vs. nursing home)[124-126], regional rurality[121], prescriber specialty[123,131], and prescriber time spent in the nursing home setting[137]. Although numerous studies have found that patients with greater dementia severity are more likely to discontinue AChEIs[122,128,133,135,137], none of these examined predictors of discontinuation within the subgroup of patients with severe dementia. In addition, only four studies were conducted among nursing home (NH) residents. As a result, little is known about how common AChEI deprescribing is in NH residents with severe dementia, or which factors are most associated with deprescribing.

The goal of this study was to identify which factors are most associated with deprescribing AChEIs in a national sample of older adult NH residents with severe dementia. This study will provide much needed insight into what factors are most influential in clinical decision-making for

treatment of severe dementia with AChEIs and will inform covariates for future studies of the downstream effects of deprescribing in this population.

4.3 METHODS

4.3.1 Design & Data Sources

This was a retrospective analysis of linked data from Medicare enrollment, Part A and B claims, Master Beneficiary Summary File (MBSF), Part D prescription drug events, the Minimum Data Set (MDS) version 3.0, the Area Health Resource File (AHRF), and Nursing Home Compare (NHC) for the years 2015-2016. The University of Pittsburgh Institutional Review Board (IRB) deemed this study to be exempt.

Data originated from a randomly selected cohort of 1 million Medicare beneficiaries age 65 and older who had continuous enrollment in Medicare Parts A, B, and D in 2015 and a diagnosis of dementia prior to 2016 based on the Chronic Conditions Warehouse algorithm for identifying Alzheimer's Disease or Related Disorders with International Classification of Diseases (ICD) codes.[139]

The MDS, a comprehensive health assessment tool administered to all residents of CMS-certified NHs at admission and at least every 90 days thereafter[46], served as the primary source of variables to identify the sample and covariates. The MDS contains hundreds of items assessing demographics, clinical health status, physical function, and psychological well-being. The Medicare MBSF and Part A and B medical claims were used to identify comorbidities present before study entry not captured by the MDS, inpatient and outpatient healthcare utilization in the

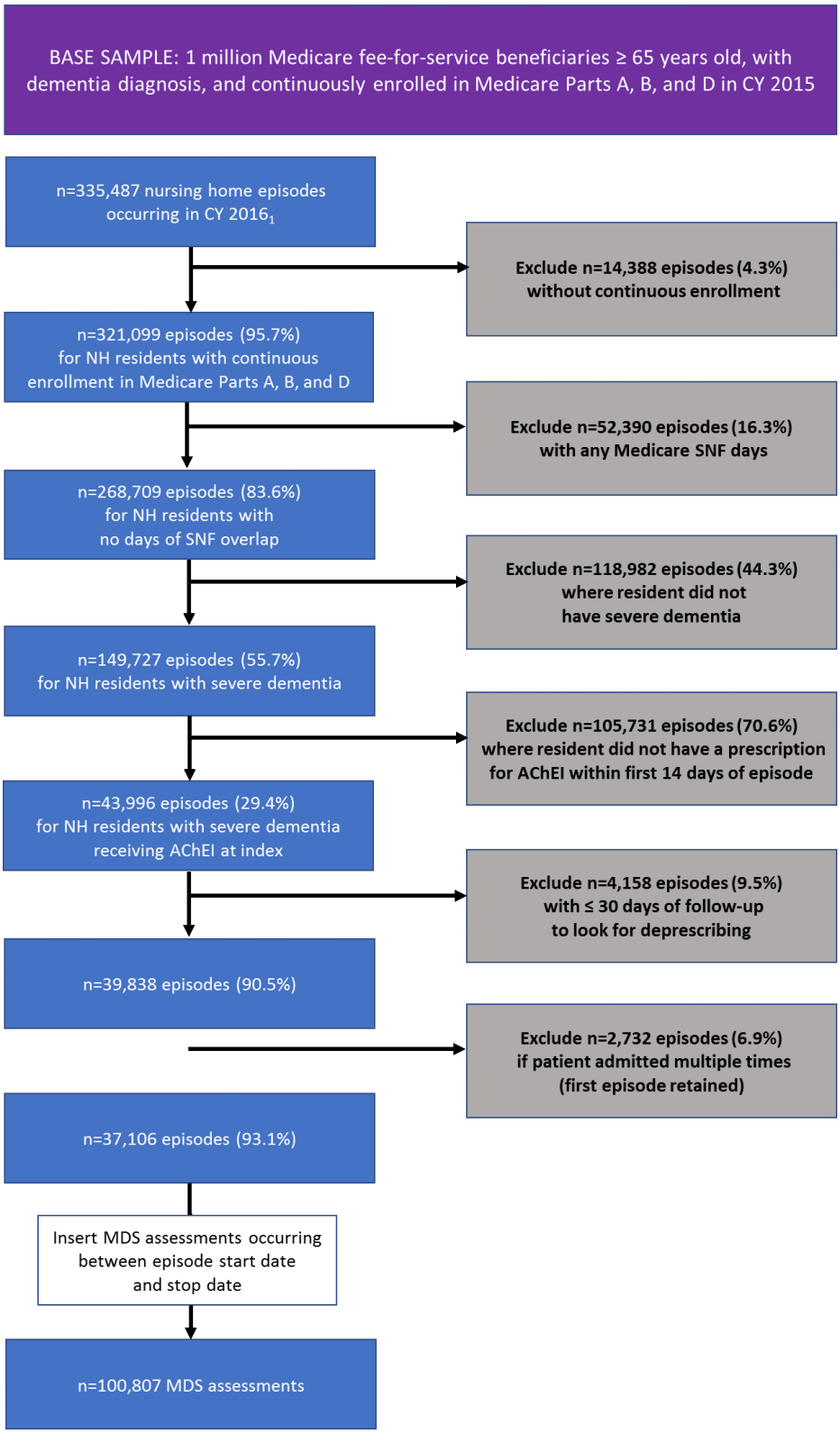
year prior to study entry, and date of death. Medicare Part D prescription drug event data provided information on prescriptions dispensed in outpatient and long-term care settings, excluding Medicare Part A-covered skilled nursing stays, for which medication data is not available. These data include drug name, National Drug Code (NDC), date filled, dose, strength, quantity, days' supply, and select prescriber characteristics.

Finally, NHC and the AHRF provided facility characteristics.[140,141] Nursing Home Compare data includes facility-level characteristics for all Medicare-certified nursing homes including geographic location, claims-based outcomes measures, MDS assessment-based quality measures, facility size, staff characteristics, and penalties.[38] Information on each facility is collected and updated on a quarterly basis and can be linked to patient-level records for nursing home stays from the MDS by facility identification codes. The AHRF contains data on health professionals and health facilities, population characteristics, and economics on the county, state and national levels. [39] This data can be linked to NHC data by zip code to extract regional characteristics for each nursing facility.

4.3.2 Sample

The final analytic cohort was derived from the 1 million base sample described above and consisted of non-skilled nursing stays for patients with severe dementia receiving AChEIs at study entry (**Figure 4-1**). We used the MDS reason for assessment fields (A0310A, A0310B) to identify all admission, quarterly, annual, and change in status MDS assessments for non-skilled NH

stays,[142-144] with an assessment start date during 2016. The assessment start date was defined as the beginning of the 14-day observation window over which the MDS items are to be evaluated.



1. Nursing home episodes included new admissions as well as prevalent nursing home stays.

Figure 4-1 – Sample Construction for Aim 1 Analyses

Nursing home episodes (n=335,487) were constructed by matching the first assessment in 2016 to the closest discharge form, or by assigning the end of the study period (12/31/2016) as the end date. We required that residents had continuous enrollment in Medicare Parts A, B, and D for the duration of all episodes and the year prior (n=14,388, 4.3% excluded). This ensured that residents would have no missing data during their nursing home stay or the year prior, which was used as a look-back period to evaluate prior healthcare utilization. We used the MDS "reason for assessment" field and MDS admission and discharge dates in combination with Skilled Nursing Facility (SNF) claims to define the duration of nursing home stays[142-144] and to distinguish between skilled and non-skilled nursing stays. Episodes in which the resident had any Medicare skilled nursing facility (SNF) claims with dates overlapping the time period from assessment start date to episode end date were excluded because medication data are not available for these stays (n=52,390, 16.3% excluded).

Episodes in which residents had severe dementia were identified using cognitive assessments contained within MDS assessment forms (n=149,727, 55.6%). The main cognitive screening tool within the MDS is the Brief Interview for Mental Status (BIMS), which uses a scoring algorithm to evaluate resident cognition in three key areas: memory, orientation, and judgement.[145,146] The BIMS ranges from 0 to 15, with lower scores being indicative of more severe cognitive impairment, and has demonstrated good agreement with the Modified Mini-Mental State Examination (3MS) scores in validation studies.[145,146] In residents unable to complete the BIMS, cognitive function can be evaluated through the combination of several MDS items that are based on staff observation of the resident, including evaluations of short-term memory, decision-making skills, ability to be understood by others, functional independence, and whether the resident is

comatose. This combination of items is called the Cognitive Performance Scale (CPS)[147] and ranges from 0 to 6, with higher scores being indicative of severe cognitive impairment. For the purposes of identifying severe cognitive impairment in this study, the BIMS was used when available; if the resident was unable to complete the BIMS, then the CPS was used. We used a BIMS score of ≤7 or a CPS score of ≥4 to identify severe dementia, which have been demonstrated to have acceptable sensitivity and specificity in identifying severe cognitive impairment, compared to 3MS scores.[145]

After identifying residents with severe cognitive impairment, the sample was then limited to those who were receiving AChEIs at baseline by searching Part D records for generic drug names (donepezil, rivastigmine, galantamine). The fields for date filled and estimated days' supply were used to determine the anticipated period of medication coverage, during which the resident was considered to be receiving AChEI therapy. Residents were considered treated at baseline if there was a prescription for an AChEI with an estimated days' supply overlapping at least one of the initial 14 days of the episode (n=43,996, 29.4%). The first day of the NH episode in which AChEI supply was observed was assigned as the AChEI index date. In order to allow enough complete observation time to observe potential deprescribing (defined as a 30-day gap in medication supply), we excluded episodes with ≤30 days of follow-up (n=4,158, 9.5% excluded). In order to avoid the potential for immortal time bias, where a period of immortal time (i.e. 30 days) is attributed incorrectly to only the treatment group[148,149], we also censored episodes 30 days prior to discharge, death, or end of data. Finally, if residents had more than one episode meeting these criteria during 2016, only the first episode was included (n=2,729, 6.9% excluded).

A longitudinal dataset was created in which each resident could have multiple MDS assessments completed from episode start until deprescribing, censoring, or the end of the study

period (December 31, 2016). This data structure was chosen to maximize the utility of the data sources being used, allowing potentially influential predictors of deprescribing, that may fluctuate with significant changes in clinical status, to vary over time. Thus, the final analytic cohort consisted of 37,106 residents contributing 100,807 MDS assessments.

4.3.3 Dependent Variable

Deprescribing of AChEIs was defined as a gap in medication supply of ≥30 days. We used prescription fill dates and days' supply to determine the probable period over which each resident was receiving AChEIs. If a gap in medication supply of ≥30 days was identified, the 1st gap day served as the discontinuation date. For example, if a patient was issued a prescription on 01/01/2015 with a 28-day supply, this prescription had an end date of 01/28/2015. If no subsequent fill is observed for any AChEI within the next 30 days (on or before 02/27/2015), this was considered deprescribing, with a discontinuation date of 1/29/2015. A 30-day gap is traditionally used in studies of community-dwelling patients and NH residents to allow for temporary medication discontinuation or non-persistence.[101,137,150,151] Non-adherence resulting in an excess of medication supply >30 days is also less likely in NH residents, as medication administration is typically managed by nursing staff, rather than patients. A gap of 30 days is also a clinically relevant definition as the time to complete elimination of AChEIs is as long as 15 days, based on the medication with the longest half-life (donepezil). This is also supported by previous studies suggesting that discontinuation-related behavioral symptoms emerge by 6 weeks after discontinuation.[152,153]

4.3.4 Independent Variables

The conceptual model presented previously (**Figure 3-1**) was used to guide selection of covariates based on a review of prior studies[30,31,121-137] and behavioral theories applied to deprescribing.[88,115-118] We identified four primary categories of covariates that were likely to influence deprescribing: demographics, clinical assessment, environment of care, and provider specialty.

Demographics were captured as time-invariant covariates using the index MDS assessment and included age, sex, race/ethnicity, and marital status.

Clinical assessment factors were measured as time-varying covariates measured at each MDS assessment. The type of each MDS assessment form (admission, quarterly, annual, significant change in status) was included as a measure of the trajectory and stability of the resident's stay. We included a scale rating ability to be understood to capture variation in cognitive ability.[145] We created indicators for specific conditions noted on the MDS that may impact AChEI deprescribing.[154-156] These included indicators of poor prognosis (poor appetite, swallowing disorder, parenteral nutrition or tube feeds, mechanically altered diet, weight loss, shortness of breath, dehydration, cancer, end-stage renal disease, heart failure) or conditions that would be further aggravated by AChEI use (urinary incontinence). Physical function was measured using MDS items assessing activities of daily living (ADLs) to create a composite score that represents overall functional ability.[157] This scale evaluates self-performance for seven items (dressing, personal hygiene, toileting, locomotion, transferring between surfaces, bed mobility, eating) and ranges from 0-28 with higher scores indicating greater dependence. Aggression was measured using the Aggressive Behavior Scale (ABS)[158], which evaluates the presence of verbal, physical, and other aggressive behaviors as well as rejection of care. Possible scores range from 0-12 and

can be categorized as none (0), moderate (1-2), severe (3-5) or very severe (6+). Depression severity was assessed using the Patient Health Questionnaire (PHQ-9) in the MDS, a structured interview that has been validated in older adults across various healthcare settings .[159] The PHQ-9 evaluates the presence and frequency of depressive symptoms, ranging from 0-27, and can be categorized as none (0-4), mild (5-9), moderate (10-14), moderately severe (15-19) or severe (≥20). Finally, we created an indicator as to whether there was documentation of limited prognosis on the MDS, based on endorsement of the item for <6 months life expectancy (item J1400), which has been shown to have good predictive accuracy for 6-month mortality[156], and/or the MDS indicator for hospice use in the last 14 days (item O0100K).

Medications used to treat other conditions may also impact deprescribing AChEIs, as they may indicate the presence of more severe, concurrent psychiatric symptoms that could worsen after deprescribing. We used Part D records to create time-varying indicators for use of antidepressants, antipsychotics, and benzodiazepines on the first day of each assessment window. We captured use of any strongly anticholinergic medications, as defined by the Beers Criteria[160]. These medications have the potential to worsen cognitive symptoms due to their effect on decreasing the cholinergic activity that AChEIs seek to maintain in order to preserve cognitive function. Therefore, it is possible that residents receiving these medications may be experiencing greater cognitive symptoms that may affect the decision to deprescribe. We also included a count of the total number of non-AChEI medications as a marker of overall medication burden. Finally, we created covariates for concurrent use of memantine, which is used in conjunction with AChEIs for treatment of severe dementia as well as the type of index AChEI (donepezil, rivastigmine, or galantamine) to account for potential differences in efficacy and adverse effects across medications.

Healthcare utilization and overall comorbidity were measured as time-varying factors using up to one year of medical claims prior to each MDS assessment period. We calculated the Charlson Comorbidity Index[161,162] using ICD-9 and ICD-10 codes from the year prior and counted the number of prior hospitalizations leading up to each MDS assessment. We identified all-cause hospitalizations as well as hospitalizations for specific conditions that may have been attributable AChEI-related adverse events. These included hospitalizations for syncope and falls or fractures, as previous studies have demonstrated that AChEI use increases the risk for bradycardia and syncopal events, which may ultimately cause an injurious fall.[14,69,163] We also identified the resident's location prior to NH residence from the MDS.

Environment of care was captured as time-invariant factors and included geographic region, facility size, and rurality. NHC data[140] was used to characterize facility size and also provided zip codes to define geographic region (Northeast, Midwest, South, West) and rurality/urbanicity (urban, rural, highly rural) by linking to rural-urban continuum codes in the AHRF.[141] Finally, we captured a time-invariant measure for the specialty of the prescriber of the index AChEI prescription (primary care, geriatrics, or other) by linking Part D records to provider specialty codes in the Part D Prescriber Characteristics file.

4.3.5 Statistical Analyses

We described the time invariant demographics, environment of care and provider specialty at the time of the index MDS assessment (i.e., episode level), and time-varying clinical assessment at both the episode and assessment levels.

Missing observations (<5% total) were addressed with single imputation using chained equations.[164,165] The chained equations procedure is advantageous in that it allows for flexible

specification of imputation models to accommodate different types of data in the same equation, including continuous, dichotomous, ordinal, and multinomial variables. The algorithm constructs a series of univariate imputation models for each covariate, using all other covariates as predictors. As variables are imputed, these values are then used for subsequent imputation of other covariates. One complication of the longitudinal nature of our data was the potential for correlation between repeated observations on the same individual, which most imputation approaches are not able to account for. Longitudinal data are typically structured and analyzed in long format, with each row serving as one observation for one individual. If an imputation procedure were employed on this data, each row would be treated as an independent observation, leading to incorrect model specification. A suggested strategy to address this problem is to restructure data in a wide format for imputation and subsequently return to long format for analysis to minimize bias. However, a recent analysis approaches for handling missing observations in longitudinal data suggests that imputation in the long format yields satisfactory results and substantively similar findings to imputation in wide format.[166] This holds true so long as imputation is limited to individual variables within existing panels of data, as opposed to imputing entire panels of missing data. Due to the size of our sample, the large number of covariates that would need to be imputed, and the relatively small number of missing observations, it was agreed that the most efficient approach was to impute our dataset in long format, acknowledging the potential for error outlined above. A comparison of sample characteristics before and after imputation can be found in the appendix (**Appendix Table A-1**).

Associations of time to deprescribing with the time invariant and time-varying factors were evaluated using Cox proportional hazards models. Each resident was followed from index date to deprescribing or censoring (death, discharge from the NH, end of study period). Bi-variable

models were estimated to determine the unadjusted associations, followed by multivariable models. Consideration was initially given to implementation of a competing risks model with death as the competing risk. However, we did not choose this approach for several reasons based on a synthesis of literature on the topic of competing risks.[167-169] First, instead of estimating the actual probability of the occurrence of deprescribing in specific sub-groups, for which competing risks models are more appropriate, our objective was to evaluate the effect of individual covariates on the rate of occurrence of deprescribing, which cause-specific regression models are appropriately suited to evaluate.[168,169] In addition, literature suggests that the difference between competing risks methods and traditional survival methods is not substantial when total follow-up time is short and occurrence of the competing event is low.[167] Given that our maximum duration of follow-up was less than 1 year and that deaths occurred less than half as frequently as deprescribing, we felt that these criteria were also applicable as justification for not incorporating competing risks in our analysis.

The proportional hazards assumption was evaluated for all variables using Schoenfeld residuals. The only variable that violated the assumption was whether or not the resident had a prior hospitalization, which was originally measured up to 1 year prior to the index date. In order to address this violation, we evaluated the potentially time-dependent effect of prior hospitalizations as a piece-wise function of time (i.e. how many days since most recent hospitalization). Analyses revealed that the strongest effect on deprescribing was seen if prior hospitalizations had occurred within the prior 90 days (**Appendix Table A-2**). Further testing revealed that this shorter look-back period for prior hospitalizations (i.e. prior 90 days) no longer violated the proportional hazards assumption. Therefore, final models only included healthcare utilization in the 90 days prior to index date.

Variance inflation factors (VIFs) were used to evaluate potential multicollinearity in our model. Variance inflation factors represent the degree to which the variance of other coefficients are increased due to inclusion of a particular variable, with deviations away from 1 indicating potential collinearity among variables. We implemented a series of linear models with each covariate being regressed on the remaining covariates to calculate VIFs and found no indication of potential collinearity.

We hypothesized that residents residing in the same facility and thus under the care of the same providers may have similar likelihood for deprescribing. Our original plan was to include an indicator variable for individual nursing home facility identifiers as a covariate in our models, but preliminary analyses revealed a rather small number of observations per cluster (median = 3 episodes per facility). Rather than modeling the variability between such a large number of clusters with few observations per cluster, we instead decided to use robust standard errors, clustered at the facility level, to account for any potential clustering effect by facility.

Two sensitivity analyses were conducted to evaluate the robustness of our findings. In the first, we followed similar methodology but stratified by patients with versus without documentation of limited prognosis to determine whether associated factors were robust in residents recognized as end-of-life, when care more explicitly shifts from prevention to palliation. We hypothesized that in the setting of limited prognosis, other prognostic factors may not be as associated with deprescribing in patients with this designation. The second analysis was intended to determine the sensitivity of our findings to a more stringent definition for deprescribing, where a 60-day gap in medication supply was required in order to account for potential measurement error associated with medication re-fill data or poor adherence. This was driven by preliminary analyses showing that a signification proportion (~30%) of residents who were deprescribed

eventually had another prescription for AChEIs issued following their 30-day gap. Analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC) and STATA 15 (College Station, TX).

4.4 Results

4.4.1 Sample Characteristics

Descriptive statistics for the sample are presented in **Table 4-1**. Baseline characteristics measured at index MDS assessment (n=37,106) are presented in the first column and assessment-level characteristics for all MDS assessments (n=100,807) are presented in the second. At the index MDS assessment, over three-fourths of the sample were ≥80 years old, primarily female (75.5%), and white (78.7%). Most residents were not married (77.9%), entered the NH following a hospitalization (68.1%), and were not newly admitted at index date (i.e. prevalent stays; 87.7%).

Table 4-1 - Characteristics of Elderly Nursing Home Residents with Severe Dementia Receiving AChEIs

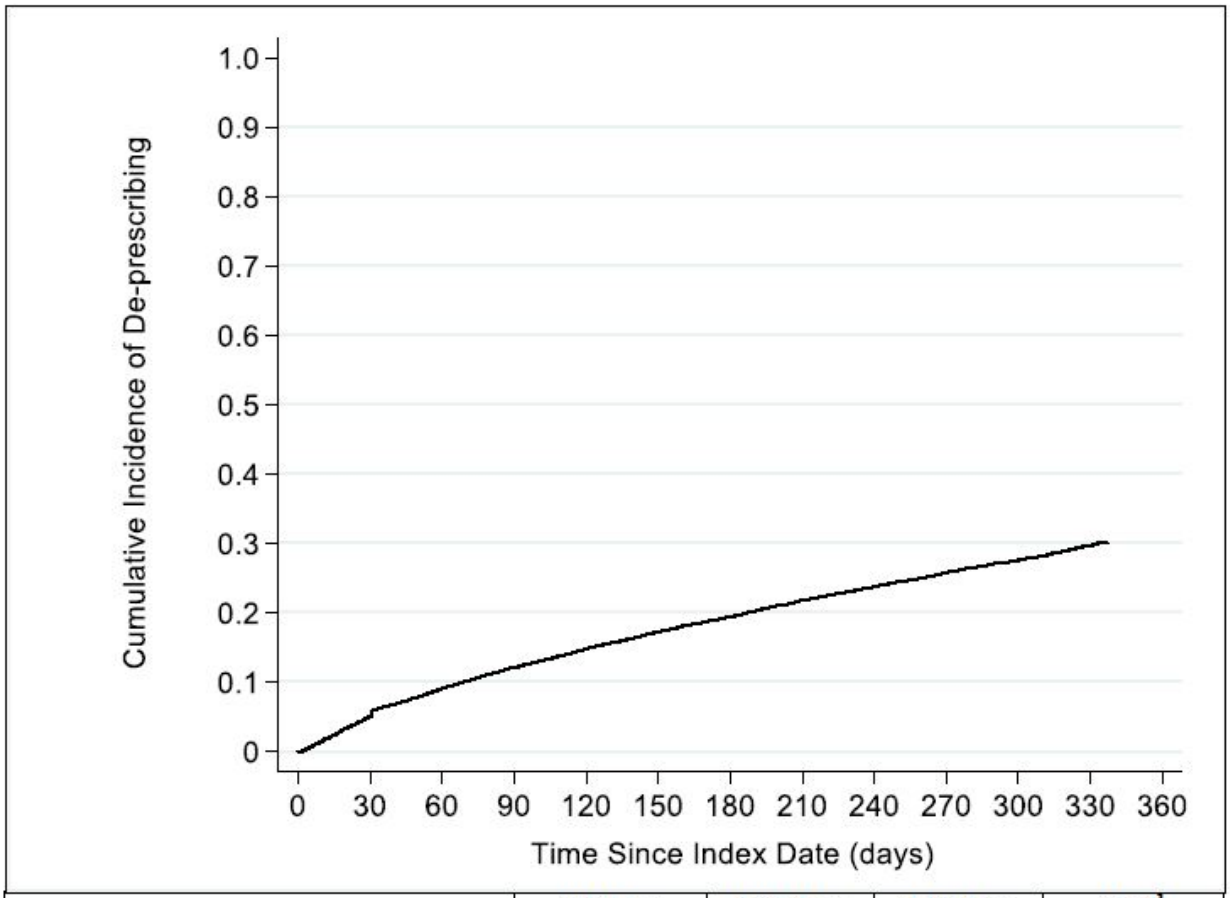
Variable	Baseline Characteristics N=37,106 episodes n (%)	Time-varying Characteristics N=100,807 assessments n (%)
DEMOGRAPHICS		
Age in years		
65-69	901 (2.4)	-
70-79	7,496 (20.2)	
80-89	17,922 (48.3)	
90+	10,787 (29.1)	
Sex		
Male	9,092 (24.5)	-
Female	28,014 (75.5)	
Race/ethnicity		
White	29,210 (78.7)	-
Black	4,405 (11.9)	
Hispanic	2,049 (5.5)	
Other	1,442 (3.9)	
Current marital status		
Married	8,176 (22.0)	-
Not Married	28,930 (78.0)	
CLINICAL ASSESSMENT		
Entered from		
Community	7,575 (20.4)	-
Hospital	25,275 (68.1)	
NH or other LTC facility	4,256 (11.5)	
MDS Assessment Type		
Admission	4,576 (12.3)	4,576 (4.5)
Quarterly	24,434 (65.9)	71,976 (71.4)
Annual	6,001 (16.2)	18,387 (18.2)
Significant Change in Status	2,095 (5.7)	5,868 (5.8)
Charlson Comorbidity Index		
0-1	6,001 (16.3)	15,514 (15.4)
2-3	9,101 (24.7)	25,761 (25.6)
4-5	8,659 (23.5)	24,614 (24.4)
≥6	13,127 (35.6)	34,918 (34.6)
Makes self understood		
Understood	14,719 (39.7)	38,964 (38.7)
Usually understood	9,961 (26.8)	27,333 (27.1)
Sometimes understood	8,086 (21.8)	21,830 (21.7)
Rarely/never understood	4,340 (11.7)	12,680 (12.6)
PHQ-9 score		
Minimal	30,155 (81.3)	82,783 (82.1)
Mild	4,808 (13.0)	12,364 (12.3)
Moderate	1,623 (4.4)	4,338 (4.3)
Moderate-severe or severe	520 (1.4)	1,322 (1.3)
Aggressive behavior scale		
None	28,391 (76.5)	78,048 (77.4)

Moderate	5,741 (15.5)	15,178 (15.1)
Severe	2,335 (6.3)	6,024 (6.0)
Very severe	639 (1.7)	1,557 (1.5)
Activities of Daily Living Score		
1 to 7	2,849 (7.7)	7709 (7.7)
8 to 14	6,033 (16.3)	15,917 (15.8)
15 to 21	19,426 (52.4)	52,903 (52.5)
22 to 28	8,798 (23.7)	24,278 (24.1)
Urinary incontinence		
Continent	3,954 (10.7)	9,893 (9.8)
Occasionally incontinent	5,439 (14.7)	13,988 (13.9)
Frequently incontinent	12,281 (33.1)	33,382 (33.1)
Always incontinent	14,644 (39.5)	41,899 (41.6)
Indwelling catheter	788 (2.1)	1,645 (1.6)
Cancer	1,557 (4.2)	4,081 (4.1)
Heart failure	5,808 (15.7)	15,490 (15.4)
End Stage Renal Disease	3,433 (9.3)	9,140 (9.1)
Short of breath	2,469 (6.7)	6,412 (6.4)
Poor appetite	4,946 (13.3)	12,811 (12.7)
Weight loss	2,392 (6.5)	5,891 (5.8)
Swallowing difficulty	1,247 (3.4)	3,266 (3.2)
Mechanically altered diet	16,780 (45.2)	47,426 (47.1)
IV/parenteral nutrition or feeding tube	1,262 (3.4)	2,892 (2.9)
Limited Prognosis	1,875 (5.1)	4,623 (4.6)
Hospitalizations/ED Visits (90 days prior)		
None	27,937 (75.3)	86,397 (85.7)
Cause-specific (fall, fracture, syncope)	3,193 (8.6)	5,560 (5.5)
Other cause	5,976 (16.1)	8,850 (8.8)
AChEI at index date		
Donepezil	28,877 (77.8)	77,772 (77.2)
Donepezil/memantine	483 (1.3)	1,926 (1.9)
Galantamine	832 (2.2)	2,280 (2.3)
Rivastigmine (oral)	1,511 (4.1)	4,230 (4.2)
Rivastigmine (transdermal)	5,403 (14.6)	14,599 (14.5)
Memantine use	15,199 (41.0)	42,692 (42.3)
Benzodiazepine and/or Z drug	5,505 (14.8)	14,282 (14.2)
Antipsychotic use	9,128 (24.6)	23,039 (22.9)
Antidepressant use	21,310 (57.4)	57,578 (57.1)
Highly Anticholinergic Drugs (Beers Criteria)	5,519 (14.9)	14,179 (14.1)
Total number of medications		
0 to 5	17,798 (48.0)	49,798 (49.4)
6 to 10	16,183 (43.6)	43,261 (42.9)
>10	3,125 (8.4)	7,868 (7.7)
ENVIRONMENT OF CARE		
Geographic region		
Midwest	10,108 (27.2)	-
Northeast	6,737 (17.9)	
South	17,286 (46.6)	
West	3,075 (8.3)	
Certified beds		
<50	1,899 (5.1)	-
50-99	10,617 (28.6)	
100-199	20,339 (54.8)	
200+	4,252 (11.5)	

Rural/urban continuum		
Urban	25,719 (69.3)	-
Rural	9,910 (26.7)	
Highly rural	1,477 (4.0)	
PROVIDER SPECIALTY		
Prescriber specialty		
Geriatrics	3,168 (8.5)	-
Primary care	29,972 (80.8)	
Other	3,966 (10.7)	

4.4.2 Primary Analysis

In total, 20.4% of the sample were deprescribed during follow-up, whereas the remainder of residents were censored either due to death (8.8%), discharge (23.7%), or end of follow-up (47.2%). The median follow-up time for continuous users of AChEIs was 242 days (IQR=83-290) and 82 days (IQR=30-165) for those who were deprescribed. **Figure 4.2** shows the cumulative incidence of deprescribing at various time points during the observation period, which was 12.1% at day 90 and 29.7% at the end of follow-up.



	90 days	180 days	270 days	End[1]
Cumulative Incidence of Deprescribing 95% CI	12.1% (11.8-12.5)	19.4% (19.0-19.9)	25.8% (25.2-26.3)	30.0% (29.0-30.1)

[1]Maximum follow-up was 337 days. Observations were censored 30 days prior to end of data.

Figure 4-2 - Cumulative Incidence of Deprescribing During Observation Period

Results from Cox models are presented in **Table 4-2**. Of the demographic variables, only resident age was significantly associated with deprescribing. In both unadjusted and adjusted analyses, being age ≥70 versus 65-69 was associated with increased likelihood of deprescribing [70-79yo aHR=1.21, 95% CI (1.02-1.43); 80-89yo aHR=1.20, 95% CI (1.02-1.41); 90+yo aHR=1.26, 95% CI (1.06-1.48)].

A number of clinical assessment variables were significantly associated with deprescribing. In both unadjusted and adjusted analyses, deprescribing was less likely following quarterly or annual assessments versus an admission assessment [aHR=0.39, 95% CI (0.36-0.43); aHR=0.36, 95% CI (0.33-0.40), respectively]. An MDS assessment for significant change in clinical status was also associated with increased likelihood of deprescribing, but only in unadjusted analyses [HR=1.77, 95% CI (1.61-1.95)]. Other clinical factors that were significantly associated with increased likelihood for deprescribing in unadjusted and fully-adjusted models were: being understood only sometimes [aHR=1.13, 95% CI (1.05-1.21)] or rarely [aHR=1.22, 95% CI (1.11-1.34)]; moderate [aHR=1.11, 95% CI (1.04-1.18)] or severe [aHR=1.24, 95% CI (1.15-1.37)] aggressive behavior; ADL impairment [ADL scale 15-21 aHR=1.26, 95% CI (1.10-1.44); ADL scale 22-28 aHR=1.41, 95% CI (1.22-1.63)]; poor appetite [aHR=1.20, 95% CI (1.11-1.28)]; recent weight loss [aHR=1.31, 95% CI (1.21-1.41)]; mechanically altered diet [aHR=1.07, 95% CI (1.02-1.13)]; MDS documentation of limited prognosis [aHR=3.92, 95% CI (3.65-4.20)]; and cause-specific [aHR=1.28, 95% CI (1.17-1.40)] or other cause hospitalization [aHR=1.25, 95% CI (1.16-1.35)] in the prior 90 days. Clinical factors associated with decreased likelihood for deprescribing were use of combination donepezil/memantine as AChEI therapy versus donepezil alone [aHR=0.65, 95% CI (0.52-0.82)]; memantine use [aHR=0.87, 95% CI (0.82-0.91)]; strongly

anticholinergic use [aHR=0.92, 95% CI (0.86-0.99)]; use of >5 concurrent medications [6 to 10 medications aHR=0.89, 95% CI (0.84-0.93); >10 medications aHR=0.79, 95% CI (0.71-0.87)].

Of the environment of care factors, region, and rurality exhibited significant relationships with deprescribing. Residing in a facility in the western U.S. versus the Midwest [aHR=0.86, 95% CI (0.76-0.96)] and residing in a rural [aHR=0.82, 95% CI (0.76-0.87)] or highly rural facility [aHR=0.77, 95% CI (0.66-0.89)] versus an urban facility, were associated with decreased likelihood of AChEI deprescribing. In addition, having an AChEI prescriber with a primary care specialty (vs. geriatrics) was associated with decreased likelihood of deprescribing [aHR=0.91, 95% CI (0.83-0.99)].

Table 4-2 - Unadjusted and Adjusted Hazards Ratios from Primary Analysis

Variable	Unadjusted Hazard Ratio [CI]	Adjusted Hazard Ratio [CI]
DEMOGRAPHICS		
Age in years		
65-69	ref	ref
70-79	1.20 (1.01-1.41)*	1.21 (1.02-1.42)*
80-89	1.19 (1.02-1.41)*	1.20 (1.02-1.41)*
90+	1.32 (1.11-1.56)^	1.25 (1.06-1.48)+
Sex		
Male	ref	ref
Female	1.03 (0.97-1.08)	1.02 (0.96-1.08)
Race/ethnicity		
White (non-hispanic)	ref	ref
Black (non-hispanic)	1.01 (0.94-1.09)	1.04 (0.96-1.13)
Hispanic	0.95 (0.85-1.06)	0.96 (0.86-1.08)
Other	0.93 (0.81-1.07)	0.97 (0.85-1.12)
Current marital status		
Married	1.05 (0.99-1.11)	0.98 (0.93-1.04)
Not Married	ref	ref
CLINICAL ASSESSMENT		
Entered From		
Community	ref	ref
Hospital	1.04 (0.98-1.10)	1.02 (0.96-1.09)
NH or other LTC Facility	1.06 (0.97-1.15)	0.99 (0.92-1.09)
Assessment Form Type		
Admission	ref	ref
Quarterly	0.38 (0.35-0.42)^	0.39 (0.35-0.43)^
Annual	0.35 (0.31-0.38)^	0.36 (0.33-0.41)^
Significant Change in Status	1.77 (1.61-1.95)^	0.93 (0.84-1.04)
Charlson Comorbidity Index		
0-1	ref	ref
2-3	0.93 (0.87-1.00)	0.97 (0.90-1.04)
4-5	0.91 (0.85-0.98)*	0.95 (0.88-1.03)
≥6	0.97 (0.90-1.04)	0.97 (0.91-1.05)
Makes self understood		
Understood	ref	ref
Usually understood	1.15 (1.08-1.22)^	1.06 (0.99-1.13)
Sometimes understood	1.42 (1.33-1.50)^	1.14 (1.07-1.22)^
Rarely/never understood	1.69 (1.58-1.81)^	1.24 (1.14-1.34)^
PHQ-9 score		
Minimal	ref	ref
Mild	1.24 (1.16-1.32)^	0.98 (0.92-1.05)
Moderate	1.50 (1.35-1.66)^	1.11 (0.99-1.23)
Mod. severe or severe	1.78 (1.50-2.11)^	1.06 (0.88-1.27)
Aggressive behavior scale		
None	ref	ref
Moderate	1.14 (1.07-1.21)^	1.12 (1.05-1.19)^
Severe	1.37 (1.23-1.49)^	1.26 (1.15-1.38)^

Very severe	1.35 (1.14-1.59)^	1.15 (0.97-1.36)
Activities of Daily Living Scale		
0 to 7	ref	ref
8 to 14	1.27 (1.13-1.45)^	1.13 (0.99-1.28)
15 to 21	1.75 (1.57-1.96)^	1.26 (1.10-1.44)^
22 to 28	2.45 (2.19-2.75)^	1.41 (1.22-1.63)^
Urinary incontinence		
Continent	ref	Ref
Occasionally incontinent	1.14 (1.02-1.27)+	0.98 (0.88-1.10)
Frequently incontinent	1.38 (1.25-1.52)^	1.03 (0.92-1.15)
Always incontinent	1.75 (1.60-1.92)^	1.09 (0.97-1.22)
Indwelling catheter	2.09 (1.74-2.51)^	1.02 (0.84-1.24)
Cancer	1.06 (0.95-1.18)	0.92 (0.82-1.04)
Heart failure	1.0 0.94-1.07)	0.99 (0.92-1.06)
End Stage Renal Disease	1.04 (0.96-1.13)	1.01 (0.93-1.10)
Short of breath	1.04 (0.95-1.15)	0.93 (0.85-1.03)
Poor appetite	1.65 (1.56-1.75)^	1.20 (1.12-1.29)^
Weight loss	2.29 (2.13-2.46)^	1.31 (1.21-1.42)^
Swallowing difficulty	1.56 (1.39-1.74)^	1.09 (0.98-1.22)
Mechanically altered diet	1.32 (1.26-1.38)^	1.08 (1.02-1.13)+
IV/parenteral nutrition or feeding tube	1.29 (1.13-1.45)^	1.02 (0.89-1.18)
Limited Prognosis	6.88 (6.43-7.36)^	3.91 (3.64-4.19)^
Hospitalizations/ED Visits (90 days prior)		
Cause-specific (fall, fracture, syncope)	1.61 (1.48-1.75)^	1.28 (1.17-1.39)^
Other cause	1.55 (1.45-1.67)^	1.25 (1.16-1.35)^
AChEI Use at Index		
Donepezil	ref	ref
Donepezil/memantine	0.61 (0.49-0.77)^	0.65 (0.52-0.83)^
Galantamine	0.90 (0.77-1.06)	0.85 (0.72-1.00)
Rivastigmine (oral)	1.00 (0.89-1.12)	1.00 (0.89-1.13)
Rivastigmine (transdermal)	1.05 (0.99-1.12)	0.97 (0.90-1.03)
Memantine	0.78 (0.74-0.81)^	0.87 (0.83-0.91)^
Benzodiazepine & Z drug	1.03 (0.97-1.10)	1.06 (0.99-1.14)
Antipsychotic	0.99 (0.94-1.05)	1.01 (0.95-1.07)
Antidepressant	0.94 (0.90-0.99)*	1.01 (0.97-1.07)
Highly Anticholinergic Drugs (Beers Criteria)	0.88 (0.83-0.95)^	0.93 (0.87-0.99)*
Total number of medications		
0 to 5	ref	ref
6 to 10	0.83 (0.79-0.87)^	0.89 (0.85-0.94)^
>10	0.75 (0.68-0.82)^	0.79 (0.72-0.88)^
ENVIRONMENT OF CARE		
Geographic region		
Midwest	ref	ref
Northeast	1.20 (1.11-1.29)^	1.12 (1.03-1.22)+
South	1.15 (1.08-1.22)^	1.07 (0.99-1.14)
West	0.91 (0.81-1.01)	0.85 (0.76-0.96)+
Certified beds		
<50	ref	ref
50-99	0.94 (0.84-1.06)	0.93 (0.82-1.05)
100-199	1.06 (0.94-1.19)	0.97 (0.86-1.09)
200+	1.09 (0.95-1.25)	0.99 (0.86-1.14)
Rural/urban continuum		
Urban	ref	ref
Rural	0.79 (0.74-0.83)^	0.82 (0.77-0.87)^

Highly rural	0.69 (0.60-0.80)^	0.76 (0.65-0.89)^
PROVIDER CHARACTERISTICS		
Prescriber specialty		
Geriatrics	ref	ref
Primary care	0.85 (0.78-0.92)^	0.90 (0.83-0.98)*
Other	0.91 (0.82-1.01)	0.94 (0.84-1.04)

*p<0.05
+p<0.01
^p<0.001

4.4.3 Sensitivity Analyses

Results of the sub-group analysis are presented in **Table 4-3 and Table 4-4**. Among patients not documented as having limited prognosis, findings were substantively similar to the primary analysis. However, in the sub-group of patients that were designated as limited prognosis, many factors originally associated with deprescribing AChEIs were no longer statistically significant (age, rarely being understood, aggressive behaviors, ADL impairment, swallowing difficulty, weight loss, mechanically altered diet, use of combination donepezil/memantine, using ≥6 medications, western region). In addition, the directionality of several variables changed, but none were statistically significant (including short of breath, memantine use, antipsychotic use, strong anticholinergic use, northeast, south, and provider specialty). The only variable to become statistically significantly associated with increased likelihood of deprescribing to was Charlson Comorbidity Index score of 4 to 5. **Figure 4-3** shows the cumulative incidence curves for time to deprescribing, stratified by limited prognosis designation

Table 4-3 - Sample Characteristics for Sub-group Analysis by Limited Prognosis Status at Index Assessment

Variable	Sub-group without limited prognosis N=35,231 episodes n (%)	Sub-group with limited prognosis N=1,875 episodes n (%)
DEMOGRAPHICS		
Age in years		
65-69	862 (2.5)	39 (2.1)
70-79	7,182 (20.4)	314 (16.8)
80-89	17,038 (48.4)	884 (47.2)
90+	10,149 (28.8)	638 (34.0)
Sex		
Male	8,594 (24.4)	498 (26.6)
Female	26,637 (75.6)	1377 (73.4)
Race/ethnicity		
White	27,657 (78.5)	1553 (82.8)
Black	4,237 (12.0)	168 (9.0)
Hispanic	1,956 (5.6)	93 (5.0)
Other	1,381 (3.9)	61 (3.3)
Current marital status		
Married	7,699 (21.9)	477 (25.5)
Not Married	27,532 (78.2)	1398 (74.5)
CLINICAL ASSESSMENT		
Entered from		
Community	7,272 (20.6)	303 (16.2)
Hospital	23,908 (67.9)	1367 (72.9)
NH or other LTC facility	4,051 (11.5)	205 (10.9)
MDS Assessment Type		
Admission	4,221 (12.0)	355 (18.9)
Quarterly	23,765 (67.5)	669 (35.7)
Annual	5,888 (16.7)	113 (6.0)
Significant Change in Status	1,357 (3.9)	738 (39.4)
Charlson Comorbidity Index		
0-1	5,797 (16.5)	262 (14.0)
2-3	8,779 (24.9)	364 (19.4)
4-5	8,277 (23.5)	419 (22.4)
≥6	12,378 (35.1)	830 (44.3)
Makes self understood		
Understood	14,138 (40.1)	581 (31.0)
Usually understood	9,509 (27.0)	452 (24.1)
Sometimes understood	7,584 (21.5)	502 (26.8)
Rarely/never understood	4,000 (11.4)	340 (18.1)
PHQ-9 score		
Minimal	28,836 (81.9)	1319 (70.4)
Mild	4,450 (12.6)	358 (19.1)
Moderate	1,483 (4.2)	140 (7.5)
Mod. severe or severe	462 (1.3)	58 (3.1)
Aggressive behavior scale		
None	26,959 (76.5)	1432 (76.4)
Moderate	5,453 (15.5)	288 (15.4)

Severe	2,225 (6.3)	110 (5.9)
Very severe	594 (1.7)	45 (2.4)
Activities of Daily Living Score		
0 to 7	2,829 (8.0)	20 (1.1)
8 to 14	5,934 (16.8)	99 (5.3)
15 to 21	18,484 (52.5)	942 (50.2)
22 to 28	7,984 (22.7)	814 (43.4)
Urinary incontinence		
Continent	3,889 (11.0)	65 (3.5)
Occasionally incontinent	5,285 (15.0)	154 (8.2)
Frequently incontinent	11,783 (33.4)	498 (26.6)
Always incontinent	13,619 (38.7)	1025 (54.7)
Indwelling catheter	655(1.9)	133 (7.1)
Cancer	1,415 (4.0)	142 (7.6)
Heart failure	5,392 (15.3)	416 (22.2)
End Stage Renal Disease	3,219 (9.1)	214 (11.4)
Short of breath	2,233 (6.3)	236 (12.6)
Poor appetite	4,441 (12.6)	505 (26.9)
Weight loss	2,039 (5.8)	353 (18.8)
Swallowing difficulty	1,117 (3.2)	130 (6.9)
Mechanically altered diet	15,645 (44.4)	1135 (60.5)
IV/parenteral nutrition or feeding tube	1,163 (3.3)	99 (5.3)
Hospitalizations/ED Visits (90 days prior)		
None	26,864 (76.3)	882 (47.0)
Cause-specific (fall, fracture, syncope)	2,911 (8.3)	539 (28.8)
Other cause	5,456 (15.5)	454 (24.2)
AChEI at index date		
Donepezil	27,483 (78.0)	1394 (74.4)
Donepezil/memantine	458 (1.3)	48 (2.6)
Galantamine	784 (2.2)	25 (1.3)
Rivastigmine (oral)	1,428 (4.1)	325 (17.3)
Rivastigmine (transdermal)	5,078 (14.4)	83 (4.4)
Memantine use	14,598 (41.4)	601 (32.1)
Benzodiazepine and/or Z drug	5,282 (15.0)	223 (11.9)
Antipsychotic use	8,174 (24.7)	414 (22.1)
Antidepressant use	20,365 (57.8)	945 (50.4)
Highly Anticholinergic Drugs (Beers Criteria)	5,263(14.9)	256 (13.7)
Total number of medications		
0 to 5	16,721 (47.5)	1077 (57.4)
6 to 10	15,526 (44.1)	657 (35.0)
>10	2,984 (8.,5)	141 (7.5)
ENVIRONMENT OF CARE		
Geographic region		
Midwest	9,588 (27.2)	520 (27.3)
Northeast	6,439 (18.3	198 (10.6)
South	16,231 (46.1)	1055 (56.3)
West	2,973 (8.4)	102 (5.4)
Certified beds		
<50	1,808 (5.1)	91 (4.9)
50-99	10,091 (28.6)	526 (28.1)
100-199	19,248 (54.6)	1091 (58.2)
200+	4,084 (11.6)	167 (8.9)
Rural/urban continuum		
Urban	24,341 (69.1)	1378 (73.5)

Rural	9,458 (26.9)	452 (24.1)
Highly rural	1,432 (4.1)	45 (2.4)
PROVIDER CHARACTERISTICS		
Prescriber specialty		
Geriatrics	3,028 (8.6)	140 (7.5)
Primary care	28,442 (80.7)	1530 (81.6)
Other	3,761 (10.7)	205 (10.9)

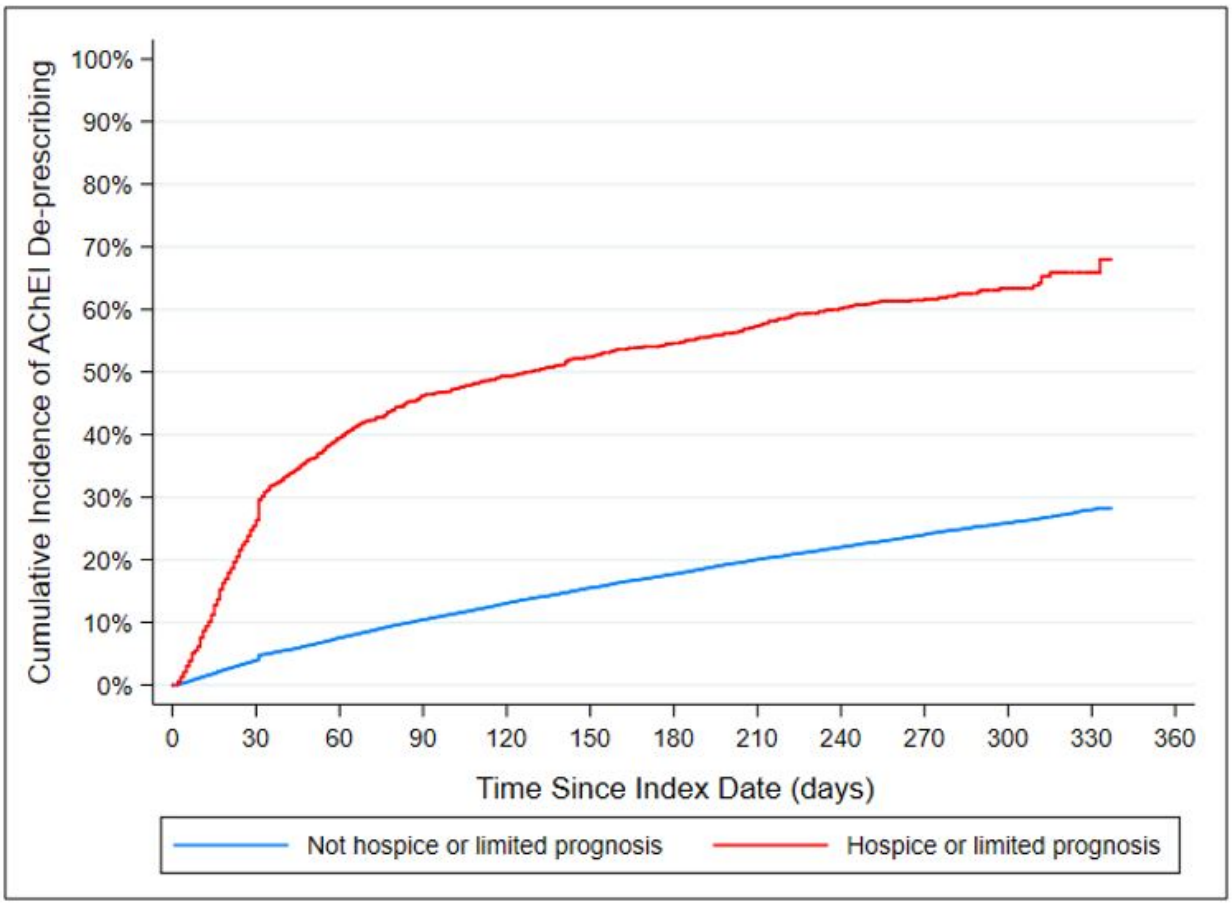
Table 4-4 - Adjusted Hazards Ratios for Sub-group Analysis by Limited Prognosis Status

Variable	Sub-group without limited prognosis Hazard Ratio [CI]	Sub-group with limited prognosis Hazard Ratio [CI]
DEMOGRAPHICS		
Age in years		
65-69	ref	ref
70-79	1.24 (1.04-1.47)*	1.08 (0.63-1.85)
80-89	1.23 (1.04-1.46)*	1.05 (0.63-1.76)
90+	1.31 (1.09-1.57)+	1.11 (0.65-1.88)
Sex		
Male	ref	ref
Female	1.02 (0.96-1.09)	0.94 (0.79-1.12)
Race/ethnicity		
White (non-hispanic)	ref	ref
Black (non-hispanic)	1.02 (0.94-1.11)	0.90 (0.70-1.17)
Hispanic	0.97 (0.86-1.09)	0.85 (0.61-1.18)
Other	0.99 (0.86-1.15)	0.64 (0.41-0.98)*
Current marital status		
Married	1.00 (0.94-1.07)	0.86 (0.73-1.03)
Not Married	ref	ref
CLINICAL ASSESSMENT		
Entered From		
Community	ref	ref
Hospital	1.03 (0.96-1.10)	0.95 (0.77-1.18)
NH or other LTC Facility	1.00 (0.92-1.10)	0.99 (0.76-1.29)
Assessment Form Type		
Admission	ref	ref
Quarterly	0.38 (0.34-0.42)^	0.38 (0.30-0.48)^
Annual	0.35 (0.31-0.40)^	0.26 (0.18-0.39)^
Significant Change in Status	1.30 (1.14-1.46)^	0.91 (0.74-1.13)
Charlson Comorbidity Index		
0-1	ref	ref
2-3	0.99 (0.91-1.07)	0.92 (0.73-1.15)
4-5	0.99 (0.92-1.08)	0.75 (0.59-0.94)*
≥6	1.01 (0.94-1.10)	0.87 (0.71-1.08)
Makes self understood		
Understood	ref	ref
Usually understood	1.05 (0.99-1.12)	1.19 (0.98-1.43)
Sometimes understood	1.14 (1.06-1.22)^	1.25 (1.04-1.51)*
Rarely/never understood	1.27 (1.17-1.38)^	1.25 (1.01-1.56)
PHQ-9 score		
Minimal	ref	ref
Mild	0.99 (0.92-1.07)	1.00 (0.83-1.20)
Moderate	1.11 (0.99-1.26)	1.16 (0.89-1.50)
Mod. severe or severe	1.12 (0.93-1.36)	1.04 (0.66-1.61)
Aggressive behavior scale		
None	ref	ref
Moderate	1.12 (1.04-1.20)^	1.06 (0.88-1.27)
Severe	1.23 (1.12-1.36)^	1.26 (0.97-1.62)

Very severe	1.12 (0.93-1.35)	0.93 (0.59-1.48)
Activities of Daily Living Score		
0 to 7	ref	ref
8 to 14	1.10 (0.97-1.26)	1.69 (0.72-3.95)
15 to 21	1.25 (1.10-1.43)^	1.53 (0.66-3.55)
22 to 28	1.47 (1.27-1.70)^	1.71 (0.73-4.03)
Urinary incontinence		
Continent	ref	ref
Occasionally incontinent	1.00 (0.81-1.12)	0.89 (0.55-1.43)
Frequently incontinent	1.01 (0.91-1.14)	1.22 (0.79-1.89)
Always incontinent	1.10 (0.98-1.24)	1.18 (0.76-1.84)
Indwelling catheter	1.05 (0.84-1.32)	1.15 (0.69-1.94)
Cancer	1.02 (0.90-1.16)	0.80 (0.59-1.08)
Heart failure	1.01 (0.94-1.09)	0.85 (0.71-1.02)
End Stage Renal Disease	0.99 (0.91-1.09)	1.14 (0.92-1.42)
Short of breath	0.98 (0.88-1.09)	0.85 (0.67-1.07)
Poor appetite	1.24 (1.15-1.34)^	1.29 (1.08-1.54)+
Weight loss	1.53 (1.41-1.66)^	1.04 (0.86-1.24)
Swallowing difficulty	1.13 (1.00-1.28)*	1.11 (0.85-1.46)
Mechanically altered diet	1.08 (1.03-1.14)+	1.13 (0.97-1.31)
IV/parenteral nutrition or feeding tube	1.02 (0.88-1.18)	0.85 (0.58-1.26)
Hospitalizations/ED Visits (90 days prior)		
Cause-specific (fall, fracture, syncope)	1.26 (1.15-1.39)^	1.30 (1.05-1.62)*
Other cause	1.19 (1.09-1.29)^	1.59 (1.33-1.90)^
AChEI Use at Index		
Donepezil	ref	ref
Donepezil/memantine	0.66 (0.52-0.85)^	0.81 (0.36-1.82)
Galantamine	0.82 (0.69-0.98)*	1.17 (0.77-1.80)
Rivastigmine (oral)	1.01 (0.89-1.14)	0.87 (0.63-1.19)
Rivastigmine (transdermal)	0.99 (0.92-1.07)	0.92 (0.77-1.10)
Memantine	0.84 (0.79-0.88)^	1.04 (0.90-1.21)
Benzodiazepine & Z drug	1.04 (0.96-1.12)	1.08 (0.86-1.35)
Antipsychotic	1.03 (0.97-1.09)	0.84 (0.70-1.00)
Antidepressant	0.98 (0.93-1.04)	1.04 (0.90-1.21)
Highly Anticholinergic Drugs (Beers Criteria)	0.93 (0.86-1.00)	1.04 (0.83-1.29)
Total number of medications		
0 to 5	ref	ref
6 to 10	0.86 (0.81-0.91)^	0.97 (0.83-1.14)
>10	0.75 (0.67-0.84)^	1.01 (0.74-1.39)
ENVIRONMENT OF CARE		
Geographic region		
Midwest	ref	ref
Northeast	1.13 (1.04-1.24)+	0.83 (0.65-1.06)
South	1.13 (1.05-1.21)+	0.80 (0.68-0.94)+
West	0.85 (0.75-0.96)+	0.73 (0.52-1.03)
Certified beds		
<50	ref	ref
50-99	0.92 (0.81-1.04)	1.05 (0.76-1.45)
100-199	0.95 (0.84-1.08)	1.01 (0.74-1.38)
200+	0.97 (0.83-1.12)	0.96 (0.64-1.42)
Rural/urban continuum		
Urban	ref	ref
Rural	0.80 (0.75-0.86)^	0.82 (0.70-0.97)*
Highly rural	0.75 (0.64-0.87)^	0.54 (0.30-0.99)*

PROVIDER CHARACTERISTICS		
Prescriber specialty		
Geriatrics	ref	ref
Primary care	0.88 (0.81-0.96)+	1.06 (0.83-1.37)
Other	0.93 (0.83-1.04)	1.06 (0.78-1.45)

*p<0.05
+p<0.01
^p<0.001



	90 days	180 days	270 days	End*
Limited prognosis Cumulative Incidence of Deprescribing (95% CI)	46.3% (43.8-18.9)	54.6% (51.9-57.3)	61.7% (58.8-64.5)	68.0% (62.8-73.2)
Not limited prognosis Cumulative Incidence of Deprescribing (95% CI)	10.5% (10.1-10.8)	17.8% (17.3-18.2)	24.1% (23.6-24.6)	28.3% (27.5-29.0)

Figure 4-3 - Cumulative Incidence of Deprescribing AChEIs Stratified by Limited Prognosis Designation

In the sensitivity analysis using a 60-day gap in medication supply to define deprescribing, adjusted associations remained substantively unchanged (**Table 4-5**). Several additional factors became statistically significantly associated with time to deprescribing, including female sex, black, significant change in status MDS form, facility size 50-99 beds, and facility size 100-199 beds. However, the magnitude and point estimates of these changed less than 12% and reached only borderline statistical significance

Table 4-5 - Unadjusted and Adjusted Hazards Ratios for Sensitivity Analysis using 60-day gap

Variable	Unadjusted Hazard Ratio [CI]	Adjusted Hazard Ratio [CI]
DEMOGRAPHICS		
Age in years		
65-69	ref	ref
70-79	1.30 (1.04-1.62)*	1.32 (1.06-1.67)*
80-89	1.26 (1.01-1.57)*	1.26 (1.01-1.58)*
90+	1.43 (1.15-1.78)^	1.34 (1.07-1.68)*
Sex		
Male	ref	ref
Female	1.09 (1.02-1.18)*	1.11 (1.03-1.21)*
Race/ethnicity		
White (non-hispanic)	ref	ref
Black (non-hispanic)	0.77 (0.70-0.86)^	0.87 (0.78-0.97)*
Hispanic	0.84 (0.72-0.97)*	0.87 (0.75-1.02)
Other	0.91 (0.76-1.08)	0.94 (0.79-1.12)
Current marital status		
Married	1.14 (1.07-1.23)^	1.03 (0.96-1.12)
Not Married	ref	ref
CLINICAL ASSESSMENT		
Entered From		
Community	ref	ref
Hospital	0.92 (0.85-0.99)*	0.92 (0.85-1.00)
NH or other LTC Facility	1.06 (0.95-1.18)	0.98 (0.89-1.11)
Assessment Form Type		
Admission	ref	ref
Quarterly	0.29 (0.26-0.32)^	0.31 (0.28-0.35)^
Annual	0.25 (0.22-0.28)^	0.28 (0.25-0.33)^
Significant Change in Status	1.81 (1.61-2.04)^	0.87 (0.76-0.98)*
Charlson Comorbidity Index		
0-1	ref	ref
2-3	0.92 (0.84-1.02)	0.98 (0.89-1.08)
4-5	0.89 (0.81-0.98)*	0.96 (0.87-1.06)
≥6	0.92 (0.84-1.01)	0.95 (0.86-1.05)
Makes self understood		
Understood	ref	ref
Usually understood	1.16 (1.07-1.26)^	1.05 (0.97-1.15)
Sometimes understood	1.52 (1.40-1.65)^	1.18 (1.08-1.28)+
Rarely/never understood	1.93 (1.77-2.11)^	1.34 (1.21-1.48)^
PHQ-9 score		
Minimal	ref	ref
Mild	1.41 (1.30-0.54)^	1.02 (0.93-1.12)
Moderate	1.76 (1.55-1.99)^	1.18 (1.03-1.36)*
Mod. severe or severe	1.80 (1.44-2.26)^	0.96 (0.76-1.22)
Aggressive behavior scale		
None	ref	ref
Moderate	1.23 (1.14-1.33)^	1.18 (1.08-1.28)^
Severe	1.45 (1.29-1.63)^	1.30 (1.15-1.46)^
Very severe	1.47 (1.19-1.83)^	1.20 (0.97-1.49)
Activities of Daily Living Score		
0 to 7	ref	ref

8 to 14	1.29 (1.09-1.54)+	1.10 (0.93-1.32)
15 to 21	1.94 (1.66-2.26)^	1.28 (1.07-1.52)+
22 to 28	2.81 (2.41-3.29)^	1.40 (1.15-1.69)^
Urinary incontinence		
Continent	ref	Ref
Occasionally incontinent	1.21 (1.04-1.40)+	1.01 (0.87-1.19)
Frequently incontinent	1.52 (1.34-1.73)^	1.05 (0.91-1.22)
Always incontinent	1.93 (1.71-2.19)^	1.13 (0.96-1.32)
Indwelling catheter	2.77 (2.20-3.48)^	1.18 (0.92-1.52)
Cancer	1.10 (0.95-1.27)	0.95 (0.81-1.10)
Heart failure	1.00 (0.92-1.09)	0.98 (0.89-1.07)
End Stage Renal Disease	1.06 (0.95-1.18)	1.02 (0.91-1.14)
Short of breath	1.11 (0.99-1.25)	0.94 (0.83-1.06)
Poor appetite	1.88 (1.75-2.03)^	1.22 (1.12-1.34)^
Weight loss	2.80 (2.56-3.06)^	1.41 (1.27-1.56)^
Swallowing difficulty	1.71 (1.48-1.96)^	1.10 (0.95-1.27)
Mechanically altered diet	1.36 (1.28-1.45)^	1.10 (1.03-1.18)+
IV/parenteral nutrition or feeding tube	1.22 (1.03-1.44)^	1.06 (0.87-1.28)
Limited Prognosis	10.0 (9.25-10.83)^	5.32 (4.89-5.79)^
Hospitalizations/ED Visits (90 days prior)		
Cause-specific (fall, fracture, syncope)	1.75 (1.57-1.95)^	1.28 (1.14-1.44)^
Other cause	1.75 (1.60-1.91)^	1.30 (1.19-1.44)^
AChEI Use at Index		
Donepezil	ref	ref
Donepezil/memantine	0.70 (0.52-0.93)*	0.78 (0.58-1.06)
Galantamine	0.96 (0.78-1.19)	0.88 (0.72-1.07)
Rivastigmine (oral)	1.10 (1.04-1.23)+	1.11 (0.96-1.30)
Rivastigmine (transdermal)	1.13 (0.95-1.28)	1.04 (0.95-1.13)
Memantine	0.73 (0.68-0.78)^	0.83 (0.78-0.89)^
Benzodiazepine & Z drug	1.08 (0.99-1.18)	1.11 (1.01-1.21)*
Antipsychotic	1.04 (0.97-1.12)	1.05 (0.97-1.13)
Antidepressant	0.95 (0.90-1.02)	1.02 (0.96-1.09)
Highly Anticholinergic Drugs (Beers Criteria)	0.91 (0.83-0.99)*	0.93 (0.84-1.02)
Total number of medications		
0 to 5	ref	ref
6 to 10	0.80 (0.75-0.86)^	0.89 (0.83-0.96)+
>10	0.80 (0.71-0.91)^	0.86 (0.75-0.98)*
ENVIRONMENT OF CARE		
Geographic region		
Midwest	ref	ref
Northeast	1.15 (1.05-1.27)+	1.16 (1.04-1.29)+
South	0.99 (0.92-1.07)	0.94 (0.87-1.03)
West	0.92 (0.80-1.04)	0.92 (0.80-1.07)
Certified beds		
<50	ref	ref
50-99	0.81 (0.70-0.93)+	0.84 (0.72-0.98)*
100-199	0.85 (0.74-0.98)*	0.86 (0.74-0.99)*
200+	0.95 (0.81-1.13)	0.95 (0.80-1.14)
Rural/urban continuum		
Urban	ref	ref
Rural	0.84 (0.78-0.91)^	0.88 (0.81-0.95)+
Highly rural	0.82 (0.69-0.97)*	0.90 (0.75-1.08)
PROVIDER CHARACTERISTICS		

Prescriber specialty		
Geriatrics	ref	ref
Primary care	0.87 (0.78-0.97)+	0.93 (0.84-1.03)
Other	0.97 (0.85-1.12)	0.95 (0.83-1.10)

*p<0.05
+p<0.01
^p<0.00

4.5 Discussion

This is the first national study of deprescribing AChEIs in U.S. Medicare beneficiaries with severe dementia residing in NHs in 2016. We found a cumulative incidence of deprescribing of just under 30% over one year of follow-up. In a time-to-event analysis, deprescribing was driven by a number of important clinical characteristics as well as a few facility and prescriber-level factors.

There are a number of strengths to our analysis that set it apart from existing literature. First, we studied a large, national sample of U.S. NH residents with severe dementia using a rich data source with hundreds of clinical assessment variables. Inclusion of both prevalent stays and newly admitted NH residents yielded a larger and more generalizable sample, thereby increasing statistical power. Second, utilization of a time-to-event analysis with time-varying covariates also strengthened our ability to identify associations between fluctuating clinical prognostic factors and deprescribing. Finally, we incorporated robust standard errors into our model by accounting for clustering at the NH facility level.

A recently published study by Maclagan et al. also examined predictors of AChEI discontinuation in NH residents in Canada.[137] In addition to country, this study differed from ours in their inclusion of all dementia severities, focus on only newly admitted residents, and use of earlier years of data (2011-2015). By including both prevalent stays and new admissions, we were able to observe that although deprescribing is more likely to occur at or around the time of NH admission, it can also occur later during a resident's stay. By limiting to residents with severe dementia, our study is the first to provide detailed information on predictors of deprescribing in

the patients for whom treatment recommendations are most controversial. Overall, however, the magnitude and direction of the associations of demographic, clinical, and facility factors with AChEI deprescribing observed in our study align with the Maclagan study, with just a few exceptions. Maclagan et al. found that older residents were less likely to be deprescribed, contradicting the findings of our analysis and others.[31,121,123,127,134] We also identified several factors associated with deprescribing that were not significantly associated with deprescribing in the Maclagan study, including several markers of poor prognosis, polypharmacy, strong anticholinergic use, and rurality. We also were able to examine the effect of memantine on deprescribing which was significantly associated with decreased likelihood of deprescribing.

The strongest predictor of deprescribing AChEIs in this study was indication of limited prognosis. Residents with severe dementia who had less than 6-months life expectancy or hospice use had almost 4 times the likelihood of deprescribing compared to residents without this designation. This is expected, as de-escalation of care, including medications, is an integral part of hospice as goals of care shift from prevention to palliation. Sensitivity analyses demonstrated that although the effect of many of the patient-level, system-level, and provider-level factors on deprescribing was eclipsed by limited prognosis in residents that fell into this category, they remained significantly associated with deprescribing in other residents.

Many of the patient-level clinical factors that were associated with increased likelihood of deprescribing included those that have been previously identified as surrogate markers for limited prognosis or decline in clinical status.[155,156] This aligns with current, albeit limited, recommendations to reconsider the use of these agents in patients with limited prognosis, given the shift in balance between benefit and potential for adverse effects.[60] We also found that deprescribing was more likely to occur during observations periods identified by MDS admission

assessments (i.e. at admission), rather than routine care (i.e. quarterly or annual assessments). Evaluations at the time of transfer to a new care setting are likely more comprehensive and medications may be scrutinized more closely for appropriateness.

Interestingly, the presence of polypharmacy and use of strongly anticholinergic medications were associated with decreased likelihood of deprescribing. One would hypothesize that polypharmacy may act as an impetus for deprescribing in an attempt to minimize the potential for drug-drug and drug-disease interactions. The same can be said for use of strongly anticholinergic medications, which have the potential to worsen cognition. We hypothesize that these act as surrogates of poor prescribing that carry over into deprescribing. It is also possible that medication use may represent preferences for more conservative prescribing driven by family preferences, as noted in prior qualitative studies.[95,96,105]

Important facility and prescriber-level factors were associated with a decreased likelihood of deprescribing, for example, residence in a NH in a rural or highly rural region was associated with decreased likelihood for deprescribing as compared to urban regions. This may represent proximity or affiliation with an academic medical center where initiatives to promote deprescribing through collaboration with pharmacists or or quality improvement initiatives may be more common. Nursing home residents who were prescribed AChEIs by a primary care physician were less likely to have the medication deprescribed than those residents whose AChEIs were prescribed by a geriatrician. Geriatricians are likely more attuned to medication-related issues, especially deprescribing, given the increased risk for adverse effects in the setting of advanced age.[114,170] These system-level factors may be seen as potential barriers (i.e. lack of specialized training and inadequate resources) and identify targets for educational interventions to improve uptake and implementation of deprescribing.

Although our study has important strengths, there are also limitations. In using Part D data, we assumed a gap in supply of 30 days corresponded to medication discontinuation, but it is possible that residents may have re-started AChEIs after this gap. However, sensitivity analyses using a 60-day gap in medication supply revealed no significant differences in our findings, although the overall proportion of deprescribing dropped considerably (20.4% vs. 12.7%). Given the uncertain potential for medication withdrawal syndromes and worsening behavioral symptoms, it is also possible that prescribers may opt for deprescribing by gradual dosage reduction, which we did not capture. Future studies should examine these different definitions for deprescribing using data sources that contain a greater level of detail, such as medication administration data from electronic health records.

4.6 Conclusions

This study found that among older NH residents with severe dementia being treated with AChEIs the cumulative incidence of deprescribing of just under 30% over one year of follow-up. A number of clinical factors that likely correspond to limited prognosis or deteriorating clinical status were found to be associated with increased likelihood for deprescribing. However, several system-level factors were also found to be associated with deprescribing and may act as barriers to implementation in practice. Future studies examining downstream effects of deprescribing should account for these potential confounders.

5.0 THE IMPACT OF DEPRESCRIBING ACHEIS ON BEHAVIORAL OUTCOMES IN SEVERE DEMENTIA

5.1 ABSTRACT

Clinical guidelines advocate for the withdrawal of cholinesterase inhibitors (AChEIs) in patients with severe dementia. However, there have been few well-designed studies of the outcomes of deprescribing AChEIs specifically in patients with severe dementia, and concerns about subsequent worsening of behavioral symptoms may serve as a barrier to ChEI discontinuation.

The objective of this study was to evaluate the impact of deprescribing AChEIs on aggressive behaviors and depression severity in older nursing home (NH) residents with severe dementia. As a secondary outcome, we also evaluated the impact of deprescribing AChEIs on the total number of medications received. We conducted a retrospective cohort study using Medicare claims, Part D prescriptions, Minimum Data Set (MDS) v3.0, Area Health Resource File, and Nursing Home Compare, for non-skilled NH residents aged 65+ with severe dementia receiving AChEIs with ≥2 MDS assessments in 2016 (n=30,788). The Aggressive Behavior Scale (ABS) and the Patient Health Questionnaire (PHQ-9) evaluated aggression and depression, respectively. Marginal structural models with inverse probability of treatment weights evaluated the association of deprescribing with outcomes, accounting for time-dependent confounding.

The sample was primarily white (78.7%), female (76.6%), >80 years old (77.6%), and 22.8% were deprescribed AChEIs. In adjusted models, deprescribing was not associated with aggression (0.002 point increase in ABS, p=0.90) or depression (0.04 point increase in PHQ-9,

p=0.50). However, deprescribing AChEIs was associated with a modest, but statistically significant reduction in the total number of medications prescribed (-0.55 decrease in total number of medications, p<0.001).

Deprescribing AChEIs in NH residents with severe dementia did not lead to an increase in aggressive behaviors or depression severity, but was associated with a decrease in the total number of medications prescribed. Our findings provide insight into the potential risks and benefits associated with deprescribing AChEIs and help inform decision-making in patients with severe dementia.

5.2 INTRODUCTION

One of the potential barriers to deprescribing AChEIs in older adults with severe dementia population is the potential for worsening of non-cognitive outcomes such as behavioral and psychological symptoms of dementia (BPSD).[96] Present in up to 80% of patients with dementia, BPSD refers a number of non-cognitive behavioral disturbances such as depression, aggression, resisting care, wandering, and delusions or hallucinations.[171,172] Previous studies have shown that BPSD tends to have greater prevalence and severity among institutionalized (hospital or long-term care) versus community-dwelling individuals.[173] Understandably, such disturbances cause a significant amount of distress and worsened quality of life in both patients and caregivers.[174,175] There is some literature suggesting that AChEIs may be effective in reducing the severity of BPSD.[65,171,176] Three randomized controlled trials have shown that donepezil and galantamine have a significant, albeit modest, effect on reducing BPSD versus no treatment with the most affected behavioral domains being apathy, anxiety, and depression.[97,177,178] In addition, a recently

published comparative effectiveness analysis found that the combination of donepezil and memantine was most effective in reducing BPSD compared to all other AChEIs alone and placebo.[68] Despite modest improvements in behavioral symptoms associated with AChEIs, no significant improvements have been shown in outcomes related to quality of life.[66] Generally speaking, the evidence presented is limited by heterogeneity in outcome ascertainment, lack of power, as most studies included BPSD as secondary outcomes, and low symptom severity at baseline. Given the safety concerns associated with use of other pharmacological agents in patients with dementia (e.g. antipsychotics) AChEIs are still often trialed for management of BPSD prior to use of other high-risk psychotropic agents.

The limited number of studies that have examined the downstream effects of deprescribing AChEIs on BPSD present conflicting results. A meta-analysis of five randomized controlled trials found that deprescribing AChEIs was associated with a statistically significant worsening of neuropsychiatric symptoms, although only a modest effect size was observed.[153] By contrast, a more recent randomized study found that in nursing home residents with moderate or severe dementia, deprescribing was not associated with significant changes in neuropsychiatric symptoms.[111] A small pilot study conducted among nursing home residents in France found no significant changes in BPDS following deprescribing.[112] Finally, a larger observational study of nursing home residents with varying dementia severity found that deprescribing was not associated with a difference in depressive symptoms, but was associated with a significant increase in aggressive behaviors.[101]

The lack of consistency in the studies presented above is likely attributable to heterogeneity across populations, with regards to dementia severity, and also small sample size. Nevertheless, there still remains a gap in the literature as to the implications of deprescribing AChEIs in patients

with severe dementia, despite the fact that these individuals are most likely to be considered for deprescribing. Therefore, the objective of this analysis was to evaluate the impact of deprescribing AChEIs on subsequent aggressive behaviors and depression severity in a large national sample nursing home residents with severe dementia. We also examined the impact of deprescribing AChEIs on the overall number of medications used, as a secondary outcome, to inform future studies evaluating changes in the use of other medications following deprescribing.

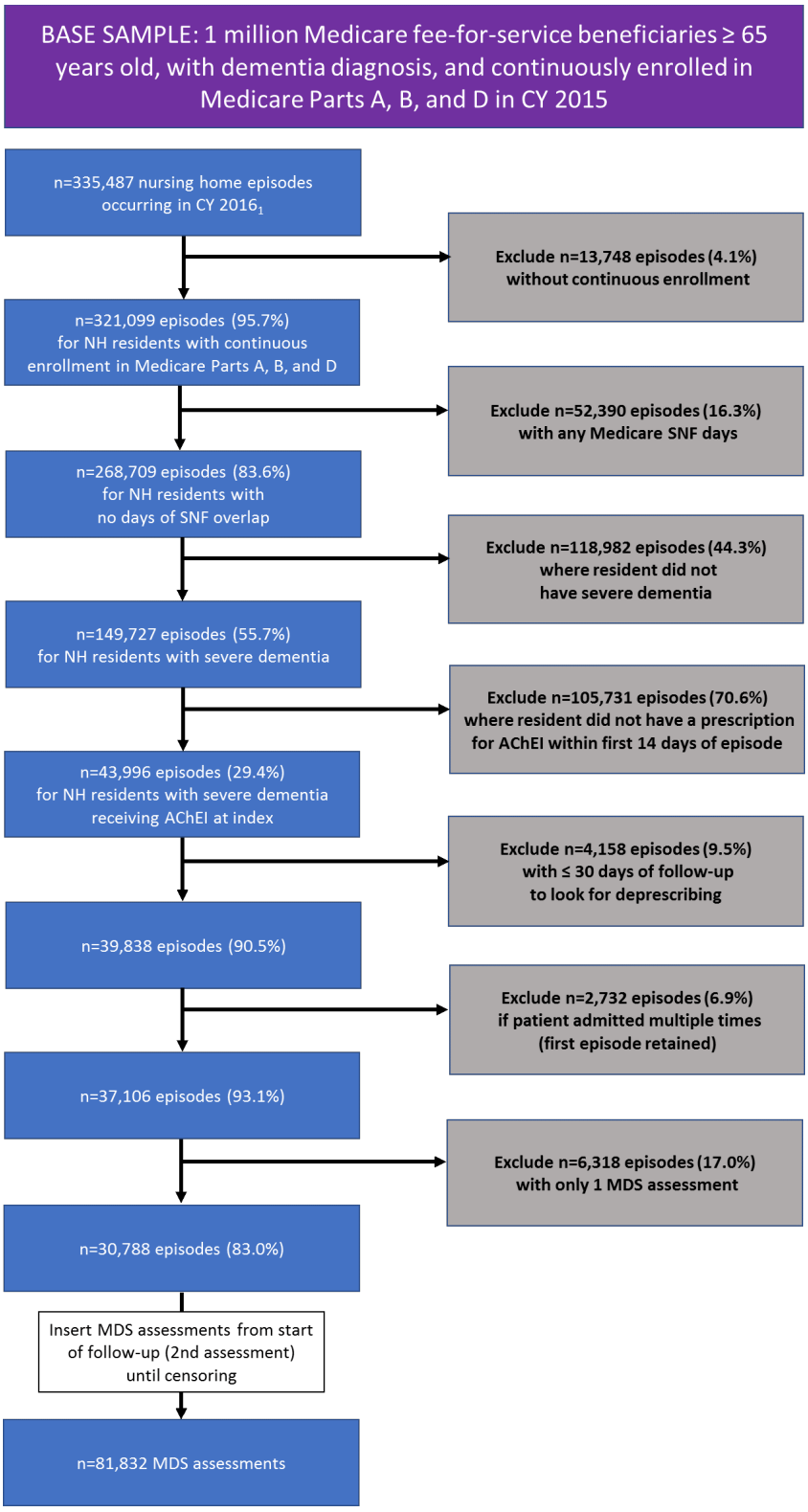
5.3 METHODS

5.3.1 Design and Data Sources

This study was a longitudinal analysis of Medicare claims, Part D prescription drug event data, and MDS assessments for a cohort of nursing home residents with severe dementia being treated with AChEIs at admission. We used MDS assessment forms to determine whether deprescribing AChEIs was associated with changes in aggressive behaviors and depression severity during follow-up. We used Medicare Part D data to evaluate the total number of medications each resident was receiving during follow-up.

5.3.2 Sample

The base cohort consisted of the same sample of non-skilled nursing home stays for patients with advanced dementia who were receiving AChEIs at baseline described previously in Chapter 4 (**Figure 5-1**). To summarize, we first identified non-skilled nursing home stays with an assessment start date during 2016 (n=335,487). Nursing home episodes were constructed by matching the first assessment in 2016 to the closest discharge form or assigning the end of the study period (12/31/2016) as the end date. We required continuous enrollment in Medicare Parts A, B, and D for the entire duration of the episode and the year prior (n=321,099). Episodes with Medicare Part A SNF claims that overlapped the period from assessment start date to discharge/study end date were excluded (n=268,709). We used MDS cognitive assessment data to identify episodes during which residents had severe dementia (n=149,727) and limited the sample to those receiving AChEIs within the first 14 days of the episode (n=43,996). The index date was assigned as the first day during which AChEI supply overlapped with the initial MDS assessment period and we required at least 30 days of follow-up from index date in order to observe deprescribing (n=39,838). We included only the first nursing home episode if residents had multiple episodes during our observation period (n=37,106). For this analysis, we imposed an additional restriction on the sample, all episodes were required to have at least two MDS assessments (index and follow-up) in order to evaluate changes in behavioral outcomes over time (n=30,788).



1. Nursing home episodes included new admissions as well as prevalent nursing home stays.

Figure 5-1 - Sample Construction for Aim 2 Analyses

5.3.3 Dependent Variables

The primary dependent variables in this analysis were changes in depression and aggression severity, as measured by the MDS. Aggressive behaviors were measured using the MDS-based Aggressive Behavior Scale (ABS)[158] while depression was measured using the Patient Health Questionnaire (PHQ-9)[159,179] in the MDS. Dependent variables were measured at the time of each MDS assessment, with each assessment serving as a repeated measure over time.

The ABS is an MDS-based measurement instrument that combines individual assessment items for verbal and physical aggression, inappropriate behavior, and resistance to care. It has been shown to be highly correlated with gold-standard assessments for aggressive behaviors in long-term care.[180,181] The ABS is coded based on observations from the prior 7 days and characterizes both the presence (yes/no) and frequency (none, occurred 1-3 days, occurred 4-6 days, or occurred daily) of behavioral symptoms. Scores for each item on the MDS are summed to yield a total score ranging from 0 to 12, with the following categorization scheme indicating marked change in status: none (ABS=0), moderate (ABS=1-2), severe (ABS=3-5), and very severe (ABS=6-12).[158] We treated the severity of aggressive behaviors measured on the ABS as a continuous score in our analyses. The MDS items included in the ABS and its scoring algorithm can be found in **Appendix Table B-1**.

The PHQ-9 is a 9-item depression interview that evaluates depressive symptoms as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[179] A complete list of items included in the PHQ-9 can be found in **Appendix Table B-2**. Residents are asked whether they were affected by each individual symptom and subsequently asked to provide how frequently they were bothered in the prior 14 days (never or 1 day, 2-6 days, 7-11 days, or 12-14 days). There

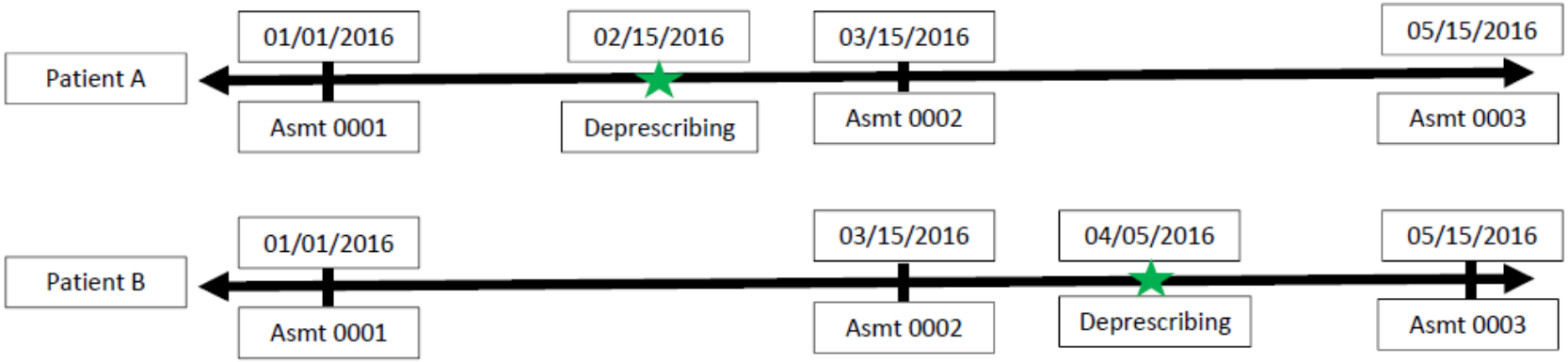
is also an observational version of the scale that may be completed by the staff member most familiar with the resident if unable to respond to interview questions. The PHQ-9 has been validated in nursing home residents, and has shown good agreement with standard diagnostic instruments.[159,182-185] A cut-off of ≥10 points on the PHQ-9 is an accepted threshold for diagnosing depression with a change of ≥5 points is considered to be clinically significant.[186] We treated depression severity measured by the PHQ-9 as a continuous score in our analyses.

We also evaluated the total number of non-AChEI medications received as a secondary outcome to inform future analyses on the impact of deprescribing AChEIs on medication use. The number of medications received was treated as a continuous variable and was defined as the total number of non-AChEI medications that each resident was receiving on the first day of each MDS assessment period, similar to the manner in which behavioral outcomes were measured above. Change over time was measured as the difference in the total number of medications received from each MDS assessment to the next.

5.3.4 Independent Variables

The primary independent variable in this analysis was whether or not a resident's AChEI was deprescribed. Deprescribing of AchEIs was defined as a subsequent gap in therapy of at least 30 days based on prescription fill dates and last day of supply, with the 31st gap day in the period serving as the discontinuation date. For example, if a patient was issued a prescription on 01/01/2015 with a 28-day supply, this prescription had an end date of 01/28/2015. If no subsequent fill was observed for any AChEI within the next 30 days (on or before 02/27/2015), this was considered deprescribing, with a discontinuation date of 02/28/2015. The discontinuation date

was defined as such to avoid the potential for immortal time bias, in which a period of immortal time, usually required for the observation of a specific event, may be incorrectly attributed to the exposed group.[148,149] Deprescribing was treated as a time-varying exposure in our dataset and was measured in the time period leading up to each MDS assessment. This is as opposed to dependent variables, which were measured at the time of each MDS assessment to ensure correct temporality between exposure and outcome. An indicator for deprescribing was set as positive for each MDS assessment with an assessment start date beyond the AChEI discontinuation date. An example of this data structure is shown in **Figure 5-2**. By using a time-dependent analysis, we avoid the problem of immortal time bias, as follow-up time in our sample was not allocated to the "exposed" group (i.e. deprescribed) until after residents fully met our definition for deprescribing (gap ≥30 days).



Patient ID	Assessment #	Assess Start Dt	Assess Stop Dt	Deprescribing AChEI	Age Category (Invariant)	ADL Category (Time-varying)	Censoring
A	0001	01/01/2016	03/14/2016	0	1	1	-
A	0002	03/15/2016	05/14/2016	1	1	2	-
A	0003	05/15/2016	06/30/2016	1	1	2	Censored
B	0001	01/01/2016	03/14/2016	0	2	3	-
B	0002	03/15/2016	05/14/2016	0	2	3	-
B	0003	05/15/2016	06/30/2016	1	2	2	Censored

ADL=Activities of Daily Living

Figure 5-2 - Data Structure and Coding for Chapter 5 Analyses

Other independent variables included as covariates included factors that may influence the decision to deprescribe AChEIs that were evaluated in our first analysis. Covariates were extracted from the MDS, Medicare Part D Prescription Drug Event records, Medicare Part A and B claims, Nursing Home Compare, and the Area Health Resource File. These included: demographics (age, sex, race/ethnicity, marital status), clinical assessment factors (MDS assessment form type, ability to complete brief interview for mental status, resident ability to be understood, poor appetite, urinary incontinence, swallowing disorder, parenteral nutrition or tube feeds, mechanically altered diet, recent weight loss, shortness of breath, dehydration, cancer, end-stage renal disease, heart failure, activities of daily living, limited prognosis or hospice utilization, antidepressant use, antipsychotic use, benzodiazepine use, strong anticholinergic use, AChEI type, memantine use, total number of medications, Charlson Comorbidity Index, all-cause and cause-specific hospitalizations in prior 90 days, location prior to nursing home residence), environment of care (nursing home geographic region, facility size, rurality), provider specialty (AChEI prescriber specialty – primary care, geriatrics, other).

Demographic, environment of care, and provider specialty variables were treated as time-invariant and were measured at the index MDS assessment. Clinical assessment factors were created as time-varying and were measured during the period immediately prior to each MDS assessment using a lagged approach to ensure correct temporality for measuring covariates and outcomes (explained in further detail below).

5.3.5 Statistical Analysis

We identified time-dependent confounding as a potential problem, hypothesizing that many of the time-varying clinical characteristics that can affect the decision to deprescribe may also have an association with the current severity of behavioral symptoms. At the same time, these clinical characteristics may change over time in response to whether deprescribing has occurred. An example is presented in **Figure 5-3** where ADLs act as a time-dependent confounder in the relationship between deprescribing and depression severity.[187] The gray lines represent the potential effect of ADLs on deprescribing AChEIs and on depression severity. In our prior analyses, we demonstrated that more severe impairment in ADLs was associated with increased likelihood of deprescribing. Severity of impairment in ADLs may also exert an influence on depression severity, in that residents with more functional limitations may have greater depression severity due to limited independence. In this case, whether or not deprescribing has occurred may affect future values for severity of ADL impairment (black dotted line), which in turn may still act as a confounder in the relationship between deprescribing and depression severity (gray dotted line).

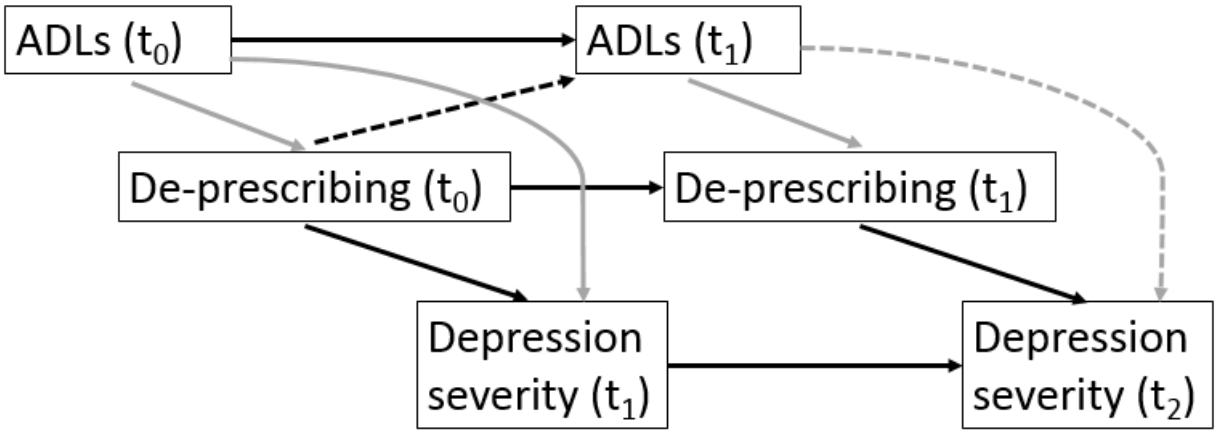


Figure 5-3 – Directed Acyclic Graph of Time-dependent Confounding

We used marginal structural models with inverse probability of treatment weights (IPTW) to address potential time-dependent confounding of deprescribing and behavioral outcomes by time-varying clinical characteristics.[188-193] We created a dataset that included baseline values for non-clinical time-invariant covariates measured at index date (demographics, environment of care, and prescriber specialty) as well as time-varying values for clinical characteristics.

Inverse probability of treatment weights were used to model each subject's propensity for being deprescribed, considering their history of time invariant and time-varying covariates. Time-varying covariates were lagged to the assessment period immediately prior to ensure that potential predictors of deprescribing were measured prior to the resident's current treatment status. Thus, treatment status was adjusted for potential time-dependent factors that may have influenced treatment status in each period leading up to the current assessment. A depiction of this approach is shown in **Figure 5-4**. As this study design required the use of values from prior MDS assessments to predict propensity for deprescribing, we only evaluated residents from the time of their second MDS assessment forward.

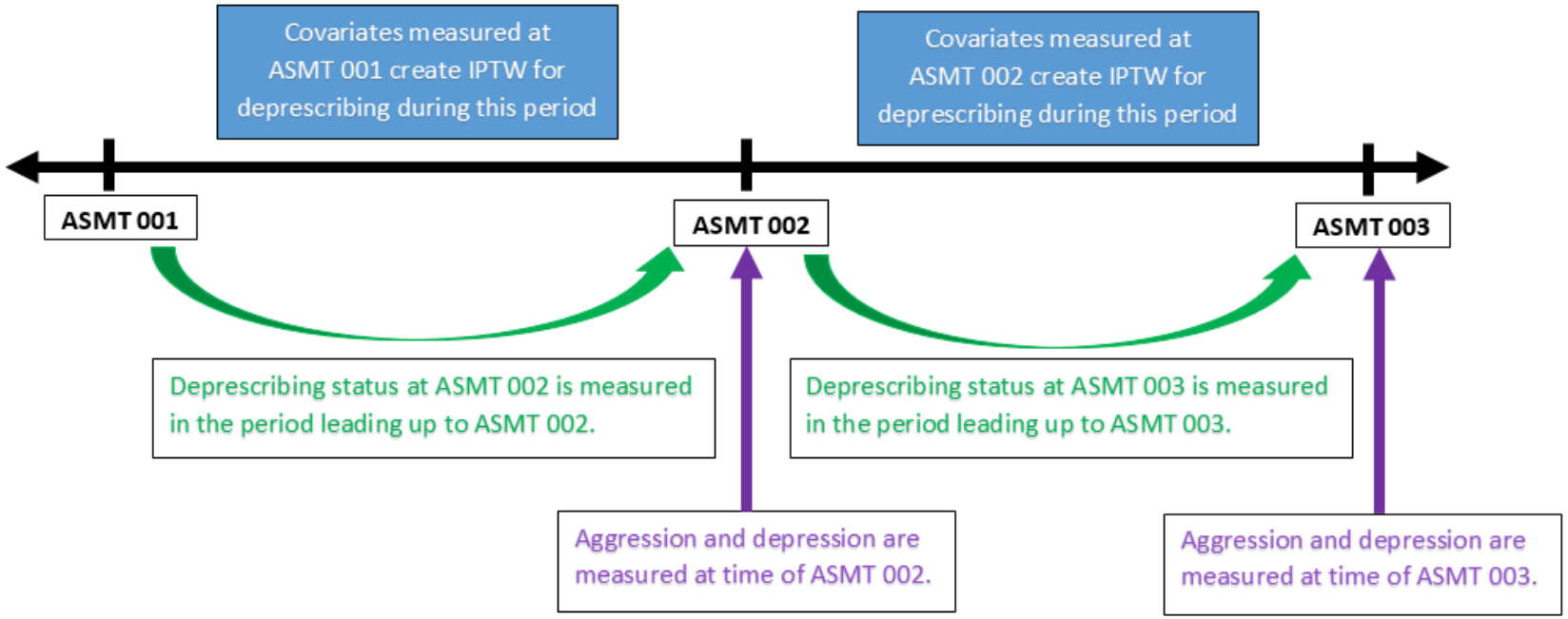


Figure 5-4 - Derivation of Inverse Propensity Treatment Weights for Chapter 5 Analyses

Inverse probability of treatment weights were calculated for each MDS assessment period up until and including each resident's first assessment where deprescribing had occurred. The IPTW for each assessment period is represented by the general formula 1 / P(Z = 1|X), which can be interpreted as the inverse of the probability of being deprescribed given the resident's observed covariates. These weights were further stabilized by including a constant, P(Z = 1), in the numerator to reduce variability and extreme weights.[189,194] In this study specifically, IPTWs were estimated for each MDS assessment using pooled logistic regression models with deprescribing status as the outcome and baseline characteristics, lagged time-varying clinical assessment variables (i.e., "lagged" in that we used the values from the assessment at the start of the interval over which exposure was assessed), and time since index date as predictors. The numerator was then estimated using the same model, but including only time-invariant baseline characteristics. The formula for deriving the stabilized IPTW for each assessment period is listed below:

$$sw_{ij} = \prod_{k=0}^{j} \frac{P(A_{ik}=a_{ik} \mid \bar{A}_{ik-1}=\bar{a}_{ik-1},\ V_i=v_i)}{P(A_{ik}=a_{ik} \mid \bar{A}_{ik-1}=\bar{a}_{ik-1},\ \bar{C}_{ik}=\bar{c}_{ik},\ V=v_i)}$$

The denominator represents the probability of being deprescribed, given the history of deprescribing leading up until the previous assessment ($\bar{a}_{ik-1}$), the observed history of time-varying clinical characteristics ($\bar{c}_{ik}$) and time-invariant covariates (v_i) measured at baseline. The numerator represents the stabilization constant, or the probability of deprescribing, given the history of deprescribing and time-invariant covariates. The stabilized weight (sw_{ij}) is the product of each MDS assessment period (t_{ij}) from baseline until the current assessment period for each resident (i).

The models used in this analysis also addressed the potential for loss to follow-up or informative censoring by using inverse probability of censoring weights (IPCW). Censoring

weights were calculated as the probability of remaining uncensored at the time of each MDS assessment, using the same formula described above for each assessment period. Inverse censoring weights were then multiplied by the IPTWs associated with each MDS assessment period to create an overall weight which was applied to the sample.

Our original approach for calculating the stabilized IPTWs was to include baseline values for all covariates, including baseline values of time-varying characteristics, as well as lagged time-varying values for clinical characteristics. However, we observed that after applying the stabilized IPTWs to our sample, there was still a significant amount of covariate imbalance between observations with deprescribing vs. no deprescribing (**Appendix Table B-3**). We believe this was attributable to a general lack of variability between baseline and subsequent repeated measures of clinical characteristics in our sample. This was confirmed upon inspection of the data, with most variables deviating from their baseline values in less than 10% of the sample (**Appendix Table B-4**). We hypothesized that the lack of variability resulted in the same covariate values being used in the estimation models of the denominator and the numerator, effectively cancelling each other out. Therefore, we made the decision to only include baseline values for time-invariant characteristics and the lagged time-varying clinical characteristics in IPTW estimation models, which resulted in substantially improved covariate balance (shown in **Table 5-3** in primary results below). A comparison of covariates included in IPTW estimation models for the original approach (**Appendix Table B-5**) versus our final models (**Appendix Table B-6**) is presented in the appendix.

Sample characteristics were calculated on the assessment-level (i.e. at the time of each MDS assessment). We then evaluated the balance of covariates across deprescribing status after

applying stabilized inverse propensity weights using standardized differences. Standardized differences were calculated using the user-written Stata program "stddiffi" using the formula:

$$d = \frac{(\overline{x_1} - \bar{x}_2)}{\sqrt{\frac{s_1^2 + s_2^2}{2}}}$$

for binary variables and continuous variables and a Mahalanobis distance generalization for multilevel categorical variables.[195] Generally speaking, standardized differences less than 0.1 are generally considered to result in minimal bias.[196] We also evaluated the adequacy of overlap in inverse propensity weights between deprescribed and not deprescribed observations using kernel density plots.

Primary analyses were conducted using an intent-to-treat approach (ITT) for deprescribing, where residents remained in this category until the end of follow-up. The primary model for the association of deprescribing with behavioral outcomes included an indicator for whether deprescribing had occurred, applying the IPTWs and IPCWs described above. We used robust standard errors to account for the correlation between repeated observations from the same individual.

In addition to the primary analyses, we also evaluated several additional iterations of generalized linear models to evaluate the robustness of the association between deprescribing and behavioral outcomes. These included an unadjusted model without IPTW weighting, a fully-adjusted model without IPT weighting, a doubly robust approach using a fully-adjusted model and IPT weights, and IPT weights with trimming and top-coding. The specifications for each of these models are described in **Table 5-1**.

Table 5-1 - Aim 2 Model Descriptions

Model	Weighted?	Covariates?	Additional Specifications (if applicable)
Unadjusted	No	None	N/a
MSM w/IPTW	Yes	None	N/a
MSM w/IPTW (trimmed at 1st & 99th)	Yes	None	Observations with propensity weights outside the 1st and 99th percentiles were dropped.
MSM w/IPTW (capped at 1st & 99th)	Yes	None	Observations with propensity weights outside the 1st and 99th percentiles were re-coded to the 1st and 99th percentile values.
MSM w/IPTW (sensitivity for overlap)	Yes	None	Observations with propensity weights outside region of overlap between those with and without deprescribing were dropped.
MSM w/IPTW Doubly Robust	Yes	Yes, all demographics, clinical assessment, environment of care, and prescriber characteristics.	Additional adjustment for factors that remained unbalanced after applying IPTWs.
MSM w/IPTW (w/baseline)	Yes	None	Preliminary approach where estimation of IPTWs included time-invariant baseline values for clinical assessment characteristics as well as lagged time-varying clinical assessment characteristics. Adequate balance was not achieved.
MSM w/IPTW (w/baseline) Doubly Robust	Yes	Yes, all demographics, clinical assessment, environment of care, and prescriber characteristics.	Preliminary approach where estimation of IPTWs included time-invariant baseline values for clinical assessment characteristics as well as lagged time-varying clinical assessment characteristics. Adequate balance was not achieved.
Adjusted model w/o IPTW	No	Yes, all demographics, clinical assessment, environment of care, and prescriber characteristics.	

*All models used generalized linear models with robust standard errors to account for correlation between MDS assessments for the same resident.

In our prior work (Chapter 4), we identified that a significant portion of residents with a 30-day gap in AChEI supply eventually filled another prescription for an AChEI (approximately 32%), thus appearing to have re-started therapy. Therefore, we also conducted sensitivity analyses in a per-protocol fashion where residents who were deprescribed were censored in the period following a fill for a new AChEI prescription.

5.4 RESULTS

5.4.1 Sample Characteristics.

At the time of study entry, the sample was primarily white (78.6%), female (77.6%), and age 80 or older (77.6%). Unweighted sample characteristics are presented in **Table 5-2**. The proportion of residents who had AChEIs deprescribed was 22.8%. Deprescribing AChEIs was more likely to have occurred during MDS assessments for residents who had greater difficulty being understood, greater ADL impairment, greater frequency of urinary incontinence, poor appetite, significant weight loss, designation as limited prognosis, did not use memantine, did not use antidepressants, and had fewer total medications. After IPTW adjustment, nearly all covariates had achieved a sufficient degree of balance across assessments with and without deprescribing, defined as a standardized difference <0.10 (**Table 5-3**). The only exceptions were MDS assessment type, memantine use, geographic region, and rurality, which had standardized differences <0.15.

Table 5-2 – Unweighted Assessment-level Characteristics for Aim 2 Analyses

Variable	AChEI Deprescribed N=10,577 assessments n (%)	AChEI Prescribed N=71,255 assessments n (%)	Standardized Difference
DEMOGRAPHICS			
Age in years			0.06
65-69	220 (2.1)	1,775 (2.5)	
70-79	2,163 (20.5)	14,196 (19.9)	
80-89	4,841 (45.8)	34,322 (48.2)	
90+	3,353 (31.7)	20,962 (29.4)	
Sex			0.04
Male	2,221 (21.0)	16,135 (22.6)	
Female	8,356 (79.0)	55,120 (77.4)	
Race/ethnicity			0.03
White	8,240 (77.9)	56,058 (78.7)	
Black	1,325 (12.5)	8,382 (11.8)	
Hispanic	652 (6.2)	4,181 (5.9)	
Other	360 (3.4)	2,634 (3.7)	
Current marital status			0.01
Married	2,206 (20.9)	14,555 (20.4)	
Not Married	8,371 (79.1)	56,700 (79.6)	
CLINICAL ASSESSMENT			
Entered from			0.03
Community	2,042 (19.3)	14,464 (20.3)	
Hospital	7,307 (69.1)	48,367 (67.9)	
NH or other LTC facility	1,228 (11.6)	8,424 (11.8)	
MDS Assessment Type			0.28*
Admission	365 (3.5)	2,600 (3.7)	
Quarterly	7,280 (68.8)	52,066 (73.1)	
Annual	1,659 (15.7)	13,433 (18.9)	
Significant Change in Status	1,273 (12.0)	3,156 (4.4)	
Charlson Comorbidity Index			0.03
0-1	1,633 (15.4)	10,591 (14.9)	
2-3	2,713 (26.7)	18,522 (26.0)	
4-5	2,540 (24.0)	17,695 (24.8)	
≥6	3,691 (34.9)	24,447 (34.3)	
Makes self understood			0.23*
Understood	3,277 (31.0)	27,967 (39.2)	
Usually understood	2,703 (25.6)	19,434 (27.3)	
Sometimes understood	2,612 (24.7)	15,188 (21.3)	
Rarely/never understood	1,985 (18.8)	8,669 (12.2)	
PHQ-9 score	2.41 (3.6)	2.07 (3.3)	0.10
Aggressive behavior scale	0.59 (1.4)	0.51 (1.3)	0.06
Activities of Daily Living Score			0.26*
1 to 7	480 (4.5)	5,685 (8.0)	
8 to 14	1,214 (11.5)	11,614 (16.3)	
15 to 21	5,477 (51.8)	37,610 (52.8)	
22 to 28	3,406 (32.2)	16,346 (22.9)	
Urinary incontinence			0.24*
Continent	696 (6.6)	7,243 (10.2)	
Occasionally incontinent	1,078 (10.2)	10,100 (14.2)	

Frequently incontinent	3,220 (30.4)	23,908 (33.6)	
Always incontinent	5,399 (51.0)	28,991 (40.7)	
Indwelling catheter	184 (1.7)	1,013 (1.4)	
Cancer	420 (4.0)	2,779 (3.9)	0.004
Heart failure	1,485 (14.0)	10,670 (15.0)	0.03
End Stage Renal Disease	972 (9.2)	6,244 (8.8)	0.02
Short of breath	633 (6.0)	4,398 (6.2)	0.01
Poor appetite	1,824 (17.2)	8,514 (12.0)	0.15*
Weight loss	1,079 (10.2)	3,641 (5.1)	0.19*
Swallowing difficulty	455 (4.3)	2,156 (3.0)	0.07
Mechanically altered diet	4,748 (44.9)	38,225 (53.7)	0.18*
IV/parenteral nutrition or feeding tube	331 (3.1)	1,866 (2.6)	0.03
Hospice or Limited Prognosis	1,898 (17.9)	1,996 (2.8)	0.51*
Hospitalizations/ED Visits (90 days prior)			0.02
None	9,155 (86.6)	62,075 (87.1)	
Cause-specific (fall, fracture, syncope)	582 (5.5)	3,555 (5.0)	
Other cause	840 (7.9)	5,625 (7.9)	
AChEI at index date			0.10
Donepezil	8,128 (76.9)	54,997 (77.2)	
Donepezil/memantine	84 (0.8)	1,261 (1.8)	
Galantamine	209 (2.0)	1,616 (2.3)	
Rivastigmine (oral)	480 (4.5)	3,001 (4.2)	
Rivastigmine (transdermal)	1,676 (15.9)	10,380 (14.6)	
Memantine use	3,203 (30.3)	30,543 (42.9)	0.26*
Benzodiazepine and/or Z drug	1,301 (12.3)	9,971 (14.0)	0.05
Antipsychotic use	2,102 (19.9)	16,166 (22.7)	0.07
Antidepressant use	5,438 (51.4)	40,716 (57.1)	0.11*
Highly Anticholinergic Drugs (Beers)	1,181 (11.2)	10,002 (14.0)	0.09
Total number of medications [Mean (SD)]	4.8 (3.0)	5.9 (3.0)	0.33*
ENVIRONMENT OF CARE			
Geographic region			0.11*
Midwest	2,505 (23.7)	19,632 (27.6)	
Northeast	2,144 (20.3)	12,965 (18.2)	
South	5,230 (49.5)	33,162 (46.5)	
West	698 (6.6)	5,496 (7.7)	
Certified beds			0.07
<50	488 (4.6)	3,425 (4.8)	
50-99	2,701 (25.5)	20,312 (28.5)	
100-199	6,021 (56.9)	39,322 (55.2)	
200+	1,367 (12.9)	8,196 (11.5)	
Rural/urban continuum			0.13*
Urban	7,839 (74.1)	48,760 (68.4)	
Rural	2,396 (22.7)	19,621 (27.5)	
Highly rural	342 (3.2)	2,874 (4.0)	
PROVIDER SPECIALTY			
Prescriber specialty			0.05
Geriatrics	1,043 (9.9)	6,114 (8.6)	
Primary care	8,403 (79.5)	57,922 (81.3)	
Other	1,131 (10.7)	7,219 (10.1)	

***Standardized Difference ≥0.10**

Table 5-3 - Inverse Propensity-Weighted Assessment-level Characteristics for Aim 2 Analyses

Variable	AChEI Deprescribed N=10,358 assessments n (%)	AChEI Prescribed N=71,474 assessments n (%)	Standardized Difference
DEMOGRAPHICS			
Age in years			0.05
65-69	233 (2.2)	1,781 (2.5)	
70-79	2,091 (20.2)	14,343 (20.1)	
80-89	4,774 (46.1)	34,472 (48.2)	
90+	3,259 (31.5)	20,877 (29.2)	
Sex			0.03
Male	2,218 (21.5)	16,343 (22.9)	
Female	8,140 (78.6)	55,131 (77.1)	
Race/ethnicity			0.04
White	8,018 (77.4)	56,169 (78.6)	
Black	1,286 (12.4)	8,412 (11.8)	
Hispanic	687 (6.6)	4,255 (6.0)	
Other	366 (3.5)	2,637 (3.7)	
Current marital status			<0.01
Married	2,187 (21.1)	14,974 (21.0)	
Not Married	8,170 (78.9)	56,499 (79.1)	
CLINICAL ASSESSMENT			
Entered from			0.05
Community	1,865 (18.0)	14,215 (19.9)	
Hospital	7,291 (70.4)	48,617 (68.1)	
NH or other LTC facility	1,202 (11.6)	8,642 (12.1)	
MDS Assessment Type			0.14*
Admission	307 (3.0)	4,128 (5.8)	
Quarterly	7,581 (73.2)	50,858 (71.2)	
Annual	1,724 (16.6)	11,846 (16.6)	
Significant Change in Status	745 (7.2)	4,641 (6.5)	
Charlson Comorbidity Index			0.03
0-1	1,515 (14.6)	11,053 (15.5)	
2-3	2,561 (24.7)	17,727 (24.8)	
4-5	2,428 (23.5)	16,733 (23.4)	
≥6	3,853 (37.0)	25,960 (36.3)	
Makes self understood			0.05
Understood	3,736 (36.1)	27,456 (38.4)	
Usually understood	2,854 (27.6)	19,135 (26.8)	
Sometimes understood	2,302 (22.2)	15,430 (21.6)	
Rarely/never understood	1,464 (14.1)	9,452 (13.2)	
PHQ-9 score [Mean (SD)]	2.3 (3.5)	2.2 (3.5)	0.03
Aggressive behavior scale [Mean (SD)]	0.54 (1.3)	0.55 (1.3)	0.01
Activities of Daily Living Score			0.06
1 to 7	645 (6.2)	5,174 (7.2)	
8 to 14	1,428 (13.8)	10,711 (15.0)	
15 to 21	5,439 (52.5)	37,121 (51.9)	
22 to 28	2,845 (27.5)	18,467 (25.8)	
Urinary incontinence			0.07
Continent	868 (8.4)	6,802 (9.5)	
Occasionally incontinent	1,287 (12.4)	9,779 (13.7)	

Frequently incontinent	3,278 (31.7)	23,033 (32.3)	
Always incontinent	4,691 (45.3)	30,369 (42.5)	
Indwelling catheter	232 (2.2)	1,489 (2.1)	
Cancer	465 (4.5)	3,158 (4.4)	<0.01
Heart failure	1,694 (16.4)	11,728 (16.4)	<0.01
End Stage Renal Disease	1,077 (10.4)	6,918 (9.7)	0.02
Short of breath	697 (6.7)	4,836 (6.8)	<0.01
Poor appetite	1,514 (14.6)	9,854 (13.8)	0.02
Weight loss	868 (8.4)	5,020 (7.0)	0.05
Swallowing difficulty	406 (3.9)	2,460 (3.4)	0.03
Mechanically altered diet	5,172 (49.9)	37,419 (52.4)	0.05
IV/parenteral nutrition or feeding tube	416 (4.0)	2,669 (3.7)	0.01
Hospice or Limited Prognosis	792 (7.7)	4,890 (6.8)	0.03
Hospitalizations/ED Visits (90 days prior)			0.07
None	8,682 (83.8)	58,300 (81.6)	
Cause-specific (fall, fracture, syncope)	678 (6.6)	4,775 (6.7)	
Other cause	997 (9.6)	8,399 (11.8)	
AChEI at index date			0.03
Donepezil	7,958 (76.8)	55,169 (77.2)	
Donepezil/memantine	141 (1.4)	1,134 (1.6)	
Galantamine	211 (2.0)	1,541 (2.2)	
Rivastigmine (oral)	410 (4.0)	2,873 (4.0)	
Rivastigmine (transdermal)	1,639 (15.8)	10,755 (15.1)	
Memantine use	3,667 (35.4)	28,787 (40.3)	0.10*
Benzodiazepine and/or Z drug	1,436 (13.9)	10,201 (14.3)	0.01
Antipsychotic use	2,247 (21.7)	16,489 (23.1)	0.03
Antidepressant use	5,699 (55.0)	40,527 (56.7)	0.03
Highly Anticholinergic Drugs (Beers)	1,398 (13.5)	10,239 (14.3)	0.02
Total number of medications [Mean (SD)]	5.6 (3.2)	5.9 (3.1)	0.09
ENVIRONMENT OF CARE			
Geographic region			0.12*
Midwest	2,349 (22.7)	19,272 (27.0)	
Northeast	2,083 (20.1)	12,777 (17.9)	
South	5,270 (50.9)	33,951 (47.5)	
West	656 (6.3)	5,474 (7.7)	
Certified beds			0.08
<50	458 (4.4)	3,434 (4.8)	
50-99	2,588 (25.0)	20,268 (28.4)	
100-199	5,947 (57.4)	39,601 (55.4)	
200+	1,365 (13.2)	8,170 (11.4)	
Rural/urban continuum			0.13
Urban	7,701 (74.3)	48,957 (68.5)	
Rural	2,304 (22.3)	19,632 (27.5)	
Highly rural	353 (3.4)	2,884 (4.0)	
PROVIDER SPECIALTY			
Prescriber specialty			0.04
Geriatrics	1,002 (9.7)	6,430 (9.0)	
Primary care	1,139 (11.0)	7,221 (10.1)	
Other	8,217 (79.3)	57,823 (80.9)	

***Standardized Difference ≥0.10**

Primary Analysis. The occurrence of depressive symptoms and aggressive behaviors was very low in our sample of nursing home residents with severe dementia. Any depressive symptoms were present in less than half of our sample and aggressive behaviors were present in less than one-fourth. Baseline depression severity and aggressive behavior scores were both non-normally distributed and skewed to the right. The mean PHQ-9 baseline score was 2.2 (SD=3.4) and the mean baseline ABS score was 0.5 (SD=1.3) (**Table 5-5**). Results for the primary analysis are presented in **Table 5-5** and **Table 5-6**. In unadjusted analyses, deprescribing AChEIs was associated with an increase in PHQ-9 score of 0.28 points (95% CI: [0.18, 0.38], $p<0.001$) and an increase in ABS score of 0.056 (95% CI: [0.027, 0.10], $p<0.001$). In adjusted analyses weighted by IPTWs, deprescribing was no longer associated with depression severity (0.044 unit increase in PHQ-9, 95% CI: [-0.086, 0.17], $p=0.50$) or aggressive behaviors (0.002 unit increase in ABS, 95% CI: [-0.036, 0.041], $p=0.90$).

Table 5-4 - Assessment-level Distribution of Behavioral Outcomes

Outcome	AChEI Deprescribing	Range	Mean (SD)	Median [IQR]
Depression Severity (PHQ-9)	Yes	0-27	2.4 (3.6)	0 [0-3]
	No	0-27	2.1 (3.4)	0 [0-3]
Aggressive Behavior Scale (ABS)	Yes	0-12	0.57 (1.3)	0 [0-0]
	No	0-12	0.51 (1.2)	0 [0-0]

Table 5-5 - Model Results for Association of Deprescribing with Depression Severity

Model	Variable	Coefficient	SE	p-value
Unadjusted+	Deprescribing	0.28 (0.18, 0.38)	0.05	<0.001
MSM w/IPTW+	Deprescribing	0.044 (-0.086, 0.17)	0.066	0.50
MSM w/IPTW (trimmed at 1st & 99th)	Deprescribing	0.022 (-0.087, 0.13)	0.056	0.69
MSM w/IPTW (capped at 1st & 99th)	Deprescribing	0.055 (-0.058, 0.17)	0.058	0.34
MSM w/IPTW (sensitivity for overlap)	Deprescribing	0.043 (-0.08, 0.17)	0.064	0.50
MSM w/IPTW Doubly Robust	Deprescribing	0.035 (-0.03, 0.097)	0.032	0.27
MSM w/IPTW (w/baseline)	Deprescribing	0.23 (0.11, 0.34)	0.058	<0.001
MSM w/IPTW (w/baseline) Doubly Robust	Deprescribing	0.021 (-0.037, 0.079)	0.030	0.48
Adjusted model w/o IPTW	Deprescribing	0.011 (-0.038, 0.061)	0.025	0.67

+Primary model

Table 5-6 - Model Results for Association of Deprescribing with Aggressive Behaviors

Model	Variable	Coefficient	SE	p-value
Unadjusted+	Deprescribing	0.056 (0.027, 0.10)	0.018	0.002
MSM w/IPTW+	Deprescribing	0.002 (-0.036, 0.041)	0.019	0.901
MSM w/IPTW (trimmed at 1st & 99th)	Deprescribing	0.012 (-0.026, 0.050)	0.019	0.53
MSM w/IPTW (capped at 1st & 99th)	Deprescribing	0.005 (-0.032, 0.043)	0.019	0.78
MSM w/IPTW (sensitivity for overlap)	Deprescribing	-0.002 (-0.041, 0.037)	0.019	0.92
MSM w/IPTW Doubly Robust	Deprescribing	0.012 (-0.009, 0.034)	0.011	0.29
MSM w/IPTW (w/baseline)	Deprescribing	0.046 (0.006, 0.087)	0.020	0.023
MSM w/IPTW (w/baseline) Doubly Robust	Deprescribing	0.014 (-0.008, 0.037)	0.012	0.21
Adjusted model w/o IPTW	Deprescribing	0.015 (-0.006, 0.035)	0.010	0.16

+Primary model

We evaluated the influence of extreme weights in our sample by conducing several additional analyses. The distribution of IPTWs is depicted using kernel density plots, stratified by deprescribing status in **Appendix Figure B-1**. Trimming IPTWs at the 1st and 99th percentiles and top-coding values at the 1st and 99th percentiles resulted in no substantive changes to our findings (**Table 5-5** and **Table 5-6**). Kernel density plots revealed two potential regions of non-overlap in IPTWs between deprescribed and non-deprescribed observations. Closer examination revealed that the main driver of extreme weights was limited prognosis designation (**Appendix Table B-7**). However, dropping these observations with IPTWs outside the region of overlap resulted in no substantive changes in our findings.

5.4.2 Secondary Analysis

In the analysis of the impact of deprescribing AChEIs on number of medications, the total number of medications received ranged from 0-22 with means of 4.4 (SD=3.0) and 5.8 (SD=3.0) for assessments with and without deprescribing, respectively (**Table 5-7**). Unadjusted and adjusted results are presented in **Table 5-8**. In unadjusted analysis, deprescribing AChEIs was associated with a significant decrease in total number of medications (-1.4 medications, 95% CI: [-1.48, -1.31], $p<0.001$). In adjusted analyses weighted by IPTWs, deprescribing remained significantly associated, although with a reduced effect size (-0.55, 95% CI: [-0.68, -0.42], $p<0.001$). Additional analyses to evaluate the influence of extreme weights in our sample again revealed no significant changes.

Table 5-7 - Assessment Level Distribution of total Number of Prescribed Medications

	Range	Mean (SD)	Median [IQR]
Total Number of Medications (full sample)	0-22	5.6 (3.1)	5 [3-8]
Assessments w/Deprescribing	0-22	4.4 (3.0)	4 [2-6]
Assessments w/o Deprescribing	0-22	5.8 (3.0)	5 [4-8]

Table 5-8 - Model Results for Effect of Deprescribing on Total Number of Medications

Model	Variables	Coefficient	SE	p-values
Unadjusted+	Deprescribing	-1.40 (-1.48, -1.31)	0.04	<0.001
MSM w/IPTW+	Deprescribing	-0.55 (-0.68, -0.42)	0.07	<0.001
MSM w/IPTW (trimmed at 1st & 99th)	Deprescribing	-0.67 (-0.77, -0.56)	0.05	<0.001
MSM w/IPTW (capped at 1st & 99th)	Deprescribing	-0.64 (-0.74, -0.53)	0.06	<0.001
MSM w/IPTW (overlap sensitivity)	Deprescribing	-0.51 (-0.63, -0.39)	0.06	<0.001
Adjusted model w/o IPTW	Deprescribing	-0.35 (-0.39, 0.31)	0.02	<0.001

+Primary model

5.4.3 Sensitivity Analyses

In sensitivity analyses, we conducted a per-protocol analysis, where residents were censored early if a new prescription for an AChEI was observed in the period following deprescribing. Residents were included up until and including the MDS assessment following AChEI restarts to avoid the problem of direct correlation between deprescribing and censoring in calculation of IPCWs (described above). Early censoring resulted in approximately 3% of MDS assessments being excluded from analyses, but ultimately did not result in a substantive change in our findings (**Table 5-9, Table 5-10, and Table 5-11**).

Table 5-9 - Results of Per-protocol Analysis for Association of Deprescribing with Depression Severity

Model	Variable	Coefficient	SE	p-value
MSM w/IPTW	Deprescribing	0.12 (-0.01, 0.25)	0.067	0.07
MSM w/IPTW (sensitivity for overlap)	Deprescribing	0.097 (-0.038, 0.233)	0.069	0.158

Table 5-10 - Results of Per-protocol Analysis for Association of Deprescribing with Aggressive Behaviors

Model	Variable	Coefficient	SE	p-value
MSM w/IPTW	Deprescribing	0.017 (-0.024, 0.057)	0.021	0.43
MSM w/IPTW (sensitivity for overlap)	Deprescribing	0.016 (-0.026, 0.058)	0.021	0.47

Table 5-11 - Results of Per-protocol Analysis for Association of Deprescribing with Total Number of Medications

Model	Variable	Coefficient	SE	p-value
MSM w/IPTW	Deprescribing	-0.62 (-0.74, -0.50)	0.06	<0.001
MSM w/IPTW (sensitivity for overlap)	Deprescribing	-0.52 (-0.65, -0.40)	0.06	<0.001

5.5 DISCUSSION

This is the first analysis of the implications of deprescribing AChEIs on behavioral outcomes conducted in a national sample of nursing home residents with severe dementia. We found that the prevalence of depressive symptoms and aggressive behavior was generally very low in this population and that deprescribing AChEIs was not associated with increased depression severity or aggressive behaviors. We also observed that deprescribing AChEIs was associated with a modest reduction in the total number of medications prescribed.

Our study has a number of strengths that enhance the clinical significance and translatability of our findings. We used a large, nationally representative sample of nursing home residents with dementia and focused specifically on those with severe dementia. This sub-population with severe dementia likely has the greatest clinical significance, given that these patients are the most appropriate candidates for deprescribing AChEIs as suggested by clinical guidelines[60,197] and have been shown in previous studies to have the greatest likelihood for deprescribing.[122,128,133,135] We also accounted for time-dependent confounding in our analytical design, which may impose a significant amount of bias in this population where many of the fluctuating clinical prognostic factors that drive deprescribing AChEIs, may subsequently be affected by the discontinuation of these medications.

Three randomized trials[97,102,198] have reported that individuals with dementia who discontinue AChEIs were observed to have increased neuropsychiatric inventory (NPI) scores (mean increase 3.8 points), indicating greater severity of behavioral disturbances and depressive symptoms.[153] The difference in results between our study and the randomized trials should be

interpreted with caution, however, as only one of the three studies included patients with severe dementia[102], whereas these patients were excluded from the others, thus limiting generalizability to our severe dementia sample. There also seemed to be a higher prevalence of neuropsychiatric symptoms at baseline in the randomized studies as compared to our sample, possibly due to differences in inclusion and exclusion criteria, which may have contributed to differences in findings.

The only previously published observational study that has examined the potential impact of deprescribing AChEIs on behavioral outcomes was an analysis by Daiello et al.[101], which was conducted in a small sample of Rhode Island nursing home residents (<200) enrolled in Medicaid. While this study also used MDS-based assessments to measure behavioral symptoms, the sample was not limited to residents with severe dementia and excluded patients with documented limited life expectancy and those who were using memantine. The primary analysis in Daiello et al.[101] found that there was a statistically significant, increase in mean monthly ABS score, and no significant difference in depression severity scores between groups (deprescribing vs. not). The authors also reported no significant difference between groups for secondary outcomes, which included cognitive decline, ADLs, incontinence symptoms, and psychoactive medication use. Despite the small sample size and heterogeneity in dementia severity among residents, the findings of our study align for the most part with those presented in this study. Although the authors did identify a statistically significant increase in ABS scores associated with deprescribing, the small magnitude of the effect (0.08 point monthly increase on a 12-point scale) does not likely represent a clinically significant difference. The clinical significance of these findings may also be limited by the inclusion of residents with both severe and non-severe dementia in the sample as well as

the exclusion of residents who were concurrently receiving memantine, which represented a significant proportion of observations in our sample (approximately 41%).

Generally speaking, the prevalence of depressive symptoms and aggressive behaviors was very low in our sample, although still comparable to what has been reported in other studies in populations with dementia using the MDS.[199,200] At least one study suggests that the MDS measures for aggressive behaviors may underreport the prevalence of behavioral symptoms in patients with severe dementia.[201] However, it is also likely that the severity of dementia symptoms in our sample precluded the emergence of aggressive behaviors, thus explaining the low prevalence observed in our study versus prior studies that have been conducted in patients with earlier stages of dementia. Our findings suggest that deprescribing AChEIs may have less of an impact on aggressive behaviors in individuals with severe dementia versus earlier stages of the disease where this effect has been shown to be significant in prior studies.[97,102,198] Given that more than 30% of residents in our sample had difficulty being understood at least some of the time, it may be possible that in severe stages of the disease, it is more difficult to ascertain the presence of depressive symptoms. However, the original validation studies for the PHQ-9 in the MDS did demonstrate adequate correlation of depression scores with gold-standard instruments even in sub-groups of patients with severe dementia.[159] It is also possible that the two MDS-based measures that were used to quantify the severity of aggressive behaviors and depression symptoms are not sensitive enough to change over time, as suggested by previous research in dementia patients.[202] Thus it is possible that our null findings may be due to low prevalence of symptoms at baseline and lack of sensitivity of the MDS-based measured to detect changes in scores over time, rather than a lack of association between deprescribing and outcomes.

In secondary analyses, we found that deprescribing AChEIs was associated with a reduction in the total number of medications being received. Due to the nature of observational study designs and the limitations of our data, we cannot say with certainty that deprescribing AChEIs was the actual cause of a reduction in the use of other medications. Rather, the discussion surrounding deprescribing could initiate a shift in goals of care that leads to the re-evaluation of the appropriateness of all medications. Changes in the use of high-risk medication classes with specific clinical relevance in dementia patients will be explored in future analyses.

In sensitivity analyses that examined the influence of extreme inverse probability of treatment weights, we found that one of the main characteristics common to observations with extreme weights was limited prognosis designation. This was not surprising as this was identified as the most influential factor associated with increased likelihood of deprescribing AChEIs in our prior analyses. Although excluding these observations from the analysis resulted in no substantive changes to our findings, it does bring up two important points. First, the extreme weights associated with this sub-group again emphasize the clear shift in goals of care associated with recognition of limited prognosis and hospice enrollment and thus deprescribing of medications being used for curative or preventive purposes. Second, these results suggest that deprescribing may be reasonable for all patients with severe dementia, even prior to designation as limited prognosis or hospice enrollment.

We previously identified that a substantial number of residents in our sample appeared to have re-started AChEI therapy, as indicated by new prescriptions for AChEIs following deprescribing. However, in per-protocol sensitivity analyses, in which we censored potential cases where AChEIs may have been re-started, we ultimately found no substantive changes to our findings. It is likely that at least a portion of restarts were due to unintentionally missed doses,

where accumulated missed doses would eventually create errors in estimating periods covered by medication supply. We also hypothesized that these may represent failed attempts to discontinue AChEIs, in which medications were restarted following a suspected medication withdrawal event or significant decline in status perceived as related to the withdrawal.

There are several limitations to this analysis that should be considered when interpreting our findings. Due to the nature of Part D prescription drug event data, we were not able to identify the actual reason for gaps in medication supply (intentional discontinuation vs. unintentional missed doses). As evidenced by the large number of restarts seen our sample, it is possible that a number of these gaps may be attributable to non-adherence, rather than intentional deprescribing. This issue warrants further exploration in future studies with alternative medication data sources (e.g. medication administration data). As mentioned above, there was also a low degree of depressive symptoms and aggressive behaviors at baseline in our sample and a lack of substantial variability in either over time. Future studies should examine whether comprehensive assessments of psychological symptoms of dementia with greater sensitivity to change would yield similar findings. We also acknowledge that our findings are limited only to those with severe dementia residing in the nursing home and may not be applicable to older adults with less severe disease.

5.6 Conclusions

Overall, the prevalence of depressive symptoms and aggressive behaviors was low in nursing home residents with severe dementia. Deprescribing AChEIs was not associated with increased depression severity or aggressive behaviors, but was associated with an overall reduction

in the use of other medications, suggesting that deprescribing may be a feasible strategy to reduce medication burden and risk for adverse effects in this population.

6.0 THE IMPACT OF DEPRESCRIBING ACHEIS ON MEDICATION-RELATED OUTCOMES

6.1 ABSTRACT

Deprescribing AChEIs in patients with severe dementia may contribute to increased antipsychotic use to manage worsening behavioral symptoms, but may also prompt discontinuation of strong anticholinergics that were potentially prescribed to mitigate AChEI-related cholinergic effects. This study evaluated the impact of deprescribing AChEIs on incident antipsychotic prescribing and strong anticholinergic discontinuation in nursing home (NH) residents with severe dementia.

We used Medicare claims, Part D prescriptions, and Minimum Data Set (MDS) v3.0. Two sub-samples were created from a cohort of NH residents aged 65+ with severe dementia receiving AChEIs in 2016: 1) non-users of antipsychotics 180 days prior to index date (n=25,188); and 2) prevalent users of ≥1 strongly anticholinergic medication from the Beers Criteria (n=5,609). AChEI deprescribing was defined as a gap in supply ≥30 days. Marginal structural models and inverse probability of treatment weights evaluated the association of deprescribing with medication use using pooled logistic regression, accounting for time-dependent confounding.

The sample was primarily white (78.7%), female (76.6%), aged >80 (77.6%). Incident antipsychotic prescribing occurred in 5.1% of episodes and anticholinergic discontinuation occurred in 32.3% of episodes. Deprescribing was associated with reduced likelihood of incident antipsychotic prescriptions (aOR=0.52, 95% CI: [0.40-0.68], p<0.001]) and strong anticholinergic discontinuation (aOR=0.51, 95% CI: [0.40, 0.67], p<0.001). When limited to antimuscarinic

anticholinergic medications, deprescribing was not significantly associated with discontinuation (aOR=1.02, 95% CI: [0.59-1.78], p=0.93)

Deprescribing AChEIs did not lead to increased use of antipsychotics, suggesting that deprescribing does not result in an increased in prescribing of potentially inappropriate medications to manage worsening behavioral and psychological symptoms of dementia. Deprescribing AChEIs did not lead to discontinuation of strong anticholinergic medications that may be implicated as part of the prescribing cascade, pointing out a potential avenue for educational interventions regarding the co-prescribing of antimuscarinic anticholinergics and AChEIs.

6.2 INTRODUCTION

One of the main barriers to deprescribing is the unknown impact that discontinuing medications may have on clinical outcomes.[96] In the case of AChEIs, this includes is the potential for worsening of the severity of behavioral and psychological symptoms of dementia (BPSD). Although there are several studies examining the impact of AChEI discontinuation on behavioral outcomes, another pertinent facet of deprescribing that warrants investigation is its potential impact on the prescribing of other medications to manage these symptoms, whether positive or negative.

One such implication is the potential for increased use of pharmacologic agents to manage worsening BPSD following deprescribing of AChEIs. One therapeutic class frequently used for the management of BPSD is antipsychotic medications.[103,176] While effective in managing BPSD, antipsychotics are generally not recommended in older adults as they carry a black box warning

for increased mortality risk when used in patients with dementia. Thus, the potential for increased use of these high-risk medications to address the potential for increased BPSD may be seen as another barrier to deprescribing AChEIs. Two prior studies[101,108] have examined changes in the use of psychoactive medications following deprescribing AChEIs and found no significant differences in usage between those who discontinued AChEIs versus those who continued on therapy, including the use of antipsychotics. However, these studies only examined these medication-related effects as secondary outcomes in relatively small samples.

In addition to the potentially negative impact on quality of medication use, there are also potential beneficial effects that may result from deprescribing AChEIs. Generally speaking, the decision to deprescribe AChEIs may be part of a chain of events that leads to discontinuation of multiple medications in a non-specific approach to reduce polypharmacy.[203,204] Results from our prior analyses support this hypothesis, where we observed a general reduction in the total number of medications associated with deprescribing of AChEIs. A more targeted approach may involve medications that are implicated as part of the cholinergic prescribing cascade. The mechanism of action of AChEIs which increase cholinergic activity in the body, causes cholinergic adverse effects including urinary incontinence, gastrointestinal upset, and cardiovascular effects, among others.[205] Unrecognized as being drug-induced, these adverse effects are subsequently treated with anticholinergic medications, rather than discontinuing or reducing the dose of the offending agent, in a phenomenon known as a "prescribing cascade".[70] One would hypothesize that deprescribing AChEIs may lead to the subsequent discontinuation of anticholinergic medications that may have been originally prescribed to manage medication-induced adverse effects, particularly given that anticholinergics have been shown to contribute to worsening cognitive function. No studies to date have been conducted that examined what is essentially the reverse of this prescribing cascade.

In addition to the potential impact on psychological symptoms in patients with severe dementia, deprescribing AChEIs may have downstream implications for the prescribing of other medications. The objective of this study was to examine the impact of deprescribing AChEIs on the use of potentially high-risk medications, including incident prescribing of antipsychotic medications and discontinuation of strong anticholinergic medications.

6.3 METHODS

6.3.1 Design and Data Sources

This study was a longitudinal analysis of Medicare claims, Part D prescription drug event data, and MDS assessments for a cohort of nursing home residents with severe dementia being treated with AChEIs at admission. We used Medicare Part D prescription drug event data to examine differences in the use of medications over time between observations where deprescribing AChEIs occurred versus those where AChEIs were continued. We conducted two analyses to examine the overall impact of deprescribing AChEIs on medication use.

The base sample for these analyses consisted of nursing home residents with severe dementia who were receiving AChEIs and had at least two MDS assessments. The first analysis evaluated the association between deprescribing and the likelihood for receiving new prescriptions for antipsychotics and was conducted in a sub-group of residents from the primary sample who had no history of antipsychotic use in the 180 days prior to index date (i.e. non-users). The second analysis examined whether deprescribing AChEIs was associated with discontinuation of strong anticholinergic medications and was conducted in a sub-group of residents from the primary

sample who were concurrently using both AChEIs and strongly anticholinergic medications at baseline.

6.3.2 Sample construction

As described above, this study utilized two different analytical samples, which were created from a base sample of nursing home residents with severe dementia who were receiving AChEIs at index (n=37,106 episodes), as described previously in Chapter 4 (**Figure 4-1**). Construction of the samples for this analysis are described below.

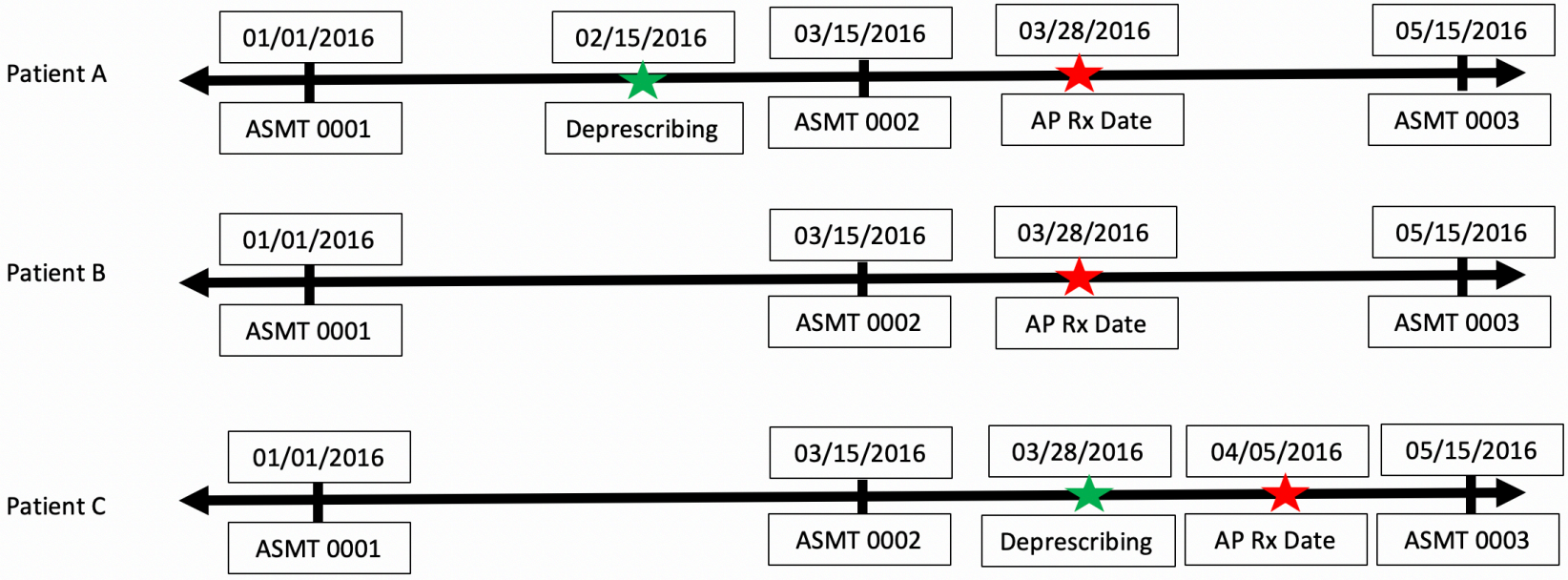
Sample 1 was limited to residents with no prescriptions for antipsychotic medications on index date or in the 180 days prior, i.e. non-users. We searched for generic drug names in Part D records to identify antipsychotic prescriptions and used the days' supply for each prescription to identify the period over which residents would have received medications and retained nursing home episodes with no antipsychotic medication supply overlapping the index date or 180 days prior. This resulted in 25,188 episodes with 80,033 MDS assessments.

Sample 2 was limited to residents who were concurrently receiving both AChEIs and strong anticholinergic medications at index date. We searched Part D records for generic names of strong anticholinergic medications listed in the Beers Criteria[160] and using the days' supply, retained nursing home episodes where residents had medication supply that overlapped with the index date. This resulted in 5,609 episodes with 14,319 MDS assessments.

6.3.3 Dependent Variables

The occurrence of incident antipsychotic prescriptions was coded as a discrete outcome and was measured prospectively in the period following the current MDS assessment start date until the start date of the next MDS assessment period using Part D prescription records (incident antipsychotic prescription equaled 1 if an antipsychotic prescription occurred after the current assessment start date and before the next assessment start date, and 0 otherwise). Discontinuation of strong anticholinergic medications was also coded in the same fashion using Part D prescription records. An indicator for discontinuation of any strong anticholinergics was coded as positive if the 30th day of gap in medication supply occurred after the current assessment start date and before the next assessment start date.

Patients were followed until time of event, censoring due to NH discharge or death, or end of follow-up. This means that if one of the medication events described above occurred, the stop date for that assessment period was re-coded as the event date and the record was ended, to ensure accuracy of follow-up time. An example of this revised data structure is shown in **Figure 6-1**.



Patient ID	Assessment #	Assess Start Dt	Assess Stop Dt	Deprescribing AChEI	Antipsychotic Rx
A	0001	01/01/2016	03/14/2016	1	0
A	0002	03/15/2016	03/28/2016	1	1
A	0003	05/15/2016	06/30/2016	Censored	censored
B	0001	01/01/2016	03/14/2016	0	0
B	0002	03/15/2016	03/28/2016	0	1
B	0003	05/15/2016	06/30/2016	Censored	Censored
C	0001	01/01/2016	03/14/2016	0	0
C	0002	03/15/2016	04/05/2016	1	1
C	0003	05/15/2016	06/30/2016	Censored	Censored

Figure 6-1 Data Structure and Coding for Chapter 6 Analysses

6.3.4 Independent Variables

The primary independent variable was whether or not a resident's AChEI was deprescribed, defined as a subsequent gap in therapy of at least 30 days based on prescription fill dates and last day of supply, with the 31st gap day in the period serving as the discontinuation date. Deprescribing was treated as a time-varying exposure. An indicator for deprescribing AChEIs was coded as positive if the 31st gap day in medication supply occurred on or after the assessment start date and before either the assessment stop date or the event date if an event occurred (see **Figure 6-1**).

Other independent variables included factors that may influence the decision to deprescribe AChEIs evaluated in our first analysis. Covariates were extracted from the MDS, Medicare Part D Prescription Drug Event records, Medicare Part A and B claims, Nursing Home Compare, and the Area Health Resource File. These included: demographics (age, sex, race/ethnicity, marital status), clinical assessment factors (MDS assessment form type, ability to complete brief interview for mental status, resident ability to be understood, poor appetite, urinary incontinence, swallowing disorder, parenteral nutrition or tube feeds, mechanically altered diet, recent weight loss, shortness of breath, dehydration, cancer, end-stage renal disease, heart failure, activities of daily living, limited prognosis or hospice utilization, antidepressant use, antipsychotic use, benzodiazepine use, strong anticholinergic use, AChEI type, memantine use, total number of medications, Charlson Comorbidity Index, all-cause and cause-specific hospitalizations in prior 90 days, location prior to nursing home residence), environment of care (nursing home geographic region, facility size, rurality), provider specialty (AChEI prescriber specialty – primary care, geriatrics, other). Demographic, environment of care, and provider specialty variables were treated as time-invariant

and were measured at the index MDS assessment. Clinical assessment factors were treated as time-varying.

6.3.5 Statistical Analyses

We used marginal structural models (MSM) with inverse probability of treatment weights (IPTW), as described in Chapter 5, to address potential time-dependent confounding of deprescribing and subsequent medication use. IPTWs modeled each subject's propensity for being deprescribed, considering their history of time invariant and time-varying covariates. Weights were calculated for each MDS assessment period up until and including each resident's first assessment where deprescribing had occurred. Inverse probability of censoring weights represented the probability of remaining uncensored at the time of each MDS assessment, considering the resident's history of covariates. The IPTW and IPCW associated with each MDS assessment period were multiplied to create an overall weight which was applied to the sample.

An example of the derivation of probability of treatment and censoring weights is illustrated in **Figure 6-2.** Here, covariates measured in the MDS were not lagged to the prior assessment period as in our prior analyses because both exposure and outcomes were coded in a prospective manner, i.e. using the period after each assessment was administered until the next assessment was administered. For these analyses, we treated each event as a discrete indicator and used pooled logistic regression models weighted by IPTWs to evaluate the association between deprescribing AChEIs and either incident antipsychotic prescriptions or discontinuation of strong anticholinergic medications. Robust standard errors were applied to account for correlation between repeated observations for the same resident.

Here covariates are being measured at the beginning of each assessment period. Deprescribing and outcomes are being measured prospectively in the period after each assessment until the next assessment occurs (i.e. assess start date + 1 to assess stop date + 1). In this manner, covariates do not need to be lagged to the prior assessment (as before) because deprescribing is being coded following measurement of the covariates. For example, covariates from ASMT001 are used to generate IPTWs that represent the propensity of subsequently being deprescribed in the assessment period from ASMT001 + 1 to ASMT002.

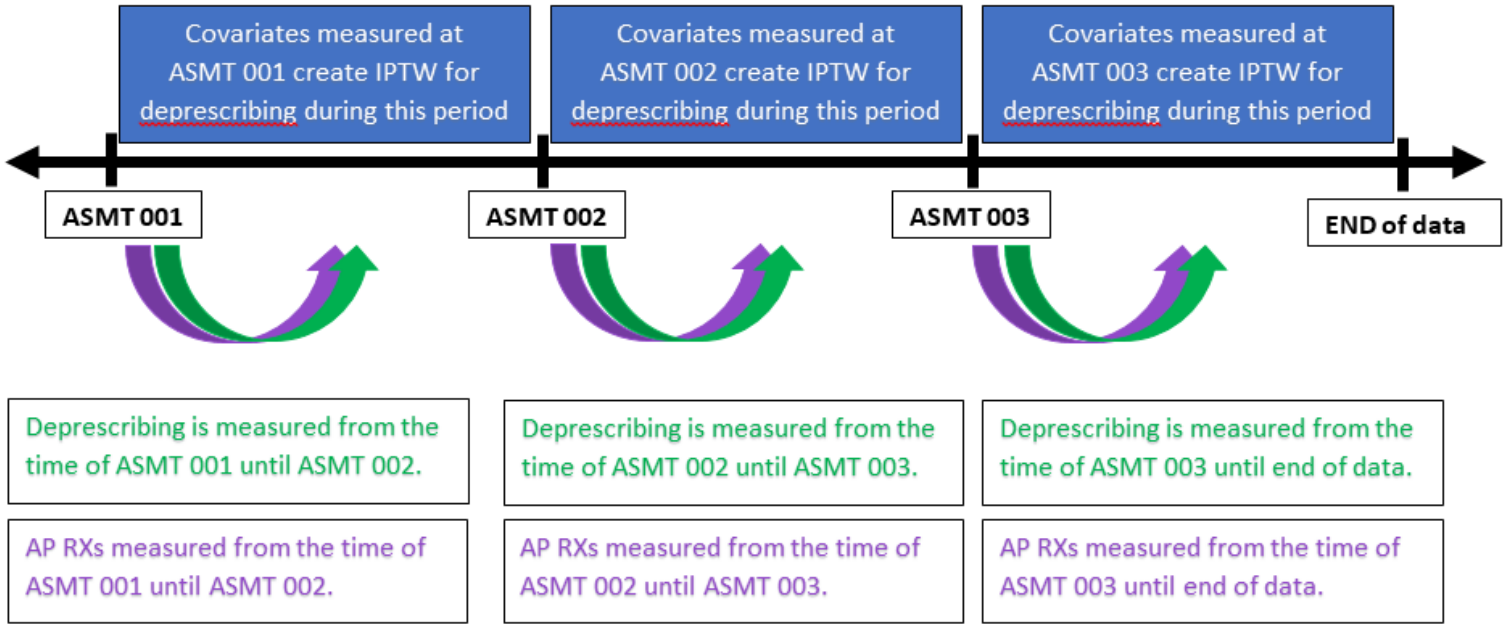


Figure 6-2 Derivation of Inverse Propensity Treatment Weights for Chapter 6 Analyses

Primary analyses for all outcomes were conducted using an intent-to-treat approach (ITT) for deprescribing, where residents remained in this category until the end of follow-up. We conducted several additional analyses that used trimmed and top-coded propensity weights, to evaluate the influence of extreme weights in our sample. We also conducted a sub-group analysis among the sample of anticholinergic users that was limited to residents who were receiving antimuscarinic anticholinergics, as this sub-class is most commonly implicated in the cholinergic prescribing cascade to mitigate AChEI-induced incontinence.[70] Finally, we conducted a per-protocol analysis where residents who were deprescribed were censored in the period following a fill for a new AChEI prescription, to account for potential re-starts.

6.4 RESULTS

6.4.1 Sample Characteristics

Unweighted episode-level and assessment-level characteristics for each of the three samples are presented in **Table 6-1**. After applying IPTWs, we identified no issues with balance between observations with and without deprescribing **(Appendix Table C-1 and Appendix Table C-2).**

Table 6-1 - Sample Characteristics for Chapter 6 Analyses (Episode-level and Assessment-level)

Variable	Incident Antipsychotic Prescribing Sample		Anticholinergic Deprescribing Sample	
	Episode-level n=25,199	Assessment-level n=80,033	Episode-level n=5,612	Assessment-level n=14,319
DEMOGRAPHICS				
Age in years				
65-69	433 (1.7)	-	220 (3.9)	-
70-79	4,181 (16.6)		1,386 (24.7)	
80-89	12,226 (48.5)		2,666 (47.5)	
90+	8,359 (33.2)		1,340 (23.9)	
Sex				
Male	5,638 (22.4)	-	1,346 (24.0)	-
Female	19,561 (77.6)		4,266 (76.0)	
Race/ethnicity				
White	19,853 (78.8)	-	4,645 (82.8)	-
Black	3,008 (11.9)		515 (9.2)	
Hispanic	1,317 (5.2)		276 (4.9)	
Other	1,021 (4.0)		176 (3.1)	
Current marital status				
Married	5,246 (20.8)	-	1,275 (22.7)	-
Not Married	19,953 (79.2)		4,337 (77.3)	
CLINICAL ASSESSMENT				
Entered from				
Community	5,447 (21.6)	-	1,187 (21.2)	-
Hospital	16,942 (67.2)		3,763 (67.0)	
NH or other LTC facility	2,810 (11.2)		663 (11.8)	
MDS Assessment Type				
Admission	2,913 (11.6)	2,913 (3.6)	927 (16.5)	927 (6.5)
Quarterly	16,719 (66.3)	57,282 (71.6)	3,536 (63.0)	9946 (69.5)
Annual	4,257 (16.9)	14,738 (18.4)	826 (14.7)	2488 (17.4)
Significant Change in Status	1,310 (5.2)	5,100 (6.4)	323 (5.7)	958 (6.7)
Charlson Comorbidity Index	4,156 (16.5)	12,559 (15.7)	849 (15.1)	1987 (13.9)
0-1	6,358 (25.2)	20,951 (26.2)	1,305 (23.2)	3435 (24.0)
2-3	5,938 (23.6)	19,448 (24.3)	1,298 (23.1)	3444 (24.1)
4-5	8,747 (34.7)	27,075 (33.8)	2,160 (38.5)	5453 (38.1)
≥6				
Makes self understood	10,370 (41.1)	31,302 (39.1)	2,428 (43.3)	6069 (42.4)
Understood	6,557 (26.0)	20,882 (26.1)	1,599 (28.5)	4122 (28.8)
Usually understood	5,179 (20.6)	16,537 (20.7)	1,112 (19.8)	2799 (19.5)
Sometimes understood	3,093 (12.3)	11,312 (14.1)	473 (8.4)	1329 (9.3)
Rarely/never understood				
PHQ-9 score	2.1 (3.2)	2.0 (3.3)	2.3 (3.3)	2.2 (3.4)
Aggressive behavior scale	0.4 (1.1)	0.4 (1.1)	0.6 (1.4)	0.6 (1.3)
Activities of Daily Living Score				
1 to 7	1,975 (7.8)	5,952 (7.4)	423 (7.5)	1,038 (7.2)
8 to 14	4,000 (15.9)	11,927 (14.9)	1,012 (18.0)	2,472 (17.3)
15 to 21	13,001 (51.6)	41,030 (51.3)	3,110 (55.4)	7,946 (55.5)
22 to 28	6,223 (24.7)	21,124 (26.4)	1,067 (19.0)	2,863 (20.0)

Urinary incontinence				
Continent	2,733 (10.8)	7,627 (9.5)	598 (10.7)	1,396 (9.7)
Occasionally incontinent	3,638 (14.4)	10,580 (13.2)	934 (16.6)	2,248 (15.7)
Frequently incontinent	8,083 (32.1)	25,424 (31.8)	2,043 (36.4)	5,229 (36.5)
Always incontinent	10,188 (40.4)	34,977 (43.7)	1,905 (34.0)	5,162 (36.1)
Indwelling catheter	552 (2.2)	1,425 (1.8)	131 (2.3)	284 (2.0)
Cancer	1,082 (4.3)	3,343 (4.2)	234 (4.2)	601 (4.2)
Heart failure	4,112 (16.3)	12,688 (15.9)	923 (16.4)	2,341 (16.3)
End Stage Renal Disease	2,454 (9.7)	7,691 (9.6)	452 (8.1)	1,150 (8.0)
Short of breath	1,658 (6.6)	5,155 (6.4)	432 (7.7)	1,098 (7.7)
Poor appetite	3,281 (13.0)	10,501 (13.1)	712 (12.7)	1,825 (12.7)
Weight loss	1,517 (6.0)	4,905 (6.1)	356 (6.3)	894 (6.2)
Swallowing difficulty	830 (3.3)	2,746 (3.4)	210 (3.7)	544 (3.8)
Mechanically altered diet	13,822 (54.8)	41,401 (51.7)	3,183 (56.7)	7,754 (54.2)
IV/parenteral nutrition or feeding tube	953 (3.8)	2,685 (3.4)	161 (2.9)	363 (2.5)
Hospice or Limited Prognosis	1,225 (4.9)	4,898 (6.1)	267 (4.8)	715 (5.0)
Hospitalizations/ED Visits (90 days prior)				
None	19,674 (78.1)	70,313 (87.9)	4,057 (72.3)	11,882 (83.0)
Cause-specific (fall, fracture, syncope)	1,904 (7.6)	3,747 (4.7)	578 (10.3)	1,013 (7.1)
Other cause	3,621 (14.4)	5,973 (7.5)	977 (17.4)	1,424 (9.9)
AChEI at index date				
Donepezil	20,087 (79.7)	63,315 (79.1)	4,344 (77.4)	10,995 (76.8)
Donepezil/memantine	309 (1.2)	1,362 (1.7)	67 (1.2)	202 (1.4)
Galantamine	541 (2.1)	1,735 (2.2)	122 (2.2)	328 (2.3)
Rivastigmine (oral)	938 (3.7)	3,059 (3.8)	230 (4.1)	596 (4.2)
Rivastigmine (transdermal)	3,324 (13.2)	10,562 (13.2)	849 (15.1)	2,198 (15.4)
Memantine use	10,126 (40.2)	31,728 (39.6)	2,344 (41.8)	6,131 (42.8)
Benzodiazepine and/or Z drug	2,806 (11.1)	8,339 (10.4)	1,125 (20.0)	2,709 (18.9)
Antipsychotic use	-	-	2,518 (44.9)	6,191 (43.2)
Antidepressant use	13,391 (53.2)	41,566 (51.9)	4,030 (71.8)	10,258 (71.6)
Highly Anticholinergic Drugs (Beers)	2,703 (10.7)	7,751 (9.7)	-	-
Total number of medications [Mean (SD)]	5.6 (3.0)	5.3 (3.0)	7.5 (3.2)	7.3 (3.1)
ENVIRONMENT OF CARE				
Geographic region				
Midwest	7,053 (28.0)	-	1,595 (8.4)	-
Northeast	4,788 (19.0)		830 (14.8)	
South	11,107 (44.1)		2,827 (50.4)	
West	2,251 (8.9)		360 (6.4)	
Certified beds				
<50	1,290 (5.1)	-	321 (5.7)	-
50-99	7,321 (29.1)		1,733 (30.9)	
100-199	13,684 (54.3)		2,963 (52.8)	
200+	2,904 (11.5)		595 (10.6)	
Rural/urban continuum				
Urban	17,724 (70.3)	-	3,645 (64.9)	-
Rural	6,540 (25.9)		1,686 (30.0)	
Highly rural	935 (3.7)		281 (5.0)	
PROVIDER SPECIALTY				
Prescriber specialty				
Geriatrics	2,194 (8.7)	-	397 (7.1)	-
Primary care	2,638 (10.5)		608 (10.8)	
Other	20,367 (80.8)		4,607 (82.1)	

6.4.2 Impact of Deprescribing AChEIs on Incident Antipsychotic Prescriptions

In the sub-sample of antipsychotic non-users, 0.8% of assessments where AChEIs deprescribing had occurred also received a new prescription for an antipsychotic medication during follow-up versus 1.7% of assessments where AChEIs were continued (**Table 6-2**). Results of pooled logistic regression models for the association of deprescribing AChEIs and incident antipsychotic prescriptions are presented in **Table 6-3**. In unadjusted analyses, deprescribing was associated with decreased likelihood for receiving a new prescription for an antipsychotic medication (pooled OR=0.47, 95% CI: [0.38, 0.59], $p<0.001$). This association remained significant in adjusted analyses weighted by IPTWs (pooled aOR=0.52, 95% CI: [0.40, 0.68], $p<0.001$). Additional analyses to evaluate the influence of extreme weights in our sample revealed no significant changes to our findings.

Table 6-2- Frequency of Incident Antipsychotic Prescribing in Sample

	Assessments w/Deprescribing	Assessments w/o Deprescribing
Total Assessments (n=75,984)	11,572 (14.5%)	68,461 (85.5%)
Assessments with Incident Antipsychotic Prescribing (n=1,091)	96 (0.8%)	1,185 (1.7%)

Table 6-3 - Model Results for Effect of Deprescribing on Incident Antipsychotic Use

Model	Variables	Pooled odds ratio	Standard Errors	p-values
Unadjusted+	Deprescribing	0.47 (0.38, 0.59)	0.05	<0.001
MSM w/IPTW+	Deprescribing	0.52 (0.40, 0.68)	0.07	<0.001
MSM w/IPTW (trimmed at 1st & 99th)	Deprescribing	0.48 (0.37, 0.60)	0.06	<0.001
MSM w/IPTW (capped at 1st & 99th)	Deprescribing	0.49 (0.38, 0.62)	0.06	<0.001
MSM w/IPTW (overlap sensitivity)	Deprescribing	0.52 (0.40, 0.67)	0.07	0.001
MSM w/IPTW (doubly robust)	Deprescribing	0.55 (0.43, 0.72)	0.07	<0.001

+Primary model

6.4.3 Impact of Deprescribing AChEIs on Discontinuation of Strong Anticholinergic Medications

Discontinuation of strong anticholinergic medications occurred in 13.1% of assessments where deprescribing AChEIs had occurred versus 8.1% of assessments where AChEIs were continued (**Table 6-4**). The most common classes of anticholinergic medications used at baseline are presented in **Figure 6-3** with the top classes being antimuscarinics, antipsychotics, and antidepressants. The proportion of residents prescribed each class of medication is represented by the full bar, while the orange portion of each bar represents the proportion of residents who discontinued that class of medication. The class with the highest proportion of medications discontinued was antiemetics (93.9%), followed by skeletal muscle relaxants (73.9%), and antispasmodics (56.4%). Results of pooled logistic regression models for the association of deprescribing AChEIs and discontinuation of anticholinergics are presented in **Table 6-5**. In unadjusted and adjusted analyses, deprescribing was associated with decreased of discontinuing strong anticholinergics (pooled OR=0.58, 95% CI: [0.47, 0.72], $p<0.001$; pooled aOR=0.51, 95% CI: [0.40, 0.67], $p<0.001$). Additional analyses to evaluate the influence of extreme weights in our sample revealed no significant changes to our findings.

Table 6-4 – Frequency of Anticholinergic Discontinuation in Sample

Outcome	Observations w/Deprescribing	Observations w/o Deprescribing
Total Assessments (n=13,797 assessments)	1,240 (8.7%)	13,079 (91.3%)
Assessments with Anticholinergic Discontinuation (n=1,639 assessments)	100 (8.1)	1,716 (13.1)

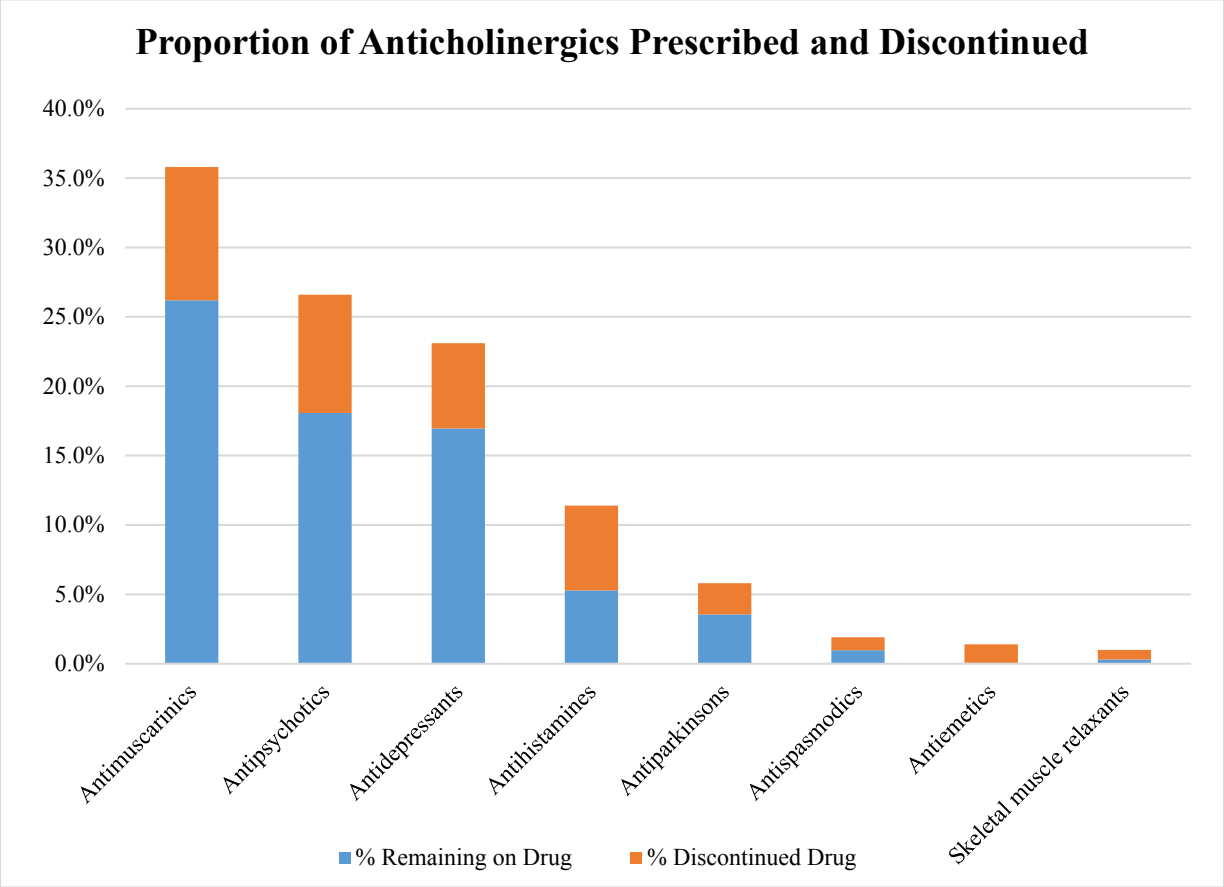


Figure 6-3 - Proportion of Anticholinergic Classes Prescribed and Discontinued

Table 6-5 - Model Results for Effect of Deprescribing on Anticholinergic Discontinuation

Model	Variables	Pooled odds ratio	Standard Errors	p-values
Unadjusted+	Deprescribing	0.58 (0.47, 0.72)	0.06	<0.001
MSM w/IPTW+	Deprescribing	0.51 (0.40, 0.67)	0.07	<0.001
MSM w/IPTW (trimmed at 1st & 99th)	Deprescribing	0.49 (0.38, 0.63)	0.06	<0.001
MSM w/IPTW (capped at 1st & 99th)	Deprescribing	0.53 (0.41, 0.67)	0.06	<0.001
MSM w/IPTW (overlap sensitivity)	Deprescribing	0.50 (0.39, 0.65)	0.07	<0.001
Adjusted model w/o IPTW	Deprescribing	0.53 (0.41, 0.68)	0.07	<0.001

+Primary model

6.4.4 Sensitivity Analyses

In per-protocol analyses, assessments were excluded if the resident had been issued a new prescription for an AChEI following deprescribing. Assessments were included up until and including the MDS assessment following AChEI restarts to avoid the problem of direct correlation between deprescribing and censoring, as mentioned in Chapter 5. This resulted in less than 1% of assessments being excluded in each analysis. Results remained substantively unchanged in per-protocol analyses for all outcomes and are presented in **Table 6-6 and Table 6-7.**

Table 6-6 - Results of Per-Protocol Analysis for Effect of Deprescribing on Incident Antispsychotic Prescriptions

Model	Variables	Pooled odds ratio	Standard Errors+	p-values
MSM w/IPTW	Deprescribing	0.53 (0.40, 0.70)	0.07	<0.001
MSM w/IPTW (sensitivity for overlap)	Deprescribing	0.53 (0.40, 0.71)	0.07	<0.001

Table 6-7 - Results of Per-Protocol Analysis for Effect of Deprescribing on Anticholinergic Discontinuation

Model	Variables	Pooled odds ratio	Standard Errors+	p-values
MSM w/IPTW	Deprescribing	0.51 (0.39, 0.67)	0.07	<0.001
MSM w/IPTW (sensitivity for overlap)	Deprescribing	0.49 (0.38, 0.65)	0.07	<0.001

We also conducted a sub-group analysis among the group of anticholinergic users, limited to those who were receiving antimuscarinic anticholinergics, which represented approximately 37% of anticholinergic users (n=2,035 residents). The most commonly prescribed antimuscarinic agent at baseline was oxybutynin, which was eventually discontinued in 30% of residents. Deprescribing AChEIs was not associated with discontinuation of anticholinergics in this sub-group (pooled aOR=1.02, 95% CI: [0.59, 1.78], p=0.93) (**Table 6-8**).

Table 6-8 - Model Results for Effect of Deprescribing on Antimuscarinic Anticholinergic Discontinuation

Model	Variables	Pooled odds ratio	Standard Errors	p-values
Unadjusted+	Deprescribing	0.99 (0.70, 1.40)	0.17	0.97
MSM w/IPTW+	Deprescribing	1.02 (0.59, 1.78)	0.29	0.93
MSM w/IPTW (trimmed at 1st & 99th)	Deprescribing	0.68 (0.42, 1.10)	0.17	0.12
MSM w/IPTW (capped at 1st & 99th)	Deprescribing	0.87 (0.56, 1.34)	0.19	0.53
MSM w/IPTW (overlap sensitivity)	Deprescribing	1.00 (0.55, 1.84)	0.31	0.98

+Primary model

6.5 DISCUSSION

This is the first analysis to examine the impact of deprescribing AChEIs on medication-related outcomes in a national sample of nursing home residents with severe dementia. We found that deprescribing was associated with a reduced likelihood of receiving new prescriptions for antipsychotic medications and was not associated with an increased likelihood of discontinuing strong anticholinergic medications.

The results from this study provide a significant contribution to the literature regarding the potential safety implications of deprescribing AChEIs. As discussed previously, one of the main barriers to deprescribing AChEIs is the potential for worsening of behavioral symptoms.[96] Although the primary concern related to worsening behavioral symptoms in dementia patients is the associated increase in distress for caregivers and nursing staff[174,175], the possibility of receiving high-risk psychotropic medications to manage these symptoms should also be considered as a potential negative effect. This is especially true for antipsychotic medications, which, although only recommended as a last-resort for managing behavioral symptoms of dementia[103,176], carry a black box warning for increased mortality risk in dementia patients. Despite this well-documented risk, over 20% of residents in our sample were using antipsychotics at baseline, emphasizing that the use of these agents in nursing home residents with dementia is not uncommon and is important to address.

While a number of studies have examined the impact of deprescribing AChEIs on behavioral outcomes, only two studies to date have examined the potential impact of deprescribing AChEIs on the use of other medications, including psychotropic medications.[101,108] Although

these two studies also found no significant increase in the use of psychotropic medications following discontinuation of AChEIs, these were conducted in much smaller and potentially less generalizable samples.

Our study confirms these findings, but has a number of strengths that set it apart from prior studies. We used a much larger and nationally representative sample of nursing home residents with severe dementia in our study, which likely increases the generalizability of our findings. We also controlled for a larger number of potential confounders and addressed the potential for time-dependent confounding in our analytical design, thereby reducing the potential for bias. Finally, we evaluated the impact of deprescribing AChEIs on medication-related outcomes with specific clinical relevance in dementia patients (e.g. antipsychotics and anticholinergics).

The finding that deprescribing AChEIs was associated with decreased likelihood of new antipsychotic prescriptions should be interpreted with caution. Due to the nature of observational study designs and the limitations of our data, we cannot causally attribute reduced likelihood of antipsychotic prescribing to deprescribing AChEIs. Our interpretation instead is that the re-evaluation of the appropriateness of all medications and translates into a reduced likelihood of prescribing new medications. Future studies should be conducted using qualitative interviews to evaluate the decision-making process of prescribers regarding goals of care and the re-evaluation of other medications when deprescribing AChEIs.

We found that there was a decreased likelihood of discontinuing strong anticholinergic medications associated with deprescribing AChEIs. Again, this finding should be interpreted with caution, as our observational study cannot prove causality between AChEI deprescribing and strong anticholinergic discontinuation. The list of strongly anticholinergic medications from the Beers Criteria consists of a variety of medication classes. Although potentially inappropriate due

to their increased anticholinergic activity, a number of these medications do have clinical utility for symptom management in patients with limited prognosis including antiemetics, antihistamines, and antiparkinsonian agents. Other classes of strong anticholinergics other than antimuscarinics that were commonly prescribed included antidepressants and antipsychotics. Therefore, our findings may also reflect a conservative approach taken by prescribers when discontinuing these psychotropic medications, allowing time to evaluate how well deprescribing is tolerated before moving on to other medications.

Antimuscarinics were the most common class of strongly anticholinergic medications from the Beers Criteria[160] prescribed in the sub-sample of patients who were receiving both AChEIs and anticholinergics. This is not surprising, given that the use of antimuscarinic anticholinergics to manage symptoms of urinary incontinence induced by AChEIs has been described previously in the literature, i.e. cholinergic prescribing cascade.[70] We originally hypothesized that deprescribing AChEIs would be associated with increased likelihood of discontinuing antimuscarinic anticholinergics, since antimuscarinic anticholinergics would no longer being necessary to manage adverse effects following removal of the offending agent. Interestingly, when we limited our sample of strong anticholinergic users to those who were prescribed antimuscarinic agents, deprescribing AChEIs was not associated with discontinuation of these medications. One potential explanation is that prescribers may be hesitant to discontinue antimuscarinic anticholinergics for fear of worsening incontinence symptoms if the cause of incontinence cannot be definitively linked to the use of AChEIs. However, it is worth noting that a significant proportion of incontinence symptoms in NH residents with severe dementia are likely attributable to impaired ability to communicate or ambulate, factors which are not modifiable with pharmacotherapy.[206] This is as opposed to urge incontinence, for which antimuscarinic anticholinergics would be effective in

managing the pathophysiologic cause of symptoms. It is also possible that the lack of association observed is at least partially attributable to the small size of this sub-sample and thus the small amount of anticholinergic discontinuation that was observed.

We acknowledge that there are limitations to our statistical approach, which utilized a pooled logistic regression model that assumes discretized observation periods. Aside from a major change in clinical status, MDS assessment forms should be administered approximately every 90 days. This means that in most cases the time between assessments in our sample was theoretically discretized to every 90 days. We confirmed this in our data, identifying that >75% of all MDS assessments in our sample spanned a period of approximately 90 days. Although we could have conducted a time-to-event analysis using fully adjusted Cox proportional hazards models to address the potential variability in follow-up time between observation periods, we decided against this approach. The rationale for not using Cox models was the potential for time-dependent confounding as a source bias, given the time-varying nature of our primary independent variable and covariates. This means that the potential for confounding in the association of deprescribing with medication outcomes by other clinical factors is dependent on whether or not deprescribing has occurred. This necessitated the use of marginal structural models with time-varying inverse probability of treatment weights, which currently cannot be easily incorporated into traditional Cox models. Given the acceptable degree of uniformity in the time between MDS assessments that we observed, we believed the potential bias due to time-dependent confounding to outweigh any bias that may have been introduced due to the limitations of a discretized pooled logistic regression model.

Other limitations of our analysis include those mentioned in previous chapters. It is possible that gaps in medication therapy may be attributable to non-adherence, rather than

intentional deprescribing. There was also low prevalence of behavioral symptoms at baseline in our sample, thus it is possible that in patients that exhibit significant behavioral problems, deprescribing AChEIs may still lead to increased use of antipsychotic medications. Finally, our findings are not generalizable to patients with mild or moderate dementia nor to community-dwelling older adults with severe dementia.

6.6 CONCLUSIONS

We identified that deprescribing AChEIs was associated with a reduced likelihood of receiving new antipsychotic prescriptions and a decreased likelihood of discontinuing strong anticholinergic medications. The conversation surrounding the decision to deprescribe AChEIs may initiate a chain of events that leads to a reduced likelihood of prescribing new medications. Future studies should evaluate the prescriber decision-making process regarding goals of care and the use of other medications when AChEIs are deprescribed.

7.0 CONCLUSIONS AND FUTURE DIRECTIONS

7.1 OVERVIEW OF SCOPE OF STUDY

The ultimate goal of this body of work was to address a major gap in the literature regarding the management of severe dementia by providing a comprehensive evaluation of the potential risks and benefits associated with deprescribing AChEIs. The primary results of our analyses are presented in Chapters 4, 5, and 6.

In the first analysis (Chapter 4), we evaluated patient-level, system-level, and provider-level factors that may drive clinical decision-making in deprescribing and may serve as potential confounders in the association of deprescribing with outcomes. In the second analysis (Chapter 5), we used a longitudinal analysis to evaluate the potential impact of deprescribing on behavioral outcomes, including aggressive behaviors and depressive symptoms, and the total number of medications received. Finally, we evaluated the potential downstream effects of deprescribing AChEIs on the use of other medications including new antipsychotic prescriptions and discontinuation of strongly anticholinergic medications.

This final chapter provides a summary of our findings, potential implications for clinical practice, a discussion of the strengths and limitations of each analysis, and suggestions and priorities for future research.

7.2 SUMMARY OF FINDINGS

In a sample of older Medicare nursing home residents with severe dementia, we identified a number of patient-level factors, that likely act as proxies for declining clinical status, which were associated with increased likelihood of deprescribing AChEIs. In addition, several important system-level factors were identified that may act as barriers to the dissemination and implementation of deprescribing in nursing homes. In analyses of the impact of deprescribing AChEIs on outcomes, deprescribing was not found to be associated with a significant change in depression severity or aggressive behaviors in this population. Finally, although we identified that deprescribing was not associated with an increased likelihood for antipsychotic prescribing, it was associated with increased likelihood of discontinuing other non-AChEI medications. The results presented in this dissertation address a major gap in the literature, providing a comprehensive evaluation of the epidemiology and outcomes associated with deprescribing AChEIs in nursing home residents with severe dementia.

A substantial number of nursing home residents had AChEIs deprescribed over our 1-year observation period. The results from our first analysis (Chapter 4) provided insight into what factors may drive clinical decision-making regarding deprescribing, despite the lack of evidence regarding the safety or tolerability of this practice. It is clear that the presence of clinical factors that suggest declining clinical status act as a trigger for re-evaluation of the appropriateness of medications. This is in agreement with several consensus papers and clinical guidelines that suggest many medications, including AChEIs, should be reconsidered in patients with severe dementia or limited life expectancy. We also noted that deprescribing was more likely at the time of admission to the nursing home and if the prescriber was a geriatrics specialist. This is likely a function of the fact that more comprehensive evaluations, including the evaluation of medications,

likely occur in the setting of care transitions and that geriatricians are especially sensitive to medication-related issues. The primary system-level factor that was associated with deprescribing AChEIs was rurality. Residing in a nursing home in a rural or highly rural region was associated with reduced likelihood of deprescribing, which we hypothesized may be a function of proximity to an academic medical center, where the integration of clinical pharmacy services and other initiatives to promote deprescribing may be more common.

In subsequent analyses, we examined the impact of deprescribing AChEIs on clinically relevant outcomes, including behavioral symptoms and high-risk medication use, which have been previously noted to be major factors in decision-making regarding deprescribing. Taken together, the findings presented suggest that deprescribing AChEIs may be a safe and reasonable approach to reduce polypharmacy and the risk for adverse drug events in older nursing home residents with severe dementia. We found no significant association of deprescribing with depressive symptoms or aggressive behaviors, but we believe this may be at least partially attributable to the fact that the presence of behavioral symptoms was low overall in our sample.

Finally, we examined the potential impact of deprescribing AChEIs on the use of other medications and observed that deprescribing AChEIs was associated with a reduction in the total number of non-AChEI medications being received. In additional analyses, we also examined the impact of deprescribing AChEIs on the prescribing of high-risk antipsychotic and strongly anticholinergic medications. In a sub-group of antipsychotic non-users, deprescribing AChEIs was associated with a decreased likelihood of receiving new antipsychotic medications that may be prescribed to manage worsening behavioral symptoms following deprescribing. In a sub-group of residents who were receiving both AChEIs and strong anticholinergic medications at baseline,

deprescribing AChEIs was not associated with an increased likelihood of subsequent discontinuation of anticholinergic medications.

7.3 IMPLICATIONS

The findings from this dissertation have a number of implications for clinical practice with regards to the management of severe dementia in the nursing home setting. We observed that the cumulative incidence for deprescribing AChEIs was approximately 30% over a 1-year period, suggesting that a proportion of prescribers in the nursing home setting are aware of the lack of benefit associated with AChEIs in the management of severe dementia. Deprescribing was more likely to occur among residents with clinical characteristics signifying a decline in clinical status or limited prognosis. This is not surprising, given the recent emphasis on individualized prevention in geriatrics literature[87] and consensus guidelines that recommend re-evaluating and deprescribing many medications used for disease prevention in patients with limited prognosis, including AChEIs[60,92].

As described in earlier chapters, the main barrier to deprescribing AChEIs in clinical practice is the lack of high-quality evidence regarding the potential downstream effects on behavioral symptoms and the use of high-risk antipsychotic medications to manage these symptoms. Deprescribing was not associated with a significant change in aggressive behaviors or depressive symptoms. However, it should be acknowledged that due to the low prevalence of behavioral symptoms in our sample at baseline, our findings may only generalizable to nursing home residents without existing behavioral issues.

Our findings suggest that deprescribing AChEIs may actually lead to a decrease in the use of other medications. Deprescribing was associated with a decrease in the total number of medications prescribed and a reduced likelihood of receiving new prescriptions for antipsychotic medications. Although it is unlikely that deprescribing AChEIs is actually the cause of decreased use of other medications, we believe that the conversation around deprescribing one medication serves as the impetus towards a shift in goals of care that leads to the re-evaluation of the appropriateness of all medications including the prescribing of new medications.

Unfortunately, our findings regarding the impact of deprescribing AChEIs on the use of other medications may not apply to the use of strong anticholinergic medications. Deprescribing AChEIs was associated with a reduced likelihood of discontinuing strong anticholinergics in residents who had already been prescribed both medications at baseline. The use of strong anticholinergics in older adults with dementia is considered to be potentially inappropriate due to their mechanism of action which directly opposes that of AChEIs and contributes to worsening cognition. We originally hypothesized that deprescribing AChEIs would lead to the discontinuation of strong anticholinergic medications, specifically antimuscarinic anticholinergics that may have been prescribed to manage adverse effects induced by AChEIs. Although antimuscarinics were the most commonly prescribed group of strong anticholinergics, antipsychotics and antidepressants were prescribed almost as frequently. We believe that this contributed to the decreased likelihood of discontinuation of anticholinergics with prescribers taking a conservative approach to discontinuing psychotropic medications to minimize the disruption of patients who may be clinically stable. When limited to antimuscarinic anticholinergics, we found no significant association in either direction supporting our hypothesis of a class-specific effect. Nonetheless, this points out a target for a potential educational

interventions for prescribers regarding the appropriateness of muscarinic anticholinergics for managing AChEI-induced incontinence following deprescribing of AChEIs.

Our findings suggest that deprescribing AChEIs is well-tolerated and does not result in negative behavioral outcomes or increased likelihood for new prescriptions for high-risk medications. We identified that there may also be a number of system-level barriers to the implementation of deprescribing, despite the evidence presented that supports deprescribing as a reasonable strategy to reduce unnecessary medication use. Therefore, targeted educational interventions aimed at non-geriatric prescribers and those practicing in rural nursing homes may help to improve the dissemination and implementation of deprescribing AChEIs as a means to improve the overall quality of prescribing for residents with severe dementia.

7.4 STRENGTHS AND WEAKNESSES

The main limitation of this work is the observational nature of our data, which introduces potential for biases. It is impossible to identify the intent behind the gaps in medication supply in administrative data that we called "deprescribing". Nonadherence and human error or systems errors can also contribute to gaps in medication fills, which may have introduced misclassification bias in our studies. However, additional analyses using a longer gap in therapy to define deprescribing (e.g. 30-day versus 60-day gap) and per-protocol analyses revealed no substantive changes to our findings, suggesting that misclassification bias may not be a significant concern.

We also acknowledge that due to the limitations of our data, we were not able to fully characterize residents' prior treatment history with AChEIs or their disease trajectory. We also

were only able to follow patients for up to 1 year, which may have limited our ability to adequately examine changes in behavioral symptoms over time that may have developed at a slower rate.

Finally, there is also the potential for unmeasured confounding. Although we used the most comprehensive administrative data source of clinical information available for nursing home residents, we were limited by what information was contained within MDS assessments. Clinical tools that are used in clinical practice to evaluate behavioral and psychological symptoms of dementia may have an enhanced ability to diagnose symptoms and may be more sensitive to change over time.

The strengths of each individual analysis have been discussed in previous chapters. However, there are a number of strengths to this body of work as a whole that also deserve discussion. This dissertation provides a comprehensive evaluation of the epidemiology and outcomes associated with deprescribing AChEIs and addresses a major gap in the literature on this topic. This work was conducted in large, nationally representative sample of nursing home residents with severe dementia, a population with the greatest relevance for deprescribing AChEIs. Prior investigations of deprescribing AChEIs are limited by small sample sizes and heterogeneity with regards to the dementia severity of patients included. We used data from the most comprehensive source of clinical information for nursing home residents, the MDS, to conduct longitudinal analyses and applied robust statistical methods to adjust for time-varying confounders. We also examined a number of clinically-relevant outcomes to fully evaluate the balance between potential risks and benefits following deprescribing AChEIs.

7.5 FUTRE DIRECTIONS

There are a number of future directions for this research. In order to provide a fully comprehensive evaluation of the potential risks associated with deprescribing AChEIs, we intend to conduct additional analyses to examine the association of deprescribing with negative events. This includes all-cause negative events (e.g. hospitalizations, emergency department visits, death) and medication-specific adverse events (e.g. falls and fractures, urinary incontinence, gastrointestinal symptoms, etc.). Additional studies with longer periods of follow-up (e.g. longer than 1 year) and additional years of past medical history would also be useful. This would allow for one more accurate characterization of AChEI treatment duration and disease trajectory for dementia and also a longer period to evaluate change in cognitive and behavioral outcomes over time.

Qualitative studies should also be conducted in order to understand the clinical thought process of prescribers regarding how deprescribing AChEIs may affect the use of other medications. This would provide insight into a number of our proposed hypotheses regarding the relationship of deprescribing AChEIs with antipsychotic prescribing and the cholinergic prescribing cascade in ways that administrative data cannot.

Finally, although observational studies using administrative data avoid many of the ethical and logistical complications of conducting a clinical trial in an older adult population, the potential for bias due to unmeasured confounding still exists. Therefore, there would also be value in conducting a large clinical trial among older nursing home residents with severe dementia that evaluates the impact of deprescribing AChEIs on behavioral outcomes as well as negative events.

Appendix A

Table A-1 – Imputation Results for Aim 1 Analyses

Variable	Missing n(%)	Non-missing Positive n(%)	Positive After Imputation n(%)	Imputed Positive n(%)
CLINICAL ASSESSMENT				
Makes self understood	124 (0.1)			
Understood		38,931 (38.7)	38,964 (38.7)	33 (26.6)
Usually understood		27,303 (27.1)	27,332 (27.1)	39 (31.4)
Sometimes understood		21,791 (21.6)	21,827 (21.7)	36 (29.0)
Rarely/never understood		12,658 (12.6)	12,684 (12.6)	26 (21.0)
PHQ-9 score	589 (0.6)			
Minimal		82,309 (82.1)	82,791 (82.1)	482 (81.8)
Mild		12,286 (12.3)	12,368 (12.3)	82 (13.9)
Moderate		4,312 (4.3)	4,332 (4.3)	20 (4.4)
Mod. severe or severe		1,311 (1.3)	1,316 (1.3)	<11
Aggressive behavior scale	105 (0.1)			
None		77,962 (77.4)	78,045 (77.4)	83 (79.0)
Moderate		15,168 (15.1)	15,181 (15.1)	13 (12.4)
Severe		6,017 (6.0)	6,024 (6.0)	<11
Very severe		1,555 (1.5)	1,557 (1.5)	<11
Activities of Daily Living Score	<11			
0 to 7		790 (0.8)	790 (0.8)	<11
8 to 14		6,918 (6.9)	6,918 (6.9)	<11
15 to 21		15,917 (15.8)	15,918 (15.8)	<11
22 to 28		52,902 (52.5)	52,904 (52.5)	<11
		24,276 (24.1)	24,277 (24.1)	<11
Urinary incontinence	24 (<0.1)			
Continent		9,892 (9.8)	9,895 (9.8)	<11
Occasionally incontinent		13,985 (13.9)	13,989 (13.9)	<11
Frequently incontinent		33,370 (33.1)	33,378 (33.1)	<11
Always incontinent		41,891 (41.6)	41,899 (41.6)	<11
Indwelling catheter		1,645 (1.6)	1,646 (1.6)	<11
Cancer	164 (0.2)	4,077 (4.1)	4,081 (4.1)	<11
Heart Failure	26 (<0.1)	15,486 (15.4)	15,487 (15.4)	<11
End Stage Renal Disease	153 (0.2)	9,121 (9.1)	9,138 (9.1)	17 (11.1)
Weight loss	528 (0.5)	5,852 (5.8)	5,892 (5.8)	40 (7.6)
Mechanically altered diet	67 (0.1)	47,393 (47.0)	47,435 (47.1)	42 (62.7)
ENVIRONMENT OF CARE				
Geographic region	946 (0.9)			
Midwest		18,110 (18.1)	18,278 (18.1)	168 (17.8)
Northeast		27,348 (27.4)	27,777 (27.6)	429 (45.3)
South		46,517 (46.6)	46,735 (46.4)	218 (23.0)
West		7,886 (7.9)	8,017 (8.0)	131 (13.8)
Certified beds	195 (0.2)			
<50		4,898 (4.9)	4,904 (4.9)	<11
50-99		28,843 (28.7)	28,896 (28.7)	53 (27.2)
100-199		55,339 (55.0)	55,446 (55.0)	107 (54.9)

200+		11,532 (11.5)	11,561 (11.5)	29 (14.9)
Rural/urban continuum	946 (0.9)			
Urban		68,787 (68.9)	69,256 (68.7)	469 (49.6)
Rural		27,121 (27.1)	27,512 (27.3)	391 (41.3)
Highly rural		3,953 (4.0)	4,039 (4.0)	86 (9.1)
PROVIDER CHARACTERISTICS				
Prescriber specialty	82 (0.1)			
Geriatrics		8,591 (8.5)	8,603 (8.5)	12 (14.6)
Primary care		81,728 (81.1)	81,788 (81.1)	60 (73.2)
Other		10,406 (10.3)	10,416 (10.3)	<11

Table A-2 – Effect of Healthcare Utilization in Prior Year by 90-day Periods

Variable	Unadj HR (CI)
Hospitalizations 0-90 days	1.54 [1.45-1.65]
Hospitalizations 90-180 days	1.10 [0.99-1.21]
Hospitalizations 180-270 days	1.03 [0.91-1.17]
Hospitalizations 270-365 days	1.03 [0.79-1.33]
ED Visits 0-90 days	1.43 [1.34-1.52]
ED Visits 90-180 days	1.09 [0.99-1.19]
ED Visits 180-270 days	1.01 [0.90-1.13]
ED Visits 270-365 days	1.10 [0.88-1.37]
Fall/fracture 0-90 days	1.38 [1.29-1.49]
Fall/fracture 90-180 days	1.05 [0.93-1.18]
Fall/fracture 180-270 days	1.10 [0.96-1.27]
Fall/fracture 270-365 days	1.31 [0.99-1.73]
Syncope 0-90 days	1.40 [1.28-1.53]
Syncope 90-180 days	1.05 [0.90-1.22]
Syncope 180-270 days	1.07 [0.88-1.29]
Syncope 270-365 days	0.67 [0.41-1.09]

Appendix B

Table B-1 - The Aggressive Behavior Scale (ABS)[158]

MDS Item	Description
E0200A	Physical behavioral symptoms directed toward others
E0200B	Verbal behavioral symptoms directed toward others
E0200C	Other behavioral symptoms not directed toward others
E0800	Did the resident reject evaluation or care that is necessary to achieve resident's goals for health and well-being?

All of the above were evaluated on the following scale: Behavior not exhibited (0); Behavior of this type occurred 1-3 days (1); Behavior of this type occurred 4-6 days (2); Behavior of this type occurred daily (3).

Table B-2 – The Patient Health Questionnaire (PHQ-9)[159]

MDS Item	Description
D0200A/D0500A	Little pleasure or interest in doing things
D0200B/D0500B	Feeling down, depressed, or hopeless
D0200C/D0500C	Trouble falling or staying asleep, or sleeping too much
D0200D/D0500D	Feeling tired or having little energy
D0200E/D0500E	Poor appetite or overeating
D0200F/D0500F	Feeling bad about yourself – or that you are a failure or have let yourself or your family down
D0200G/D0500G	Trouble concentrating on things, such as reading the newspaper or watching television
D0200H/D0500H	Moving or speaking so slowly that other people could have noticed. Or the opposite, being so fidgety or restless that you have been moving around a lot more than usual.
D0200I/D0500I	Thoughts that you would be better off dead, or of hurting yourself in some way.

All of the above are evaluated on:

1) Presence of symptom: yes/no
2) Frequency of symptom: never or 1 day (0); 2-6 days (1); 7-11 days (2); 12-14 days (3)

Table B-3 – Sample characteristics stratified by deprescribing status after applying preliminary IPTWs (unbalanced)

Variable	AChEI Deprescribed N=10,577 assessments (%)	AChEI Prescribed N=71,255 assessments (%)	Standardized Difference
DEMOGRAPHICS			
Age in years			0.06
65-69	2.49	2.13	
70-79	19.9	20.4	
80-89	48.3	45.9	
90+	29.3	31.5	
Sex			
Female	77.3	78.7	0.03
Race/ethnicity			0.04
White	78.7	77.8	
Black	11.7	12.7	
Hispanic	5.9	6.2	
Other	3.7	3.3	
Current marital status			0.01
Married	20.6	21.0	
CLINICAL ASSESSMENT			
Entered from			0.05
Community	18.5	20.2	
Hospital	70.1	67.8	
NH or other LTC facility	11.4	12.0	
MDS Assessment Type			0.11*
Admission	4.1	4.5	
Quarterly	70.8	71.7	
Annual	16.6	18.2	
Significant Change in Status	8.5	5.7	
Charlson Comorbidity Index			0.01
0-1	15.0	14.7	
2-3	26.1	26	
4-5	24.4	24.8	
≥6	34.6	34.5	
Makes self understood			0.22*
Understood	31.3	39.2	
Usually understood	25.6	27.1	
Sometimes understood	24	21.2	
Rarely/never understood	19.1	12.6	

PHQ-9 score	2.4	2.1	0.07
Aggressive behavior scale	0.58	0.52	0.05
Activities of Daily Living Score 1 to 7 8 to 14 15 to 21 22 to 28	 4.5 11.5 51.7 32.2	 7.9 16 52.5 23.6	0.25*
Urinary incontinence Continent Occasionally incontinent Frequently incontinent Always incontinent Indwelling catheter	 6.6 10.2 30.2 51.2 1.8	 10.1 14.1 33.2 41.1 1.5	0.23*
Cancer	4.3	4.0	0.01
Heart failure	14.3	15.0	0.02
End Stage Renal Disease	9.3	8.7	0.02
Short of breath	6.0	6.3	0.02
Poor appetite	16.4	12.8	0.10*
Weight loss	9.3	6.0	0.13*
Swallowing difficulty	4.2	3.2	0.05
Mechanically altered diet	45.0	53.1	0.16*
IV/parenteral nutrition or feeding tube	3.3	2.7	0.04
Hospice or Limited Prognosis	12.6	4.2	0.31*
Hospitalizations/ED Visits (90d prior) None Cause-specific (fall, fracture, syncope) Other cause	 85.0 6.1 8.9	 85.2 5.6 9.2	0.02
AChEI at index date Donepezil Donepezil/memantine Galantamine Rivastigmine (oral) Rivastigmine (transdermal)	 76.3 0.9 2.0 4.6 16.3	 77.0 1.7 2.3 4.2 14.8	0.09
Memantine use	33	42.0	0.18*
Benzodiazepine and/or Z drug	13.4	14.0	0.02
Antipsychotic use	21.1	22.6	0.04
Antidepressant use	53.8	56.8	0.06
Highly Anticholinergic Drugs (Beers)	12.1	14.0	0.06

Total number of medications [Mean]	5.1	5.8	0.24*
ENVIRONMENT OF CARE			
Geographic region			0.12*
Midwest	22.9	27.4	
Northeast	20.2	18.1	
South	50.5	46.8	
West	6.5	7.7	
Certified beds			0.09
<50	4.4	4.8	
50-99	25.1	28.4	
100-199	57.4	55.3	
200+	13.0	11.5	
Rural/urban continuum			0.13*
Urban	74.3	68.5	
Rural	22.6	27.5	
Highly rural	3.1	4.0	
PROVIDER SPECIALTY			
Prescriber specialty			0.05
Geriatrics	10	8.8	
Primary care	10.6	10.1	
Other	79.4	81.1	

*** Standardized difference >10%**

Table B-4 – Variability in Characteristics During Nursing Home Episode (resident-level)

Variable	% of Residents with Constant Values	% of Residents with Varying Values
MDS Assessment Type	44.9	55.1
Charlson Comorbidity Index	99.9	0.1
Makes self understood	84.1	15.9
Activities of Daily Living Score	80.1	19.9
Urinary incontinence	74.9	24.1
Cancer	99.1	0.9
Heart failure	97.8	2.2
End Stage Renal Disease	97.9	2.1
Short of breath	95.7	4.3
Poor appetite	87.9	12.1
Weight loss	91.7	8.3
Swallowing difficulty	96.9	3.1
Mechanically altered diet	93.2	6.8
IV/parenteral nutrition or feeding tube	99.3	0.7
Hospice or Limited Prognosis	97.0	3.0
Hospitalizations/ED Visits (90 days prior)	82.0	18.0
Memantine use	89.5	10.5
Benzodiazepine and/or Z drug	92.0	8.0
Antipsychotic use	88.0	12.0
Antidepressant use	93.0	7.0
Highly Anticholinergic Drugs (Beers Criteria)	94.9	5.1

Table B-5 – Estimation of Inverse Propensity Treatment Weights – Version 1 (not used)

Variable	Time-invariant (measured at baseline)	Time-varying (lagged to prior assessment)
DEMOGRAPHICS		
Age in years	x	
Sex	x	
Race/ethnicity	x	
Current marital status	x	
CLINICAL ASSESSMENT		
Entered from	x	x
MDS Assessment Type	x	x
Charlson Comorbidity Index	x	x
Makes self understood	x	x
PHQ-9 score	x	x
Aggressive behavior scale	x	x
Activities of Daily Living Score	x	x
Urinary incontinence	x	x
Cancer	x	x
Heart failure	x	x
End Stage Renal Disease	x	x
Short of breath	x	x
Poor appetite	x	x
Weight loss	x	x
Swallowing difficulty	x	x
Mechanically altered diet	x	x
IV/parenteral nutrition or feeding tube	x	x
Hospice or Limited Prognosis	x	x
Hospitalizations/ED Visits (90 days prior)	x	x
AChEI at index date	x	x
Memantine use	x	x
Benzodiazepine and/or Z drug	x	x
Antipsychotic use	x	x
Antidepressant use	x	x
Highly Anticholinergic Drugs (Beers Criteria)	x	x
Total number of medications	x	x
ENVIRONMENT OF CARE		
Geographic region	x	
Certified beds	x	
Rural/urban continuum	x	
PROVIDER SPECIALTY		
Prescriber specialty	x	

Table B-6 – Estimation of Inverse Propensity Treatment Weights – Version 2 (used in primary analysis)

Variable	Time-invariant (measured at baseline)	Time-varying (lagged to prior assessment)
DEMOGRAPHICS		
Age in years	x	
Sex	x	
Race/ethnicity	x	
Current marital status	x	
CLINICAL ASSESSMENT		
Entered from		x
MDS Assessment Type		x
Charlson Comorbidity Index		x
Makes self understood		x
PHQ-9 score		x
Aggressive behavior scale		x
Activities of Daily Living Score		x
Urinary incontinence		x
Cancer		x
Heart failure		x
End Stage Renal Disease		x
Short of breath		x
Poor appetite		x
Weight loss		x
Swallowing difficulty		x
Mechanically altered diet		x
IV/parenteral nutrition or feeding tube		x
Hospice or Limited Prognosis		x
Hospitalizations/ED Visits (90 days prior)		x
AChEI at index date		x
Memantine use		x
Benzodiazepine and/or Z drug		x
Antipsychotic use		x
Antidepressant use		x
Highly Anticholinergic Drugs (Beers Criteria)		x
Total number of medications		x
ENVIRONMENT OF CARE		
Geographic region	x	
Certified beds	x	
Rural/urban continuum	x	
PROVIDER SPECIALTY		
Prescriber specialty	x	

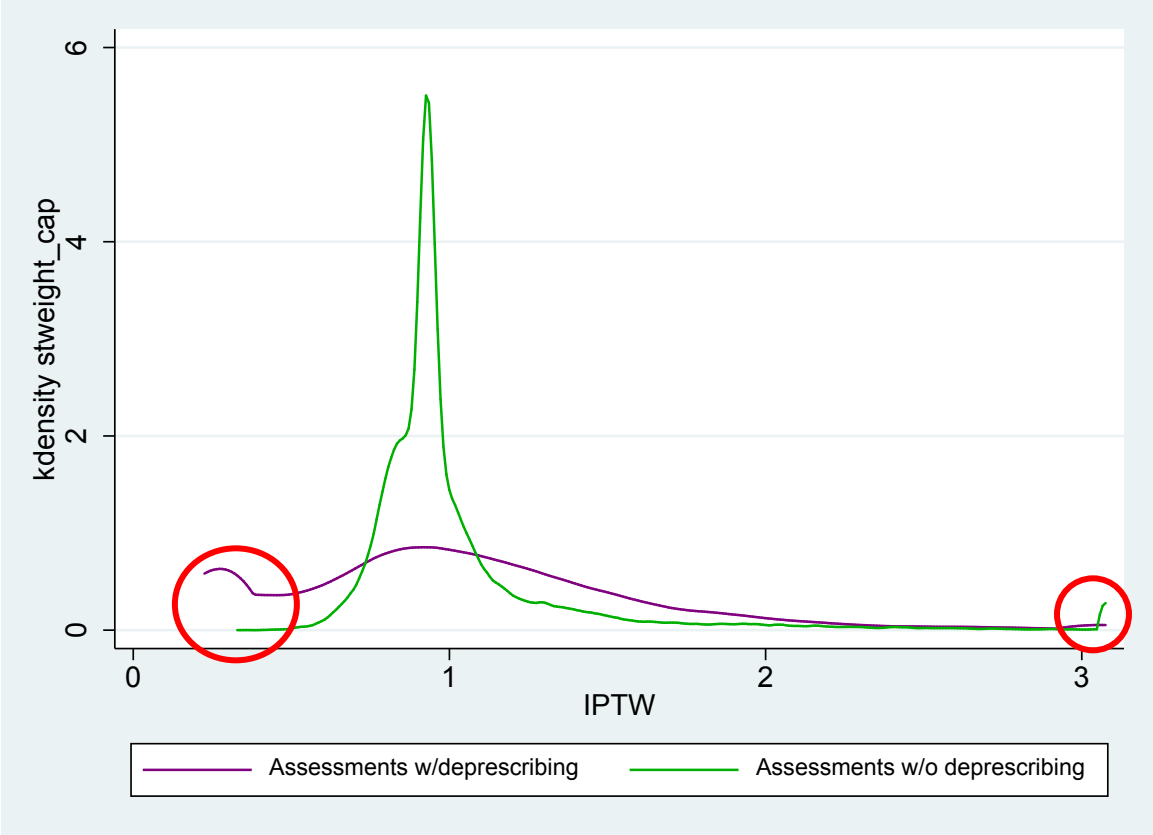


Figure B-1 – Kernel Density Plot of Inverse Propensity Treatment Weights Stratified by Deprescribing Status

Table B-7 – Characteristics of Observations Excluded due to non-overlap in IPTWs

Variable	Removed N=1,293 (1.6%) assessments	Retained N=80,539 (98.4%) assessments
DEMOGRAPHICS		
Age in years		
65-69	28 (2.2)	1,967 (2.4)
70-79	250 (19.3)	16,109 (20.0)
80-89	576 (44.6)	38,587 (47.9)
90+	439 (33.9)	23,876 (29.7)
Sex		
Male	260 (20.1)	18,906 (22.5)
Female	1,033 (79.9)	62,443 (77.5)
Race/ethnicity		
White	1,090 (84.3)	63,208 (78.5)
Black	113 (8.7)	9,594 (11.9)
Hispanic	69 (5.3)	4,764 (5.9)
Other	21 (1.6)	2,973 (3.7)
Current marital status		
Married	284 (22.0)	16,477 (20.5)
Not Married	1,009 (78.0)	64,062 (79.5)
CLINICAL ASSESSMENT		
Entered from		
Community	265 (20.5)	16,241 (20.2)
Hospital	866 (67.0)	54,808 (68.1)
NH or other LTC facility	162 (12.5	9,490 (11.8)
MDS Assessment Type		
Admission	1,138 (88.0)	59,493 (73.9)
Quarterly	44 (3.4)	15,242 (18.9)
Annual	111 (8.6)	5,804 (7.2)
Significant Change in Status		
Charlson Comorbidity Index		
0-1	198 (15.3)	12,026 (14.9)
2-3	301 (23.3)	20,934 (26.0)
4-5	306 (23.7)	19,929 (24.7)
≥6	488 (37.7)	27,650 (34.3)
Makes self understood		
Understood	274 (21.2)	30,967 (38.5)
Usually understood	290 (22.4)	21,874 (27.1)
Sometimes understood	354 (27.4)	17,466 (21.7)
Rarely/never understood	375 (29.0)	10,279 (12.8)
PHQ-9 score	3.3 (4.2)	2.1 (3.4)
Aggressive behavior scale	0.62 (1.4)	0.52 (1.3)
Activities of Daily Living Score		
1 to 7	<	6,155 (7.6)
8 to 14	54 (4.2)	12,774 (15.9)
15 to 21	578 (44.7)	42,509 (52.8)
22 to 28	651 (50.4)	19,101 (23.7)
Urinary incontinence		
Continent	29 (2.2)	7,910 (9.8)
Occasionally incontinent	68 (5.3)	11,110 (13.8)
Frequently incontinent	332 (25.7)	26,796 (33.3)

Always incontinent	830 (64.2)	33,560 (41.7)
Indwelling catheter	34 (2.6)	1,163 (1.4)
Cancer	54 (4.2)	3,145 (3.9)
Heart failure	187 (14.5)	11,968 (14.9)
End Stage Renal Disease	112 (8.6)	7,104 (8.8)
Short of breath	113 (8.7)	4,918 (6.1)
Poor appetite	434 (33.6)	9,904 (12.3)
Weight loss	296 (22.9)	4,424 (5.5)
Swallowing difficulty	93 (7.2)	2,518 (3.1)
Mechanically altered diet	386 (29.9)	42,587 (52.9)
IV/parenteral nutrition or feeding tube	41 (3.2)	2,156 (2.7)
Hospice or Limited Prognosis	1,178 (91.1)	2,716 (3.4)
Hospitalizations/ED Visits (90 days prior)		
None	1,065 (82.4)	70,165 (87.1)
Cause-specific (fall, fracture, syncope)	76 (5.9)	4,061 (5.0)
Other cause	152 (11.8)	6,313 (7.8)
AChEI at index date		
Donepezil	978 (75.6)	62,147 (77.2)
Donepezil/memantine	<	1,341 (1.7)
Galantamine	21 (1.6)	1,804 (2.2)
Rivastigmine (oral)	59 (4.6)	3,422 (4.3)
Rivastigmine (transdermal)	231 (17.9)	11,825 (14.7)
Memantine use	242 (18.7)	33,504 (41.6)
Benzodiazepine and/or Z drug	112 (8.6)	11,160 (13.9)
Antipsychotic use	191 (14.8)	18,077 (22.5)
Antidepressant use	542 (41.9)	45,612 (56.6)
Highly Anticholinergic Drugs (Beers Criteria)	97 (7.5)	11,806 (13.8)
Total number of medications [Mean (SD)]	2.2 (2.2)	5.7 (3.0)
ENVIRONMENT OF CARE		
Geographic region		
Midwest	417 (32.3)	21,720 (26.9)
Northeast	177 (13.7)	14,932 (18.5)
South	617 (47.7)	37,775 (46.9)
West	82 (6.3)	6,112 (7.6)
Certified beds		
<50	48 (3.7)	3,865 (4.8)
50-99	379 (29.3)	22,634 (28.1)
100-199	742 (57.4)	44,601 (55.4)
200+	124 (9.6)	9,439 (11.7)
Rural/urban continuum		
Urban	917 (70.9)	55,682 (69.1)
Rural	343 (26.5)	21,674 (26.9)
Highly rural	33 (2.6)	3,183 (3.0)
PROVIDER SPECIALTY		
Prescriber specialty		
Geriatrics	99 (7.7)	7,058 (8.8)
Primary care	1,075 (83.1)	62,250 (81.0)
Other	119 (9.2)	8,231 (10.2)

Appendix C

Table C-1 Weighted Sample Characteristics for Sample of Antipsychotic Non-Users at Baseline

Variable	AChEI deprescribed (n=11,567 assessments) n (%)	AChEI not deprescribed (n=64,416 assessments) n (%)	Standardized Difference
DEMOGRAPHICS			
Age in years			0.07
65-69	167 (1.5)	1,102 (1.7)	
70-79	1,917 (16.6)	10,515 (16.6)	
80-89	5,275 (45.6)	31,315 (48.6)	
90+	4,206 (36.4)	21,485 (33.4)	
Sex			<0.01
Male	2,367 (20.5)	13,254 (20.6)	
Female	9,200 (79.5)	51,162 (79.4)	
Race/ethnicity			0.04
White	8,963 (77.5)	50,790 (78.9)	
Black	1,469 (12.7)	7,608 (11.8)	
Hispanic	715 (6.2)	3,517 (5.5)	
Other	419 (3.6)	2,499 (3.9)	
Current marital status			0.02
Married	9,423 (81.5)	52,017 (80.8)	
Not Married	2,144 (18.5)	12,399 (19.3)	
CLINICAL ASSESSMENT			
Entered from			0.03
Community	2,261 (19.6)	13,399 (20.8)	
Hospital	8,016 (69.3)	43,780 (68.0)	
NH or other LTC facility	1,289 (11.2)	7,237 (11.2)	
MDS Assessment Type			0.05
Admission	237 (2.2)	1,679 (2.6)	
Quarterly	8,393 (72.6)	46,603 (72.4)	
Annual	2,129 (18.4)	12,183 (18.9)	
Significant Change in Status	808 (7.0)	3,951 (6.1)	
Charlson Comorbidity Index			0.03
0-1	1,693 (14.6)	9,979 (15.5)	
2-3	3,032 (26.2)	17,052 (26.5)	
4-5	2,897 (25.1)	15,776 (24.5)	
≥6	3,944 (34.1)	21,610 (33.6)	
Makes self understood			0.06
Understood	4,260 (36.8)	25,373 (39.4)	
Usually understood	3,075 (26.6)	16,771 (26.0)	
Sometimes understood	2,407 (20.8)	13,258 (20.6)	
Rarely/never understood	1,824 (15.8)	9,015 (14.0)	
PHQ-9 score [Mean (SD)]	2.05 (3.3)	2.00 (3.3)	0.01

Aggressive behavior scale [Mean (SD)]	0.40 (1.1)	0.39 (1.1)	<0.01
Activities of Daily Living Score			0.05
1 to 7	767 (6.6)	4,908 (7.6)	
8 to 14	1,662 (14.4)	9,704 (15.1)	
15 to 21	5,911 (51.1)	33,057 (51.3)	
22 to 28	3,228 (27.9)	16,747 (26.0)	
Urinary incontinence			0.07
Continent	980 (8.5)	6,204 (9.6)	
Occasionally incontinent	1,444 (12.5)	8,572 (13.3)	
Frequently incontinent	3,532 (30.5)	20,533 (31.9)	
Always incontinent	5,381 (46.5)	28,058 (43.6)	
Indwelling catheter	231 (2.0)	1,050 (1.6)	
Cancer	480 (4.1)	2,631 (4.2)	<0.01
Heart failure	1,804 (15.6)	10,133 (15.7)	<0.01
End Stage Renal Disease	1,189 (10.3)	6,046 (9.4)	0.03
Short of breath	696 (6.0)	4,097 (6.4)	0.01
Poor appetite	1,604 (13.9)	8,249 (12.8)	0.03
Weight loss	817 (7.1)	3,717 (5.8)	0.05
Swallowing difficulty	435 (3.8)	2,150 (3.3)	0.02
Mechanically altered diet	5,779 (49.1)	33,468 (52.0)	0.06
IV/parenteral nutrition or feeding tube	401 (3.5)	2,069 (3.2)	0.01
Hospice or Limited Prognosis	839 (7.3)	3,478 (5.4)	0.08
Hospitalizations/ED Visits (90 days prior)			0.08
None	10,540 (91.1)	57,286 (89.0)	
Cause-specific (fall, fracture, syncope)	459 (4.0)	2,801 (4.3)	
Other cause	569 (4.9)	4,329 (6.7)	
AChEI at index date			0.04
Donepezil	9,098 (78.7)	50,742 (79.0)	
Donepezil/memantine	154 (1.3)	1,118 (1.7)	
Galantamine	232 (2.0)	1,406 (2.2)	
Rivastigmine (oral)	465 (4.0)	2,451 (3.8)	
Rivastigmine (transdermal)	1,619 (14.0)	8,561 (13.3)	
Memantine use	4,064 (35.1)	26,134 (40.6)	0.10*
Benzodiazepine and/or Z drug	1,170 (10.1)	6,699(10.4)	<0.01
Antipsychotic use	-	-	-
Antidepressant use	5,760 (50.2)	33,766 (52.4)	0.05
Highly Anticholinergic Drugs (Beers)	1,017 (8.8)	6,265 (9.7)	0.03
Total number of medications [Mean (SD)]	5.0 (2.9)	5.2 (2.9)	0.07
ENVIRONMENT OF CARE			
Geographic region			0.05
Midwest	2,995 (25.9)	17,806 (27.6)	
Northeast	2,289 (19.8)	12,573 (19.5)	
South	5,386 (46.6)	28,578 (44.4)	
West	896 (7.8)	5,458 (8.5)	
Certified beds			0.04
<50	514 (4.4)	3,120 (4.8)	
50-99	3,141 (27.2)	18,406 (28.6)	
100-199	6,458 (55.8)	35,221 (54.7)	
200+	1,453 (12.6)	7,668 (11.9)	
Rural/urban continuum			0.02
Urban	8,212 (71.0)	45,244 (70.2)	
Rural	2,908 (25.1)	16,815 (26.1)	
Highly rural	448 (3.9)	2,357 (3.7)	

PROVIDER SPECIALTY			
Prescriber specialty			0.02
Geriatrics	1,071 (9.3)	5,792 (9.0)	
Primary care	9,302 (80.4)	52,218 (81.1)	
Other	1,193 (10.3)	6,405 (9.9)	

*Standardized Difference ≥0.10

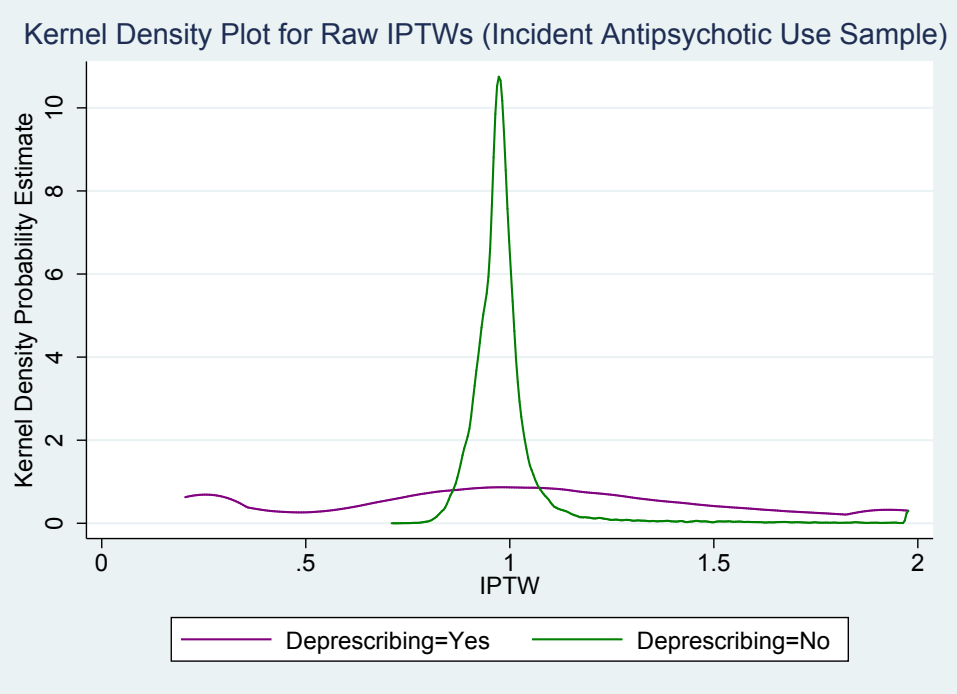


Figure C-1 – Kernel Density Plot of Raw Inverse Propensity Treatment Weights in Antipsychotic Non-users

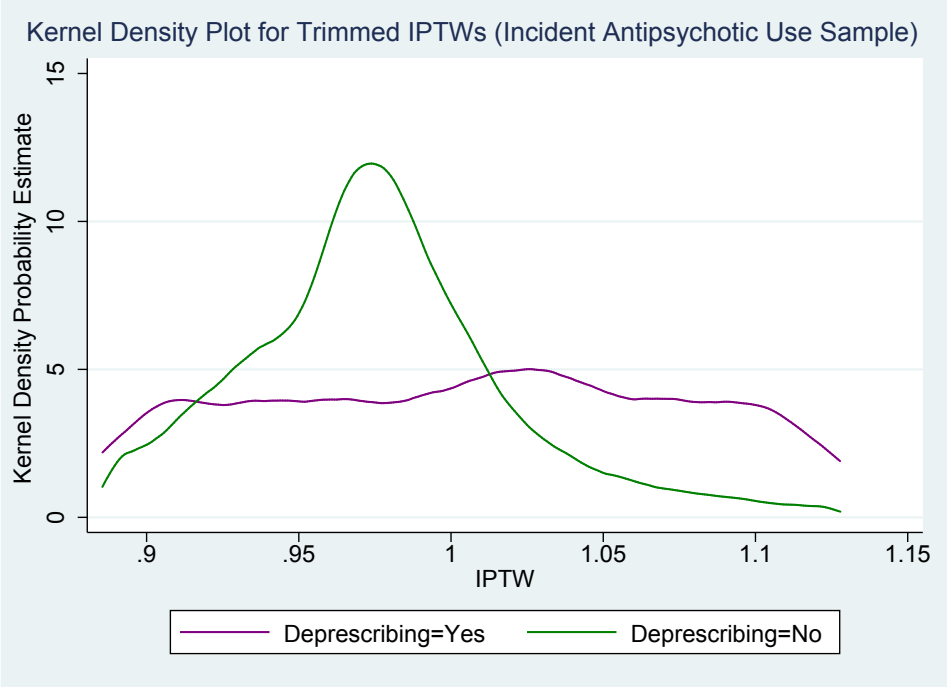


Figure C-2 – Kernel Density Plot of Trimmed Inverse Propensity Treatment Weights in Antipsychotic Non-users

Table C-2 - Weighted Sample Characteristics for Sample of Anticholinergic Users

Variable	AChEI deprescribed (n=1,215 assessments) n (%)	AChEI not deprescribed (n=12,052 assessments) n (%)	Standardized Difference
DEMOGRAPHICS			
Age in years			0.06
65-69	41 (3.4)	513 (4.3)	
70-79	296 (24.3)	2,871 (23.8)	
80-89	598 (49.2)	5,681 (47.1)	
90+	280 (23.1)	2,986 (24.7)	
Sex			0.03
Male	270 (22.3)	2,733 (22.7)	
Female	994 (77.8)	9,319 (77.3)	
Race/ethnicity			0.10*
White	969 (79.8)	10,006 (83.0)	
Black	138 (11.4)	1,046 (8.7)	
Hispanic	82 (6.8)	611 (5.1)	
Other	25 (2.1)	389 (3.2)	
Current marital status			0.03
Married	940 (77.4)	9,504 (78.9)	
Not Married	274 (22.6)	2,548 (21.1)	
CLINICAL ASSESSMENT			
Entered from			0.02
Community	238 (19.7)	2,443 (20.3)	
Hospital	834 (68.6)	8,201 (68.1)	
NH or other LTC facility	143 (11.7)	1,408 (11.7)	
MDS Assessment Type			0.05
Admission	60 (4.3)	525 (4.4)	
Quarterly	975 (70.0)	8,459 (71.2)	
Annual	246 (17.7)	2,094 (17.6)	
Significant Change in Status	112 (8.0)	796 (6.7)	
Charlson Comorbidity Index			0.06
0-1	157 (13.0)	1,641 (13.6)	
2-3	311 (25.6)	2,813 (23.3)	
4-5	302 (24.8)	2,951 (24.5)	
≥6	445 (36.7)	4,647 (38.5)	
Makes self understood			0.08
Understood	474 (39.1)	5,041 (41.8)	
Usually understood	358 (29.5)	3,420 (28.4)	
Sometimes understood	241 (19.8)	2,469 (20.5)	
Rarely/never understood	142 (11.7)	1,122 (9.3)	
PHQ-9 score [Mean (SD)]	2.35 (3.3)	2.30 (3.4)	0.01
Aggressive behavior scale [Mean (SD)]	0.56 (1.2)	0.55 (1.3)	<0.01
Activities of Daily Living Score			0.08
1 to 7	84 (6.9)	852 (7.1)	
8 to 14	188 (15.4)	1,983 (16.5)	
15 to 21	643 (53.1)	6,644 (55.1)	
22 to 28	301 (24.8)	2,572 (21.3)	
Urinary incontinence			0.07
Continent	104 (8.5)	1,127 (9.4)	
Occasionally incontinent	173 (14.3)	1,828 (15.2)	
Frequently incontinent	420 (34.6)	4,296 (35.7)	

Always incontinent	488 (40.2)	4,589 (38.1)	
Indwelling catheter	29 (2.4)	212 (1.8)	
Cancer	58 (4.8)	615 (5.1)	0.02
Heart failure	176 (14.5)	1,986 (16.5)	0.05
End Stage Renal Disease	104 (8.5)	966 (8.0)	0.02
Short of breath	92 (7.6)	927 (7.7)	<0.01
Poor appetite	172 (14.1)	1,578 (13.1)	0.03
Weight loss	89 (7.4)	766 (6.4)	0.02
Swallowing difficulty	55 (4.5)	473 (3.9)	0.03
Mechanically altered diet	589 (48.5)	6,420 (53.3)	0.09
IV/parenteral nutrition or feeding tube	28 (2.3)	330 (2.7)	0.03
Hospice or Limited Prognosis	87 (7.2)	816 (6.8)	0.02
Hospitalizations/ED Visits (90 days prior)			0.10*
None	1,060 (87.2)	10,204 (84.7)	
Cause-specific (fall, fracture, syncope)	81 (6.7)	785 (6.5)	
Other cause	74 (6.1)	1,063 (8.8)	
AChEI at index date			0.09
Donepezil	955 (78.6)	9,270 (76.9)	
Donepezil/memantine	<11 (<1.0)	187 (1.6)	
Galantamine	24 (2.0)	269 (2.3)	
Rivastigmine (oral)	49 (4.0)	517 (4.3)	
Rivastigmine (transdermal)	180 (14.8)	1,809 (15.0)	
Memantine use	475 (39.1)	5,191 (43.1)	0.08
Benzodiazepine and/or Z drug	195 (16.1)	2,215 (18.4)	0.05
Antipsychotic use	532 (43.8)	5,239 (43.5)	<0.01
Antidepressant use	854 (70.3)	8,582 (71.2)	0.02
Highly Anticholinergic Drugs (Beers)	-	-	-
Total number of medications [Mean (SD)]	7.0 (3.1)	7.3 (3.1)	0.09
ENVIRONMENT OF CARE			
Geographic region			0.04
Midwest	329 (27.1)	3,249 (27.0)	
Northeast	175 (14.4)	1,843 (15.3)	
South	619 (50.8)	6,157 (51.1)	
West	92 (7.6)	804 (6.7)	
Certified beds			0.07
<50	76 (6.3)	644 (5.4)	
50-99	358 (29.5)	3,699 (30.7)	
100-199	669 (55.1)	6,441 (53.4)	
200+	111 (9.2)	1,268 (10.5)	
Rural/urban continuum			0.01
Urban	785 (64.6)	7,800 (64.7)	
Rural	370 (30.5)	3,692 (30.6)	
Highly rural	59 (4.7)	560 (4.7)	
PROVIDER SPECIALTY			
Prescriber specialty			0.05
Geriatrics	82 (6.8)	885 (7.3)	
Primary care	1,016 (83.6)	9,857 (81.8)	
Other	117 (9.7)	1,310 (10.9)	

*Standardized Difference ≥0.10

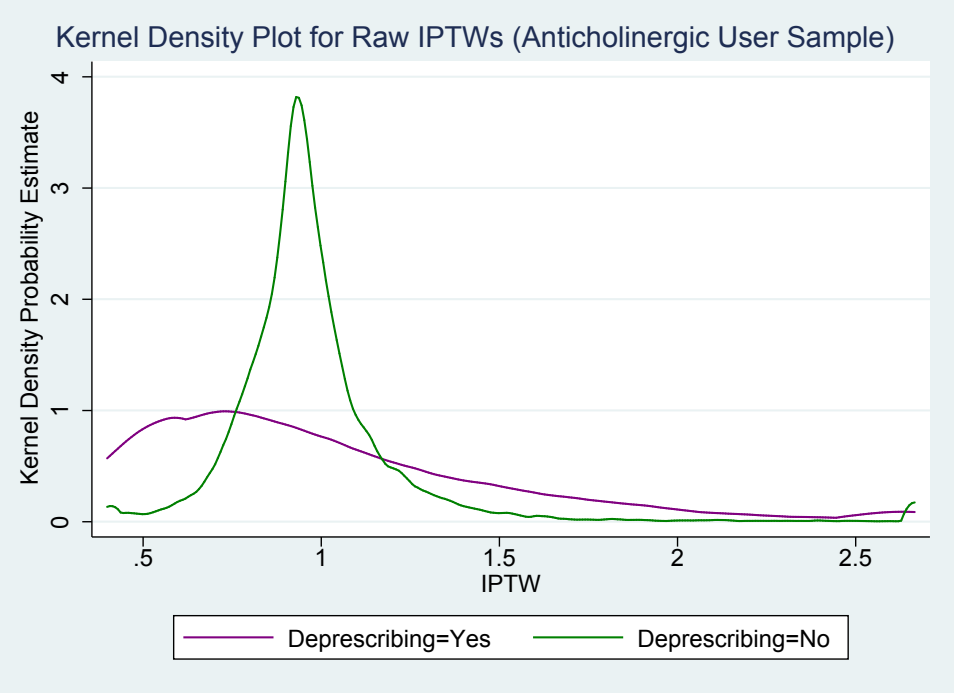


Figure C-3 – Kernel Density Plot of Raw Inverse Propensity Treatment Weights in Anticholinergic Users

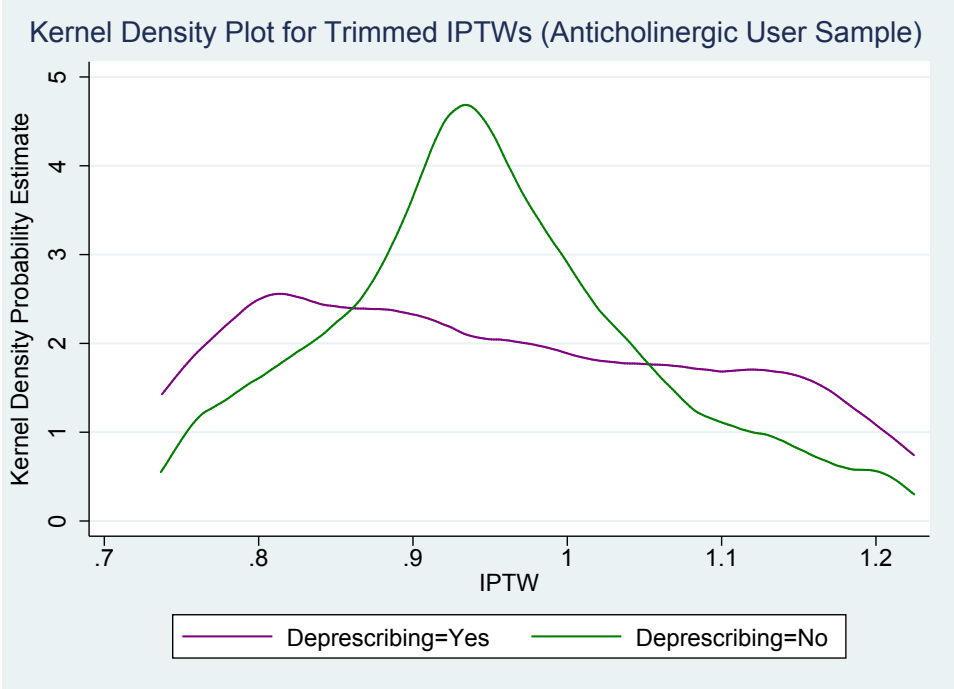


Figure C-3 – Kernel Density Plot of Trimmed Inverse Propensity Treatment Weights in Anticholinergic Users

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