PHARMACOLOGIC MANAGEMENT OF MAJOR NEUROCOGNITIVE DISORDERS IN THE UNITED KINGDOM: A POPULATION-BASED DRUG UTILIZATION STUDY

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ABSTRACT

Background: Major neurocognitive disorders (MNCD) affect 1 in 11 persons over age 65. Cholinesterase inhibitors (ChEIs, i.e. donepezil, galantamine, and rivastigmine) and memantine are the only approved drugs for the management of MNCD in both the United Kingdom (UK) and Canada. The objective of this thesis was to describe the sex, age, and clinical characteristics associated with MNCD drug utilization, and to examine how prescription patterns vary with these characteristics.

Methods: I assembled a retrospective, population-based inception cohort of all patients aged 65+ years with a new diagnosis of MNCD between 1997 and 2017 in the Clinical Practice Research Datalink, a primary care database with 15 million patient records from over 700 primary care practices in the UK. Patients were followed from MNCD diagnosis until the date of departure from the general practitioner practice, death, or March 2017. MNCD drug utilization patterns included time from date of diagnosis to medication initiation, switches, adherence and persistence, which were described overall, by sex, age group (65-74, 75-84, 85-94, 95+) and MNCD subtype (Alzheimer's, vascular, mixed, other [dementia with Lewy bodies, frontotemporal and Parkinson's] and non-specific). Associations between patient characteristics and drug initiation, switches, discontinuation and non-adherence were compared using Cox proportional hazards regression models, presented as hazard ratios (HR) with 95% confidence intervals (CI), adjusted for relevant demographic and clinical covariates.

Results: A total of 91,025 patients with MNCD were identified, among whom 25,071 (28%) received at least 1 MNCD drug prescription during follow-up and 13% of initiators switched to a second MNCD drug. Persistence was low (82% after the first trial, 56% after 6 months, 19% after 2 years), and adherence was modest among those who were persistent (53% at 2 years). Compared to male patients, female patients were more likely to initiate treatment with donepezil (adjusted HR=1.10, 95% CI 1.07-1.14), less likely to discontinue treatment with donepezil (adjusted HR=0.96, 95% CI 0.93-0.99) and less likely to become non-adherent (adjusted HR=0.91, 95% CI 0.87-0.96) to donepezil treatment. As compared to patients diagnosed at age 65-74, those diagnosed over age 95 were more frequently prescribed memantine (28%, versus 9%), less likely to switch medications (adjusted HR=0.25, 95% CI 0.23-0.28), were less persistent and had a higher rate of non-adherence. There were observed differences among the 5

dementia subtypes with respect to MNCD treatment initiation, switches and persistence but not adherence.

Conclusion: In this population-based inception cohort, the largest MNCD primary care drug utilization study conducted to date, MNCD drug utilization varied by sex, age and MNCD subtype.

RÉSUMÉ

Contexte : Chez les personnes de 65 ans et plus, les troubles neurocognitifs majeurs (TNM) touchent 1 sujet sur 11. Les inhibiteurs de la cholinestérase (c.-à-d. donépézil, galantamine et rivastigmine) et la mémantine sont les seuls médicaments approuvés pour la prise en charge des TNM au Royaume-Uni (R.-U.) et au Canada. Cette thèse vise à décrire le genre, l'âge et les caractéristiques cliniques associés à l'emploi des médicaments pour les TNM, ainsi qu'à examiner comment les schémas de prescription varient en fonction de ces caractéristiques.

Méthodes : À partir de la *Clinical Practice Research Datalink*, une base de données sur les soins primaires qui comporte 15 millions de dossiers de patients provenant de plus de 700 pratiques de soins primaires du R.-U., j'ai réuni une cohorte rétrospective populationnelle formée de tous les patients âgés de 65 ans et plus, ayant reçu un nouveau diagnostic de TNM entre 1997 et 2017 et qui étaient suivis depuis le diagnostic de leur maladie. Les patients ont été suivis entre le moment de leur diagnostic de TNM et l'arrêt du suivi par leur omnipraticien, leur décès ou le mois de mars 2017. Les schémas d'utilisation des médicaments pour les TNM incluaient : délai entre la date du diagnostic et l'instauration du traitement médicamenteux, passages à d'autres médicaments, observance et persistance. Ces schémas ont été décrits pour l'ensemble de la population et selon le genre, le groupe d'âge (65 à 74 ans, 75 à 84 ans, 85 à 94 ans, 95 ans et +) et le sous-type de TNM (maladie d'Alzheimer, vasculaire, mixte, autre [démence à corps de Lewy, frontotemporal et maladie de Parkinson] et non spécifique). Les associations entre les caractéristiques des patients et l'instauration du traitement médicamenteux, les passages à d'autres médicaments, l'arrêt du traitement et la non-observance ont été comparées au moyen de modèles de régression des risques proportionnels de Cox et présentées sous forme de rapport des risques instantanés (RRI) avec intervalles de confiance (IC) à 95 %, ajustées en fonction des covariables démographiques et cliniques pertinentes.

Résultats : Au total, 91 025 patients atteints de TMN ont été repérés; 25 071 (28 %) d'entre eux avaient reçu au moins 1 ordonnance de médicament pour les TNM pendant le suivi, et 13 % étaient passés à un second médicament pour les TNM. La persistance était faible (82 % après le premier essai, 56 % après 6 mois et 19 % après 2 ans), et l'observance était élevée chez les patients affichant une persistance élevée (77 % à 2 ans). Comparativement aux hommes, les femmes étaient davantage susceptibles de recevoir un traitement avec le donépézil (RRI

ajusté : 1,11; IC à 95 % : 1,07 à 1,14), moins susceptibles d'arrêter le traitement avec le donépézil (RRI ajusté : 0,96; IC à 95 % : 0,93 à 0,99) et moins susceptibles d'être non observantes (RRI ajusté : 0.91, IC à 95 % : 0,87 à 0,96) au traitement avec le donépézil. Comparativement aux patients diagnostiqués entre 65 et 74 ans, les patients diagnostiqués après 95 ans avaient reçu plus fréquemment de la mémantine (28 % p/r à 9 %), étaient moins susceptibles de passer à un autre médicament (RRI ajusté : 0,25; IC à 95 % : 0,23 à 0,28), affichaient moins de persistance et présentaient un taux plus élevé de non-observance. Des différences ont été observées entre les 5 sous-types de démence quant à la prescription de médicaments pour les TNM, aux passages à d'autres médicaments et à la persistance, mais pas en ce qui a trait à l'observance.

Conclusion : Dans cette cohorte populationnelle de patients suivis depuis le début de leur maladie, qui constitue la plus vaste étude sur l'usage de médicaments pour les TNM en soins primaires menée à ce jour, l'utilisation de ces médicaments variait en fonction du genre et de l'âge des patients, et du sous-type de TNM.

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LIST OF ABBREVIATIONS

ACh	Acetylcholine
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's disease Assessment Scale-cognitive
BMI	Body mass index
ChEI(s)	Cholinesterase inhibitor(s)
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
GP	General practitioner
HR	Hazard ratio
MMSE	Mini-Mental State Examination
MNCD	Major neurocognitive disorders
MPR	Medication possession ratio
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMDA	N-methyl D-aspartate
NPS	Neuropsychiatric symptoms
OR	Odds ratio
PDC	Proportion of days covered
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
SD	Standard deviation
SMD	Standardized mean difference
UK	United Kingdom

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PREFACE

The following thesis follow a manuscript-based format.

CONTRIBUTIONS OF AUTHORS

In her role as an MSc candidate and as first author of the enclosed manuscript, Kayte Andersen was involved in all aspects of the research study. In collaboration with her thesis supervisors, Drs. Machelle Wilchesky and Kristian Filion, Kayte assisted with the development and submission of the protocol to the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink. She was also responsible for study coordination, data management (under the supervision of an experienced data analyst), creating operationalized variable definitions, programming and statistical analysis of all primary data, drafting and revising the enclosed manuscript and corresponding thesis.

Dr. Machelle Wilchesky, as primary supervisor, and Dr. Kristian B. Filion, as co-supervisor, were instrumental in the completion of this thesis. Both supervisors aided in developing the research topic and contributed to data acquisition, study design, the analytic approach, and interpretation of data.

CONFERENCE PRESENTATIONS

The research was accepted for oral presentation at:

- McGill Family Medicine Research Symposium on May 4, 2017 in Montreal, QC.
- 3-Minute Thesis Competition, Department of Epidemiology, Biostatistics and Occupation Health at McGill University on December 6, 2017 in Montreal, QC.
- McGill Family Medicine Research Symposium on May 30, 2018 in Montreal, QC.
- Alzheimer's Association International Conference on July 24, 2018 in Chicago, IL, United States of America.

The research was accepted for poster presentation at:

- North American Primary Care Research Group on November 20, 2017 in Montreal, QC.
- McGill University's Department of Epidemiology, Biostatistics and Occupational Health Research Day on March 16, 2018 in Montreal, QC.

CHAPTER 1: BACKGROUND

Major neurocognitive disorders (MNCD), formerly known as dementia, is a syndrome, or a group of symptoms, that represent a substantial yet insidious cognitive decline that interferes with independence[1]. It is estimated that 35,600,000 people worldwide have MNCD. Due to an increased awareness and diagnostic capability, coupled with the aging population, the prevalence of MNCD is expected to double every 20 years[2,3]. Referrals to old age psychiatry specialists and geriatricians are on the rise[4], and the number of memory clinics has also increased[5].

1.1 DIAGNOSIS AND NATURAL HISTORY OF MNCD

The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) defines MNCD as including the following subtypes: MNCD due to Alzheimer's disease (AD), vascular MNCD, MNCD with Lewy bodies, frontotemporal MNCD, MNCD due to Parkinson's disease and MNCD due to multiple etiologies (formerly mixed dementia)[6]. The most common subtype is AD[2] (approximately 60% of MNCD cases), a progressive, degenerative illness that specifically affects areas of the brain responsible for thought, memory and language. AD is most often diagnosed according to standard clinical criteria, last updated by the National Institute of Aging in 2011[7], which include impairments in 2 or more areas of cognition[8]. AD can only be formally diagnosed, however, by histopathology examination on autopsy or biopsy, and the vast majority of cases are diagnosed without invasive tissue examination and thus are considered "probable AD" or "possible AD"[8]. Laboratory tests and imaging, such as magnetic resonance imaging, can be used to rule out other causes of cognitive decline such as brain tumors.

As MNCD progresses, mental abilities, emotions, behavior and physical functioning become affected[9]. Functional decline leads to a decreased quality of life[10], increased need for formal care and institutionalization costs[11,12], as well as an increased need for informal care (with higher caregiver burden in the case of rapid decline)[13,14]. Disease management goals vary by disease severity: in mild disease, pharmacologic treatments aim to reduce cognitive decline; in moderate disease, strategies are employed to control neuropsychiatric symptoms (NPS) and delay nursing home placement; and in severe disease, behavior management and a 'comfort care' approach are recommended[15].

Patients with MNCD survive on average 8 years after diagnosis[16]; exact duration of survival depends heavily on age at diagnosis, sex, disease severity and other factors[17]. From 2000 to 2008, there was a 66% increase in deaths directly related to MNCD in North America. MNCD is the sixth leading cause of death in North America, but is the only among the top ten that cannot be prevented, delayed or cured[18].

1.2 CLINICAL CONTEXT OF MNCD

Worldwide, the point prevalence of MNCD in a community-only setting among patients over 60 years old is approximately 40.2 per 1000 persons, with higher rates in North America (103.6 per 1000 persons) than Europe (31.3 per 1000 persons) or other continents. The incidence rate of AD in the United Kingdom (UK) is approximately 11.1 per 1000 person-years, which is lower than the global average incidence of 15.8 per 1000 person-years[19]. Incidence increases with age and is more common in women (in the UK 13.3 per 1000 person-years vs 7.0 per 1000 person-years)[20]. An estimated 61% of people with MNCD in the UK present to their general practitioner complaining of memory problems[21]; the rest present to memory clinics with specialists, provided by the National Service Framework for Older People[21]. Patients with MNCD should only be referred to a memory clinic in cases where "the diagnosis is uncertain, if certain behavioral and psychological symptoms are present or if there are safety concerns with anti-NCD medications, in accordance with local protocols"[21]. Thus, the majority of MNCD management and treatment in the UK is done in a primary care setting. This is not unlike the MNCD context in Canada, where a shift from long-term care to community-based care has been noted[22], and guidelines from the 2012 Canadian Consensus Conference on Dementia suggest that MNCD treatment is the responsibility of primary care[23].

1.3 MEDICATIONS APPROVED FOR MNCD

Cholinesterase inhibitors (ChEIs) and memantine are currently the only approved medications for MNCD (Table 1.1). Uptake of these medications has been rapid[21]. Canadian[24] and European[21] guidelines recommend a trial of ChEIs in mild to moderate MNCD for a minimum of 6 months, with regular monitoring for side effects and effectiveness. While these medications aim to manage symptoms of the disease, they have no substantial impact on disease course and they offer no cure. Due to the degenerative nature of the disease, a successful medication is one which reduces or delays disease symptoms as compared to a control group. While most medications show statistically significant improvement on MNCD-specific measurement scales, the clinical importance of these results on daily life is less clear[25-27]. It has been proposed that the medications work well for some patients but do not work at all in others, thus showing a dilution of effect in statistical analyses[28]. The following literature review and study will focus on the use of these medications in the UK.

Table 1.1: Overview of MNCD drugs

Drug (UK trade name)	Drug type	Mechanism of action	Dose	Route	MNCD stage	Regulatory approval		
						European Medicines Agency	Food and Drug Administration (US)	Health Canada
Donepezil (Aricept®)	ChEI	Delays acetylcholine breakdown when released into synaptic clefts	5-10 mg	Tablet	Mild-moderate	1996	1996	1997
			23 mg	Tablet	Severe	Not approved	2010	Not approved
Galantamine (Reminyl®)	ChEI	Inhibits acetylcholinesterase, while stimulating nicotinic acetylcholine receptors to release more acetylcholine	4-24mg, once or twice daily	Tablet	Mild-moderate	2000	2001	2000
Rivastigmine (Exelon®)	ChEI	Inhibits acetylcholine and butyrylcholine action	1.5-12mg	Tablet	Mild-moderate	1998	2000	1999
			9.4mg/24 hour	Transdermal patch	Mild-moderate	2006	2007	2008
			13.3mg/24 hour	Transdermal patch	Severe	2007	2007	2008
			2 mg/mL	Oral solution	Mild-moderate	2009	Not approved	2002
Memantine (Axura®, Ebixa®)	N-methyl D-aspartate receptor antagonist	Regulates glutamate activation and blocks glutamatergic toxicity	5-20mg	Tablet	Moderate – severe	2002	2003	2004

CHAPTER 2: LITERATURE REVIEW

2.1 CHOLINESTERASE INHIBITORS

2.1.1 PHARMACOLOGIC PROFILE OF CHOLINESTERASE INHIBITORS

In 1974, Drachman proposed the cholinergic hypothesis[29], whereby reduced acetylcholine (ACh) transmission in the brain causes the memory and learning deficits seen in AD. The hypothesis was supported by several subsequent studies, which found pronounced deterioration in basal[30] and rostral[31] forebrain cholinergic corticobasal projections[32], marked decreases of cholinergic cell bodies in the nucleus basalis, and degeneration of the hippocampus. These areas of the brain represent locations for ACh production[33,34], as well as short-term and spatial memory[35,36]. Furthermore, pre-clinical and clinical studies with cholinergic antagonists found significant memory deficits in subjects[31]. There appears to be a dose-response relationship, with more substantial degeneration found in those with more advanced cognitive deficits[37].

ChEIs were developed to prevent the breakdown of choline and increase cholinergic transmission in the brain. There are 2 main cholinesterase enzymes in the body: acetylcholinesterase in the brain, and butyrylcholinesterase in the periphery. All ChEIs are ACh-specific, and rivastigmine has an additional mechanism of butyrylcholinesterase inhibition. Beyond symptomatic control, there is emerging evidence that ChEIs may also help preserve regional blood flow[38,39] and reduce metabolic demands[40,41].

Tacrine was a first-generation ChEI. In 1994, a meta-analysis of 7 studies found "insufficient evidence to show significant benefit on cognitive or behavioral measures", while also reporting that 6 out of 7 included studies showed elevated alanine aminotransferase and other hepatic abnormalities[42]. Concerns about hepatotoxicity, coupled with low efficacy, limited the clinical utility of this medication[43] and ultimately led to tacrine manufacturing discontinuation in 1996.

Discussed below are the 3 second-generation ChEIs currently approved for MNCD: donepezil, galantamine and rivastigmine. Most clinical trials in MNCD have been placebo controlled; there are only a handful of head-to-head comparisons. High-quality RCTs and meta-

analyses have produced conflicting results as to whether significant differences in efficacy[44-49] or safety[46] between the 3 ChEIs exist; in general, shorter studies appear to show a superiority of donepezil that is lost after 3 months of follow-up[50].

2.1.1.1 Pharmacologic profile of donepezil

Donepezil (Aricept®) is a reversible highly-selective ChEI that prevents ACh degradation at the synaptic cleft by inhibiting acetylcholinesterase, thereby facilitating cholinergic transmission. Donepezil is approximately ~100% bioavailable, reaching peak concentration in 3-4 hours with a half-life of 70 hours[51]. Donepezil is metabolized by the liver, and excreted in urine. Standard doses are 5 and 10 mg once per day. In the UK, only oral capsules, liquid suspensions and rapidly-dissolving tablet formulations are available; in Japan, jelly and transdermal formulations have been approved to increase feasibility of administration[52]. A 23-mg formulation for severe MNCD is available in the United States and several Asian countries, but is not approved in Europe nor Canada.

2.1.1.2 Pharmacologic profile of galantamine

Galantamine (formerly Reminyl®, changed in the US to Razadyne® in 2005 to avoid confusion with the diabetes medication Amaryl®) is both an acetylcholinesterase inhibitor and an allosteric ligand potentiator of the nicotinic ACh receptor to increase ACh release[53,54]. Galantamine has approximately 90% oral bioavailability, reaching maximal concentration the fastest of the ChEIs (in 1 hour) with a half-life of 7 hours. Galantamine is metabolized in the liver, by the cytochrome P450 2D6 and 3A4 isoforms, and is excreted in urine[55]. Galantamine is available in 4, 8, 16 and 24mg formulations in tablets, solutions and extended-release capsules; several generics have been approved. Approved maintenance doses range from 8-24mg[56]. Twice daily administration required with immediate-release options makes the feasibility of administration more challenging than extended-release formulations.

2.1.1.3 Pharmacologic profile of rivastigmine

In additional to traditional acetylcholinesterase inhibition, rivastigmine (Axura®, Ebixa®) is also a butyrylcholinesterase inhibitor, which is the main cholinesterase enzyme in key regions of the brain (hippocampus, thalamic nuclei and amygdala) affected by MNCD[57], and in the periphery as the main cholinesterase in blood. Rivastigmine has pseudo-irreversible effects on both cholinesterases that lead to longer enzyme inhibition than other ChEIs[58]. Importantly,

rivastigmine is metabolized by esterases and excreted by the kidneys; the extrahepatic metabolism decreases the likelihood of interactions with other medications and comorbid conditions[59].

Rivastigmine is available as 1.5-12mg capsules, usually administered twice daily, 2mg/ml oral solutions, and as 4.6 mg/24hr, 9.4mg/24hr or 13.3mg/24hr transdermal patch. The patches, while only available in daily formulations rather than extended release, offer an advantage over the oral formulations which require multiple administrations throughout the day. Greater than 90% of rivastigmine patch users report no or limited skin irritation from use[60], which is excellent compared to other prescription patches available for other diseases[61].

Rivastigmine patches were developed and approved in the 2000s, to circumvent the gastrointestinal side effects seen with capsule administration[62] by 2 mechanisms. Firstly, they deliver a continuous dose that leads to less variability in medication concentration over the day, with the peaks and valleys from metabolism of oral medication concentration leading to the increase in ACh known to cause gastrointestinal side effects[63]. Secondly, the transdermal administration bypasses the first pass effect, where an oral medication is metabolized by the gastrointestinal system, and thus reduces gastrointestinal side effects[61,64]. A 2015 Cochrane Review[65] found: 1) fewer adverse events occur with patch formulations; 2) both capsules and patches show similar efficacy on cognition, function and global impressions of change, and 3) no significant effects on behavior. The transdermal patches have shown a dose-response effect, with improved benefits on cognition seen at 13.3mg vs 9.4mg formulations[66-68]. The low-dose patch is equivalent in efficacy to the highest dose capsules, and the highest dose patch is superior in efficacy to the low-dose patch[69]. Importantly, patches show gastrointestinal side effect incidence equivalent to placebo and significantly lower than capsules (6.2% vs 17.0% vomiting, 7.2% vs 23.1% nausea)[70], indicating a superior tolerability profile with equivalent or superior efficacy[61,69-72]. It is important to remove the previous day's patch before administering a new one, as overdoses have been reported from failure to remove old patches[73].

2.1.1.4 Other uses of ChEIs

ChEIs have been investigated, but not approved for use, in other indications.

Table 2.1 Non-approved indications for ChEIs

Drug	Condition for which treatment is not an approved indication
Donepezil	Vascular MNCD[74], mild cognitive impairment, attention deficit hyperactivity disorders[75], migraine
Galatamine	Mild cognitive impairment[76-78], vascular MNCD, tardive dyskinesia, attention deficit hyperactivity disorder, post-traumatic headache, postoperative delirium, depression, Tourette's syndrome, bipolar disorder, impaired cognition in schizophrenia, stroke, chronic fatigue, fibromyalgia, nicotine or cocaine cessation aid[79]
Rivastigmine	Vascular MNCD[80-82], Down's syndrome, supranuclear palsy, delirium, traumatic brain injury, cocaine dependence

2.1.2 Efficacy and effectiveness of ChEIs

While many trials do show a statistically significant benefit to ChEI monotherapy, these observed benefits are rarely clinically relevant. Specifically, most ChEI efficacy trials, comparing to placebo, and effectiveness cohorts, comparing to untreated controls, show 2-3 points of superiority over placebo on the 70-point Alzheimer's Disease Assessment Scale-cognitive (ADAS-Cog)[83] after a minimum of 6 months of treatment[26,44,84-90]. These results have been shown in mild-moderate[91-98] and severe disease[99,100], which appear to persist over months of treatment[101,102]. However, this represents a less than 10% change, within the test-retest error of the scale, which fail to meet the minimum definition of response[44]. All three major medication regulatory agencies (European Medicines Agency, Health Canada, Food and Drug Administration) use the same definition of a "cognitive responder", which was developed by expert panel in 1989[26]: an individual who has undergone a clinically-relevant ADAS-Cog improvement of at least 4 points[103,104]. There is a dose-response relationship seen where higher doses have larger effects, but even the highest doses produce an effect size (d) of 0.28, which is considered "modest"[105]. Furthermore, most trials show 6-12 weeks of improvement in

comparison to placebo; after 12 weeks, scores fall parallel to those of placebo groups, and by 24 weeks scores return to baseline values. A landmark systematic review, conducted in 2005 without industry sponsorship, concluded that "Recommendations for the use of ChEIs do not seem to be evidence based. Benefits measured on rating scales were minimal. The methodological quality of the available trials was poor"[26]. Thus, existing evidence fails to show a clinically meaningful benefit of ChEIs treatment on cognition.

ChEIs have stronger benefits on functional outcomes, which are often referred to as activities of daily living. These drugs show stronger magnitude of benefit[106,107], but results from functional outcome scales (e.g., Bristol ADL Scale, ADCS-ADL, Interview for Deterioration in Daily living activities in Dementia, Disability Assessment for Dementia, Alzheimer's Disease Functional Assessment and Change Scale, Progressive Deterioration Scale) were found to be less consistent[89,108]. It is difficult to interpret function as a measurement of efficacy or effectiveness, as it is not widely used as a primary outcome in MNCD trials[108]. Furthermore, the magnitude of functional improvement does not return the individual back to pre-diagnosis levels of capacity (such as the ability to manage personal finances or drive)[44,109]. Additionally, global clinical change measures could be masking improvements in subdomains, like behavior control[27].

ChEIs have also been used for management of neuropsychiatric symptoms (NPS). Greater than 80% of MNCD patients will experience MNCD-related NPS[110-112], most commonly agitation or aggression (50%) and irritability (45%)[113]. Other MNCD-related NPS include verbal aggression, hallucinations, delusions, dysphoria or depression, anxiety, disinhibition, euphoria, apathy and aberrant motor behavior. MNCD-related NPS are assessed using the Neuropsychiatric Inventory[114], which measures caregiver-reported frequency and severity of symptoms. NPS most commonly present when patients are still in the home setting, and increase in frequency and severity with disease progression but eventually stop when disease worsens towards the end of life[110]. NPS are known to increase stress in both formal and informal caregivers, which are important drivers for transfers to nursing homes[115]. A 2009 systematic review found that only 3 of 14 published studies report significant improvements in MNCD-related NPS with ChEIs (9 studies with donepezil[86,87,116-122], 3 galantamine[92,97,123] and 2 rivastigmine[70,124]) on MNCD-related NPS[125]; specifically, the depression, anxiety and apathy domains are improved by ChEI administration[120]. These results should be interpreted with

caution, as study participants often have low symptom prevalence at baseline, limiting signal detection ability, and MNCD-related NPS assessment is often a secondary outcome. Rivastigmine appears to be the most effective choice for the management of behavioral symptoms, possibly due to the mechanism of action on 2 different cholinesterases[126]. MNCD patients with hallucinations, as compared to MNCD patients without hallucinations, respond better to rivastigmine[127,128]; related, rivastigmine treatment has been shown to reduce concomitant use of antipsychotic medication use[129].

Four studies have examined the effect of ChEIs on patient quality of life. ChEIs could improve quality of life by extending independence, thereby delaying institutionalization. Two studies found no difference between donepezil and placebo[130,131], 1 cross-sectional study found a statistically significant but clinically unimportant effect (10 points of improvement on a 350-point scale)[132], and the fourth paradoxically found a benefit of placebo with a deterioration in the donepezil group[133]. Caregiver quality of life is also important in MNCD, given the high burden and long duration of disease. The AD2000 trial found no difference in caregiver quality of life, as measured using the 30-point General Health Questionnaire, between medication and placebo groups as well[119]. In short, there is no existing evidence that ChEIs improve quality of life of MNCD patients[134] or their caregivers[135,136].

An important theoretical benefit of ChEI therapy is the possibility of delaying long-term care placement[137], which would both improve quality of life and lead to significant savings in healthcare costs[138,139]. However, most studies on this topic have been of low quality. One nonrandomized trial by Geldmacher and colleagues compared groups that were adherent versus non-adherent to their ChEIs, defined as >80% of prescribed doses taken, and reported that donepezil delayed nursing home placement in the adherent group by 1-2 years, as compared to the non-adherent group[140]. However, several letters to the editor were subsequently published criticizing the Geldmacher study for significant, yet unreported, differences between groups (the adherent group were more likely male and more likely to have a spouse-caregiver, both of which are known to improve adherence), a “lack of a detailed analysis plan, resulting, in reality, in data dredging”[141], and “an effect size (RR=0.380, 95% CI 0.282-0.512) that would defy plausible biologic mechanisms”[141].

Another cohort with median of 4.3 years of follow-up showed a significant delay (RR=0.33, 95% CI 0.57–0.70, p=0.004) to institutionalization, but not death[142,143]. However, this study has also been criticized for several important methodologic limitations. First, the authors used historical controls, which was likely inappropriate given the changes of MNCD treatment with calendar time. Second, there was a strong potential for information bias as participants had access to care at a specialized memory disorder clinic in the United States. Specialized clinic patients tend to be followed more frequently and, potentially, would have better medication management. Third, there were important systematic differences between included and excluded participants (n=943, and n=596 without follow-up beyond consult, respectively), in that those who were excluded were significantly older, had less education, were more likely to be African American, had different medication use profiles, and had more advanced disease. Fourth, there was significant, yet unaccounted for, confounding by indication where patients with more aggressive disease received more aggressive treatment regimens. Lastly, the use of a stepwise method for estimating a proportional hazards model chooses statistically-significant confounders rather than select by theoretical or empirical evidence of importance.

In summary, most higher-quality studies have failed to find significant delays to institutionalization[119,144,145]. A recent longitudinal study found functional decline to be the strongest predictor of institutionalization. Thus, ChEIs may be delaying institutionalization indirectly, by slowing functional decline[106].

2.1.3 Safety of cholinesterase inhibitors

It is important to consider the risks associated with any treatment. While increased ACh in the brain is therapeutic in the treatment of MNCD, excess peripheral ACh can lead to hyperactivation of the parasympathetic nervous system, representing the mechanism behind most ChEI side effects[33]. These include increased salivary gland secretion, decreased heart rate (bradycardia)[146] and contraction[147,148], syncope and atrioventricular block[149], bronchial constriction, increased insulin secretion, increased intestinal tone and motility, and urinary incontinence due to sphincter relaxation[150]. A 2015 pharmacovigilance study[151] analyzing the VigiBase, a World Health Organization International Drug Monitoring Program database of 58 countries, found that 15.9% of reported adverse ChEI reactions were cardiovascular and 11.7% were gastrointestinal. Additionally, a larger percentage (31.4%) were neuropsychiatric, but given

the nature of pharmacovigilance data, it is not possible to determine if these were true medication-related events or if these events were result of protopathic bias, where an individual shows early symptoms related to an outcome, for which the medications were initially prescribed. The VigiBase data are interesting given their scope regarding time and countries included, but have important limitations: 1) do not allow for an estimation of incidence, given that there is no data available on exposed but unaffected patients, and 2) the spontaneous nature of voluntary reporting is known to be an underestimation. As a result, pharmacovigilance data can be considered as hypothesis-generating for pharmacoepidemiologic studies. A second pharmacovigilance analysis of the Canadian and American reporting databases found a disproportionately higher rate of death in rivastigmine as compared to the other ChEIs[152].

Serious adverse events, defined as a treatment-related diagnosis, hospitalization or death, arise from direct cholinergic effects[153] or via increased vagal tone[154]. Caution regarding ChEIs use is currently advised in patients with sick sinus syndrome and other bradyarrhythmias[155,156], chronic obstructive pulmonary disease or asthma, urinary retention, and in those with a history of peptic ulcer; absolute contraindications include severe liver impairment and end stage renal disease[157]. Available safety data have been from relatively small, short duration trials, with relatively healthy patients[44], while patients with MNCD seen in clinical practice often have more complex medical illness and are arguably at greater risk for side effects and pharmacologic interactions[89]. Additionally, there is evidence of suboptimal reporting of adverse events[44,158,159]. To the extent that safety affects drug utilization, a challenging drug safety profile could lead to decreased and shorter duration utilization.

2.2 MEMANTINE

2.2.1 PHARMACOLOGIC PROFILE OF MEMANTINE

In contrast to the ChEIs, memantine (Axura® or Ebixa®) is a moderate affinity open channel N-methyl D-aspartate (NMDA) receptor antagonist. Memantine mimics magnesium by holding the NMDA receptor in an open configuration[160], thereby preventing calcium-mediated neurotoxicity thought to be involved in later stages of MNCD[161-165]. Memantine is available in 5mg tablets, with a maximum approved daily dose of 20mg (often administered as 10mg twice daily)[56]. Bioavailability is approximately 100%, with wide distribution throughout the body and

plasma protein binding of 45%. Maximal medication concentration is reached in 3-7 hours, with a half-life of 60-80 hours. Memantine undergoes minimal hepatic metabolism, and is excreted mostly unchanged in urine[166].

Memantine has also been studied, but not approved, for vascular MNCD[167,168], frontotemporal MNCD, Down syndrome[169], AIDS-related MNCD and cognitive dysfunction, autism, Asperger syndrome, glaucoma, neuropathic pain and diabetic neuropathy[170,171].

2.2.2 Efficacy and effectiveness of memantine

Memantine is approved for moderate and severe MNCD. Modest improvements in cognition[172-179], global well-being[174,180], daily function[181] and independence have been observed[180] in moderate-to-severe MNCD as compared to placebo. An open label extension of a large RCT found the clinically meaningful benefit lasted for 1 year but then was lost[182].

Memantine can be also used for MNCD-related NPS, specifically delusions, hallucinations, agitation, aggression and irritability[177,183-185]. Notably, memantine shows significant reduction in patients with existing behavioral disturbances, but also has been shown to significantly reduce incidence in patients without MNCD-related NPS at baseline[185]. The small but beneficial effects of memantine on MNCD-related NPS[116,117,186-193] are important for both the MNCD patient but also their caregiver, as uncontrolled MNCD-related NPS symptoms are a known predictor of institutionalization[194] and caregiver burnout[115,195,196].

2.2.3 Safety of memantine

Memantine is well tolerated[173,178,184] due to the strong voltage-dependency mechanism of action, which allows for rapid blocking and unblocking of the NMDA receptor and thereby reduces receptor potentiation side effects[162,197]. Dose needs to be adjusted to renal function[198]. Side effects of memantine include dizziness, headache and confusion at similar prevalence to placebo-controlled groups[56,163,172,178].

2.3 COMBINATION THERAPY

The 2 classes of medications (ChEIs and memantine) work on different pathways, and have theoretically complementary mechanisms of action[199], given the well-described interconnections between the cholinergic and glutamatergic signaling pathways[200-203]. Pre-clinical studies have shown greater cognitive improvement through the combined pathways than either alone[199]. An additional, and perhaps more important, application is that memantine increases ChEI tolerability: memantine is a 5-HT3 receptor antagonist, which can decrease the nausea that often results in ChEI discontinuation[204]. Phase I (healthy adults) and phase II (patients with AD) interaction studies have not found evidence of harmful interactions between ChEIs and memantine[205-207].

Evidence of combination therapy efficacy or effectiveness is mixed; some studies have shown favorable outcomes[143,178,208,209] while others have found null effects[210]. Evidence is building that combination therapy might be most effective during the period in which the individual progresses from mild to moderate MNCD[137,211]. Combination therapy effects, like ChEI monotherapy, wane after the first 6-12 months of administration[182,212]. One RCT of 433 patients with mild-to-moderate MNCD on any ChEI randomized participants to the addition of 20mg memantine or placebo for 24 weeks. Despite successful randomization and rigorous blinding procedures, this study[210] failed to replicate earlier findings[208] of combination therapy efficacy when comparing combination therapy to ChEI monotherapy. However, there are 4 important factors to consider which may have biased results towards the null. First, patients could be on any of the 3 ChEIs, which introduces pharmacologic heterogeneity (see sections 2.1.1.1-2.1.1.3 for details regarding different pharmacologic properties among the ChEIs). Second, patients with mild MNCD were included, but evidence is conflicting regarding memantine efficacy in mild disease and memantine is not approved for this indication. A separate sub-group analysis of this trial's data including only those with moderate to severe MNCD found significantly less functional and cognitive decline[213]. Third, the study had a relatively short study duration (6 months) compared to average disease duration (8 years). Fourth, there was a lack of statistical power. The observed effect size was 0.118, which was well below the 0.325 cutoff used for sample size calculation.

The discrepancy between the aforementioned trials results shaped the guidelines for combination therapy towards non-recommendation[214], with UK guidance documents saying "there is a lack of evidence of additional clinical efficacy compared with monotherapy"[56]. A meta-analysis which informed the British guidelines was met with much controversy, as the author did not pool cognitive or functional outcome data between the two included RCTs, and included patients with mild AD, despite the published subgroup analysis of moderate MNCD only[212]. Moreover, given that there were only 2 studies, a meta-analysis was likely not appropriate.

Shortly after the release of the 2011 UK guidelines, a second large RCT also failed to demonstrate efficacy for the addition of memantine to established donepezil therapy on both cognitive and functional autonomy measures[179]. Once again, there were important weaknesses with the study design: 1) differences in participant baseline characteristics, suggesting a failure of randomization; 2) small sample size (2x2 factorial design, with 73-76 participants per treatment arm) may have limited effect detection ability; 3) bias due to the inclusion of prevalent users and the corresponding depletion of susceptible subjects[215]. Given that the inclusion criteria required stable doses of donepezil for 3 months before study entry, patients who were susceptible to donepezil and could not tolerate the medication were excluded from the trial; and 4) high (46%) and differential participant dropout patterns, with less treatment withdrawal in the active treatment groups.

In summary, existing literature is heterogeneous with respect to efficacy and effectiveness of combination therapy. Several studies show statistically, but not clinically, significant slowing of cognitive and functional decline over several years of observation. Studies which have shown a lack of effect have suffered from serious methodologic flaws. While systematic reviews and meta-analysis of combination therapy do exist[211,213,216-218], their results are contingent on the quality of the primary trials that were included, and thus the existing body of pooled analyses are also potentially flawed.

Rates of adverse events in combination therapy are approximately that of ChEI monotherapy[213].

2.4 COST CONSIDERATIONS

The UK is a constitutional monarchy made up of four independent countries: England, Scotland, Wales (when combined, comprise Great Britain) and Northern Ireland[219]. In Northern Ireland[220], Scotland[221] and Wales[222], all prescriptions are free for all ages. In England, patients over age 60 do not pay for prescriptions[223]; thus there are no cost incentives related to medications for patients in the UK over age 60. The governments of each country are responsible for all healthcare-related and prescription medications costs.

While there are direct costs to the governmental healthcare system such as physician office visits and prescription medications, the main cost associated with MNCD is institutionalization[224]. Most pharmacoeconomic studies have found donepezil[143,225-227] to be cost-effective from the payer's perspective, where the benefit under consider is not clinical improvement or stabilization, but rather that medications may delay time to long-term care facility institutionalization[228]. Galantamine[229,230], rivastigmine[231] and memantine[232-234] are similarly considered to be cost-effective in the long-term, as they reduce total costs of patient care, improve quality of life and delay placement in long-term care facilities.

2.4.1 FORMULARY RESTRICTIONS PERTAINING TO MEDICATIONS FOR MNCD IN THE UK

In the UK, the National Institute for Health and Care Excellence (NICE) forms evidence-based health economic decisions as to which medications should be covered by the National Health Service (NHS). In 2006, NICE revised their 2001 guidelines, so as to only approve donepezil, but not galantamine or rivastigmine, and only for use in patients with moderate MNCD or MNCD with significant NPS[235]. Specifically, the 2006 guidelines stated that while ChEIs did delay cognitive impairment for up to 6 months with a small benefit, they were not cost-effective (£2.50/day, approximately $5.00 CAD in 2006) for use in patients with mild MNCD. Pfizer, the British distributor of donepezil, and Eisai, the Japanese-based manufacturer of donepezil, launched the first-ever legal challenge to a NICE decision, on the grounds of "procedural unfairness, irrationality, and discrimination"[236]. Ultimately, Britain's High Court upheld the challenge, but patients with mild MNCD who were started on ChEIs before the decision could continue their treatment[237]. In 2011, a revised guidance once again approved all 3 ChEIs for mild-to-moderate MNCD[56,238], but contained a decision of non-approval pertaining to

combination therapy, due to "insufficient evidence of additive effects". There were no major updates to medication formulary coverage in the UK from 2011 – March 2017.

2.5 FACTORS IN MNCD MANAGEMENT

In addition to cost considerations, there are several other factors that influence MNCD management. Described below are the implications of sex, MNCD subtype and age at diagnosis.

2.5.1 SEX-BASED DIFFERENCES IN MNCD

Approximately 75% of patients with MNCD are women[239-242]. The prevalence of disease may be confounded by age, due to the known longer survival among females than males. This explanation is further supported by recent data from the Framingham Heart Study, which found that males who survive past the critical middle age period, where males are known to have higher rates of cardiovascular disease and related deaths than women, have a lower risk of MNCD than females of the same age[243,244]. Additionally, there is the potential for detection bias, given that females of all ages[245] and specifically elderly women[246] are known to seek healthcare more frequently than males.

The epidemiology of MNCD may differ between males and females. Evidence of the incidence of MNCD between the 2 sexes is currently inconclusive: the large Canadian Study of Health and Aging did not find differences[247], while other international results have found females to be at higher risk[248-250]. Possible reasons for sex-related incidence differences include biological factors (sex-determining genes and hormones, specifically in brain development, structure, function and biochemistry[251]), genetic factors (higher levels of estrogen known to be an effect modifier in the apolipoprotein E4 allele-associated increased risk of the development of MNCD[252-256]) and lower education level[248,249,257-263].

Females have a longer duration of MNCD than men, perhaps due to their increased general life expectancy[264]. Females also have more aggressive disease, as evidence by autopsy findings such as faster hippocampal atrophy[265], more amyloid plaques, and greater load of neurofibrillary tangles[266].

There are well-documented differences in the ways that males and females absorb, distribute, metabolize and excrete medications[267,268]. Body weight, plasma volume, gastric

emptying time, plasma protein levels, metabolizing enzymes (specifically, the cytochrome p450 3A isoform[269-272], the predominant metabolizing enzyme class in the gastrointestinal tract), medication transporter function and clearance activity all differ between males and females[273-276]; in brief, each of these make females more susceptible. Females are also at higher risk of adverse medication reactions[277].

Sex-based analyses and treatment guidelines are an emerging area of interest, with approximately 35% of Canadian clinical practice guidelines containing sex-related diagnostic or treatment recommendations[278]. The regulatory bodies of Europe, the United States and Canada all have established initiatives to report medication data by sex. A 2013 Health Canada Guidance Document stated that "the prevalence and nature (severity) of adverse events may differ between men and women, depending on the product type and condition treated"[279]. Substantial sex differences have been observed with utilization of antidepressants, antipsychotics, antibiotics and antiarrhythmics, all medications with high prevalence of use in the elderly[280]. Furthermore, preclinical (animal) studies suggest that sex may influence the response to ChEIs, in particular via testosterone-mediation of ChEIs crossing the blood-brain barrier[281]. In the context of MNCD however, a 2017 systematic review did not find any published literature that examined treatment differences by sex[282].

2.5.2 AGE AT MNCD DIAGNOSIS

Approximately 5% of cases are diagnosed before age 65, and are considered "early onset". Early onset cases are clinically distinct from those diagnosed after age 65, and as such will not be considered in this review[283].

In general, anti-MNCD prescriptions are highest in the 75-84 and 85-94 range, but lower both in 65-74 and >95 years old[284-286]. ChEI users are younger than memantine users[284,287]. Older MNCD patients are less likely to be persistent than younger patients[288].

2.5.3 MNCD SUBTYPES

The 5 MNCD subtypes, in order of decreasing prevalence, are: AD (approximately 50%)[289], vascular MNCD (30%)[289], MNCD due to multiple etiologies (defined as the co-occurrence of both AD and vascular MNCD, 15-20%)[290], and other MNCDs (MNCD with Lewy bodies, frontotemporal MNCD and MNCD due to Parkinson's disease, combined for 5-10%)[291].

In clinical practice, it is common for an individual to be initially diagnosed as "non-specific", and then have their classification revised over time as the specific clinical characteristics of disease subtypes emerge. Similarly, MNCD due to multiple etiologies diagnoses become more prevalent later in disease trajectory, and therefore with increased age, as the person must meet clinical criteria for both AD and vascular MNCD[292,293].

ChEIs and memantine are indicated in the UK for AD and MNCD due to multiple etiologies. ChEIs, but not memantine, are indicated for MNCD with Lewy bodies and MNCD due to Parkinson's disease. Neither medication class are approved for use in vascular MNCD nor frontotemporal MNCD[294].

2.6 MEDICATION UTILIZATION PATTERNS IN MNCD

2.6.1 TREATMENT INITIATION

In the UK, 77% of ChEI prescriptions are for donepezil[56]. Despite being the only pharmacologic agents available for symptomatic control of mild-to moderate MNCD, ChEIs are used in approximately 30% of MNCD patients. Two factors have been postulated to be the reason for low-uptake: 1) concerns about interactions with other medications, given the exposure to complex polypharmacy in many elderly patients; and 2) concerns about tolerability. Qualitative interviews of a sample of 40 primary care physicians found that 82% of the physicians had negative impressions of ChEIs; specifically, that lack of knowledge and experience made ChEIs prescribing decisions challenging. However, the study also reported that these physicians felt pressured by family members to prescribe ChEIs, simply to be able to offer something.

While not officially approved for use in early stages of the disease, available data suggest that memantine is frequently prescribed in mild MNCD[295,296]. Two explanations are possible: 1) because memantine does not work via the cholinergic pathway, memantine can be used in patients who have contraindications to ChEI treatment, such as heart and lung comorbid conditions, or gastrointestinal intolerance to ChEIs; 2) physicians are using memantine as a more aggressive treatment option. It is also possible that memantine may appear to be inappropriately initiated in studies that used administrative or clinical databases that do not contain disease severity indicators, when in fact the patient's MNCD has progressed to an advanced stage.

2.6.2 TREATMENT SWITCHES

Switches from one treatment option to a second, either within class or across classes, could arise for 3 reasons: 1) lack of effectiveness; 2) intolerable side effects or an adverse event; or 3) physician decision[297]. Switching rates are highest for oral rivastigmine[298-301], similar for donepezil and galantamine[298,299,302], and lowest for transdermal rivastigmine. To date, only 1study has assessed time-dependent switching[302], and found early switches are due to treatment-related harms while later switches are due to decreased efficacy or effectiveness over time. However, this study was relatively small and did not include memantine. ChEI non-responders or partial responders can be switched to memantine with either an abrupt or stepwise discontinuation, with acceptable safety and tolerability[173,178,184,303].

2.6.3 TREATMENT ADHERENCE

Medication adherence is defined by the Strom "Textbook of Pharmacoepidemiology" as "the idea of a treatment alliance where the patient implements the provider's recommendations"[304]. The terms "compliance" and "adherence" are often used interchangeably, although compliance is the most popular term in the literature[305]. Some believe that compliance implies a judgmental framework and thus should not be used. However, the International Society for Pharmacoeconomics and Outcomes Research Adherence Working Group commissioned a systematic review which found "no authoritative evidence to support the assumption that 'adherence' is a less derogatory term or whether it is preferred by patients"[305]. The term 'adherence' will be used henceforth, to emphasize the shared decision-making process of medication decisions.

2.6.3.1 Measurement of adherence

In studies involving direct patient contact, adherence can be measured by objective (e.g., tablet counts, electronic monitoring of medication containers and medication concentrations using blood or urine tests[304]) and self-reported (e.g., patient diaries and validated questionnaires such as the Morisky Medication Adherence Scale[306]) measures. However, objective measures are time consuming, expensive and potentially invasive, while self-reported data are limited by inherent recall bias and social desirability bias, where patients may report being adherent to therapies, even when they are not, to avoid embarrassment and disappointing their doctor. In general, self-reported measures tend to over-estimate adherence, and direct measurements can

modify behavior (known as a Hawthorne effect[307]), as patients are aware they are being watched. Adherence estimates derived from clinical trials may not be applicable to real-world clinical practice, as patients who participate in trials may be more motivated to remember to take medications given financial incentives to participate in some studies[304]. Finally, evidence suggests that adherence estimates obtained from physicians are unreliable[304] given that they have been shown to produce estimates that offer no improvement over those obtained at random, and are therefore not recommended for use.

In retrospective database studies, where direct patient contact is not possible, adherence can be assessed through provider prescription records or pharmacy refill data[308]. A continuous measure of medication availability, such as the medication possession ratio (MPR), is a fraction of the number of days for which medication was dispensed divided by the total length of prescribed therapy[309]. The MPR is the most commonly used measure[297], and has been previously used in the CPRD[310], despite being sensitive to errors. Good adherence has been defined as an MPR $\geq$ 0.80 in previous MNCD[311,312] and non-MNCD studies[313], which would represent a refill of a 28-day prescription within 35 days. An important consideration is that the MPR can exceed unity, which indicates an oversupply of medication; some studies truncate the value to 1 while others use the exact value[297]. A second continuous measure indicates the proportion of days not covered by medication. It is the sum of the days without medication between refills, divided by the days between the first dispensing and the end of the last refill period. A third measure is a proportion of days covered (PDC), using a set of algorithms to avoid double-counting covered days. The PDC method is generally considered preferable over the MPR, as it provides more conservative estimates and is better suited for medication therapies with frequent switches and concomitant administration[314]. The PDC has been endorsed by both the National Quality Forum[315] and the Pharmacy Quality Alliance[316].

Measuring adherence using administrative prescription data has limitations, including the possibilities that the patient filled the prescription but never took the medication, the patient did not take the medication as prescribed, the patient has variable adherence within a treatment period, the use of sample packs which are not recorded in databases, and failure to capture in-patient prescriptions during hospitalizations[312].

2.6.3.2 Evidence of adherence in the general elderly population

Adherence is a major challenge in the management of most chronic medical conditions[317] and can be a major determinant of treatment outcome, as biologically-relevant effects will only be seen with continuous dosing regimens in chronic disease[62,318]. Studies in patients over age 60 have shown adherence rates range from 40-75%, which decrease over time in chronic disease management[319,320]. Poor adherence in the general elderly population is associated with a higher incidence of treatment and disease-related complications[321], hospitalization[322], institutionalization, disability and premature death[321]. Additionally, medication utilization is known to increase with old age[323,324], especially in females[325], and having four or more active prescriptions has been shown to reduce adherence[326]. Further challenging the probability of adherence is an increased sensitivity to side effects and adverse events, given the normal changes of aging that alter the pharmacokinetics and pharmacodynamics of medications in the body; namely, decreased renal and hepatic function, with relative increases in body fat and decreases in body water[327,328].

General barriers to adherence include: 1) patient-level factors, including patient's motivation and beliefs about their disease, disagreement with their physician's decisions, failing to fill a prescription on time, forgetting to take medication, purposefully missing doses to avoid side effects, number of chronic comorbid conditions, total number of medications currently prescribed, psychosocial factors such as educational and health literacy levels, depression or lack of support; 2) system-level factors, in particular logistical difficulty in obtaining medication from pharmacy, sporadic medication unavailability due to pharmacy stocking, cost; and 3) medication specific barriers, such as polypharmacy, medication regimen complexity, adverse effects, and inability to take medication as prescribed due to trouble swallowing[304,329,330].

2.6.3.3 Framework of key factors which impact medication adherence in patients with MNCD

It is important to distinguish the MNCD population from that of the general elderly population, as patients with MNCD have decreased decisional capacity[331,332], adherence ability due to cognitive decline, and ability to detect and communicate adverse events when occurring[333]. Thus, MNCD-specific adherence frameworks and measures are necessary. The first study to identify an MNCD-specific qualitative framework for adherence[334] elucidated both

intentional (patient and physician-level beliefs and expectations surround disease trajectory and treatment effectiveness) and unintentional factors (age-related limitations, comorbid illnesses, adverse events). However, this work was limited to ChEIs, and did not perform a comparative assessment of the relative importance of the different factors on medication adherence. Six additional studies examined patient, caregiver and prescriber perceptions of MNCD[335], but none have evaluated the impact of these perceptions on treatment adherence[336-338].

A mixed-methods systematic review[339] synthesized all available qualitative, quantitative and mixed methods studies of MNCD adherence published up to October 2013. MNCD-specific adherence factors were ultimately categorized into 5 groups: patient, patient and caregiver, caregiver, prescriber and healthcare system. The 5 domains were highly inter-related, suggesting the importance of a holistic approach to MNCD adherence. Probable facilitators of adherence include decreased functional status and increased caregiver assistance with medications (suggesting that with a loss of autonomy, increased specialized care needs introduce formal healthcare providers who can assure adherence), more frequent contact with healthcare system, positive perception of treatment effectiveness, higher levels of both education and health literacy, Caucasian race and male sex. Probable barriers to adherence include general and specific cognitive functional impairment, attitude of resisting care, living in a rural setting, decreased caregiver coping ability, adverse event(s) after medication administration, oral (rather than transdermal) rivastigmine administration, and increased medication cost burden. Upon examination of multiple studies, there was no results that could be pooled for meta-analysis.

2.6.3.4 Evidence of adherence to MNCD medications

In general, evidence pertaining to medication adherence rates by patients with MNCD suggest that adherence is suboptimal[62,318], mostly attributable to high rates of side effects, but also due to physical impairments of aging and advanced disease such as dysphagia (trouble swallowing) which can make it harder to ingest medications[62,340,341], the inherent cognitive decline of the disease[62,334,342,343], and problems with efficacy and effectiveness (see sections 2.1.2, 2.2.2 and 2.3.2). Variables associated with better adherence to MNCD medications include being male, age $\geq$ 86 years, and frequent healthcare provider contact[62,344,345]. Several studies have measured medication adherence in AD patients, ranging from 58 – 93%[298-302,311,312,344,346]. However, it is difficult to interpret these results due to significant intra-study heterogeneity with

respect to: 1) inconsistent definitions for the length of time to define discontinuation (ranges from 30-120 days); 2) heterogeneous patient populations (studies of patients in the community versus those who are institutionalized); and 3) most studies have bundled all medications together to measure adherence, despite variations in adherence between medications. Most studies did not report adherence according to MNCD subtype.

While a donepezil patch is available in Asia, rivastigmine is the only ChEI available in a once-daily patch formulation in Europe and North America. Most studies report increased adherence with rivastigmine patches over capsules[61,347-350]. Possible reasons include smooth and constant medication delivery[63,351] thereby avoiding peaks in medication concentration levels known to lead to gastrointestinal side effects[61,63-65], visual prompting from seeing the patch on the skin (as opposed to remember to take a pill)[352] and caregiver preference to administer once-daily patches over the pills which need repeated administration throughout the day[60,347,353,354].

A 2017 pragmatic randomized trial of new ChEI users warrants discussion. The trial randomized patients in a large city in the United States with a diagnosis of possible or probable Alzheimer's to each of the three ChEIs, and followed them for 18 weeks[355,356]. The primary objective was to assess caregiver-reported adherence, and results showed high prevalence of non-adherence, primarily due to caregiver-reported adverse events (73%) and cost (25%).

The validity of the study results come into question for several reasons. Firstly, inclusion criteria allowed for prior exposure to ChEIs, and did not specify a washout period duration before study enrollment eligibility. Patients were not eligible for the trial if they were currently receiving a ChEI, or if they experienced an adverse event on a previous course of ChEI. This could introduced prevalent user bias[215], a form of selection bias where the study population may be an oversampling of those patients at lower risk of discontinuation and adverse events, and thus an underestimation of harms and an overestimation of persistence. Secondly, information bias was potentially introduced as the trial was open-labelled, meaning that the study physicians were not blinded to treatment, and could change dose at their clinical discretion. Furthermore, randomization could be broken. Thirdly, by the end of study follow-up, 50% of the study population "discontinued or did not initiate the treatment they were randomized to receive in the intent to treat analysis". The intention-to-treat analysis, which is generally considered to be more conservative than an as-treated analysis, showed significant differences between groups but the

as-treated analysis did not. These results are counterintuitive, but may have arisen because the as-treated analysis is confounded by the crossovers. Fourthly, while not traditionally considered high quality measures in other clinical contexts in the literature, caregiver reports may be more relevant in the MNCD setting given the caregiver's role. Lastly, rivastigmine patches and pills were analyzed together, despite known differences in the profile of study outcomes (adherence and adverse events) across the formulations. Furthermore, galantamine at both standard doses (n=24) and extended release (n=42) was similarly analyzed as one.

The external validity, or generalizability, of the study results is similarly controversial. Firstly, there was a small sample size (n=196, randomized to three groups) for a short duration of follow-up (18 weeks). Ideally, the study would have been larger and lasted for a longer duration, to better reflect the disease under study. Secondly, restrictive inclusion criteria led to a homogenous patient population (Alzheimer's patients only, excluding related MNCDs) and pharmacologic profile (memantine and combination therapy not considered) that is not representative of that seen in everyday clinical practice. Thirdly, there was no information provided regarding time since MNCD diagnosis, which would be important as a proxy of disease severity. Lastly, the second-most common reason for discontinuation in this American cohort was cost, which is unlikely to be applicable in many jurisdictions. Thus, this study may not reliably answer questions of adherence in MNCD.

2.6.4 Treatment persistence

Medication persistence is defined as "how long the patient continues to follow the regimen"[304], and is calculated by the continuous refill sequence model (typically, failure to refill within length of last prescription plus a grace period)[357]. The NICE guidelines explicitly stipulate that "patients who continue on the medication should be reviewed every 6 months by Mini-Mental State Examination (MMSE) score and global, functional and behavioral assessment. The medication should only be continued while the patients (sic) MMSE score remains at or above 10 points and their global, functional and behavioral conditions remains at a level where the medication is considered to have a worthwhile effect"[56]. Given the drug's limited effectiveness in relieving symptoms, persistence in patients who are able to initially tolerate the drug may be discouraged after several months, as MNCD medications often fail to meet expectations among patients and caregivers[62,109].

2.6.4.1 Persistence to MNCD medications

In the published literature, ChEI persistence beyond 3 months is associated with slower rates of cognitive, functional and behavioral decline[109,358]; benefits of persistence are lost with treatment interruptions[359]. It is possible that reverse causation, whereby individuals with slower rates of cognitive decline are more able to persist to their medications, may be partly responsible for the observed phenomenon. Due to high rates of side effects and low clinical effectiveness[360], approximately 15-57% of individuals who receive a ChEI prescription will persist on therapy beyond 3 months[26,44,89,179,361], and 35-60% persist to 1 year[193,362-369]. Importantly, dropouts and withdraws are significantly more common (OR = 2.32, 95% CI 1.95-2.76) in ChEIs versus placebo groups[44].

The Cochrane review "Cholinesterase Inhibitors for Alzheimer's Disease" which included results from 13 randomized double blinded trials found that withdrawal was more common in ChEI-exposed patients rather than placebo arms of trials (30% vs. 18% respectively), with many patients dropping out due to adverse events. This finding is in direct contrast with the meta-analysis for memantine, which showed similar rates of withdrawal due to adverse events in 12 trials stratified by MNCD severity and subtype. In memantine trials, rates of withdrawals favored the memantine intervention group among the moderate-to-severe MNCD disease group (OR= 0.66, 95% CI: 0.49-0.88)[370-374].

Persistence with MNCD medications, in order of highest to lowest, is as follows: rivastigmine patch[302,375,376], galantamine[302,311,365,366,368,377,378], donepezil[44,299,365,379], rivastigmine capsules[368,378,380-384]. Specifically, the rivastigmine patch shows superior persistence than capsules due to better tolerability[342,350,351] (often, gastrointestinal tolerability[66,70,347]) and increased patient[63,347] and caregiver satisfaction[347]. In studies that did not stratify rivastigmine by patch or capsules, rivastigmine appeared to have a similar persistence profile to donepezil[379,385,386]. Combination therapy persistence rates appears to be equivalent to that of ChEI monotherapy persistence in some studies[387] , yet increased in others[208,210].

2.6.4.2 Relationship between adherence and persistence

It is important to note that rates of persistence in MNCD are considerably lower than rates reported for most chronic disease medications, and persistence is more of a challenge in

MNCD than adherence[62]. Persistence to MNCD medications decreases with age and initial disease severity[367], and is lower in males than females[365].

2.7 RATIONALE FOR PRESENT THESIS

To my knowledge, there do not appear to be any high-quality studies which examine clinical and other patient-related characteristics associated with MNCD drug utilization that compare both oral and transdermal ChEIs, memantine and combination therapy. The following 4 reasons are important justification for the present thesis:

1. RCTs include relatively healthy patients with few comorbidities and with mild to moderate MNCD. In the real-world setting, patients with AD seen in clinical practice often have more complex medical illness and are, arguably, at greater risk for side effects and pharmacologic interactions than those included in RCTs. Specific pharmacokinetic and pharmacodynamics alterations in older people with MNCD have been described elsewhere[388]. Multiple studies have shown that MNCD RCT populations do not represent real-world populations, given their multiple comorbidities, older age and rates of institutionalization[389,390]. Furthermore, participating physicians and hospitals are not representative, and prescription patterns may not be representative as well. In the case of RCTs, treatment may be dictated by the protocol. Hence, RCTs have limited generalizability, and offer limited evidence regarding medication-medication and medication-disease interactions. An unselected patient population is needed to describe MNCD prescription patterns in a real-world setting.
2. Several previous observational studies have used historical controls[142,143,209], which is problematic given the time-varying nature of medication prescription as new medications gain regulatory approval and diagnosis is happening earlier in disease progression over time.
3. To date, there are only a few studies[298-302,311,365] which describe ChEI adherence and switching. Furthermore, there is only 1 study which evaluated prescription patterns of the rivastigmine patch formulation with respect to other ChEIs[302], but this study did not include memantine. Currently, there does not appear to be any study which compares adherence, switching and persistence with each of the ChEIs, memantine and

combination therapy or population-based studies that examine the association between patient characteristics and these prescription patterns.

4. Despite clear differences in disease phenotype among men and women, a 2017 systematic review failed to find any published literature that examined MNCD treatment differences by sex, and concluded "*Observational, longitudinal studies, such as post-marketing surveillance studies, should also be analyzed with the same objective of finding out if and how sex and/or gender may affect the effectiveness and/or safety and tolerability of AD medications*"[282].

Thus, the existing body of literature fails to clearly examine patterns of MNCD therapies between the sexes, age groups and MNCD subtypes in a large-scale, unselected patient population. A high-quality population-level analysis is needed for a richer understanding of the use of MNCD medications in everyday clinical practice and the patient characteristics associated with this use, to assist physicians in their treatment decisions.

CHAPTER 3: METHODS

3.1 OBJECTIVES

3.1.1 OVERALL OBJECTIVE

The overall objective of this thesis was to describe prescription patterns of MNCD, and the patient characteristics associated with patterns of MNCD treatment.

3.1.2 SPECIFIC OBJECTIVES

3.1.2.1 Primary objective

The primary objective of this thesis was to determine if female sex was associated with initiation, switching, adherence and persistence to MNCD treatments.

3.1.2.2 Secondary objectives

Secondary objectives were:

- To determine if age was associated with initiation, switching, adherence and persistence to MNCD treatments.
- To determine if MNCD subtype was associated with initiation, switching, adherence and persistence to MNCD treatments.

3.2 HYPOTHESES

3.2.1 HYPOTHESIS, WITH RATIONALE, OF THE PRIMARY OBJECTIVE

MNCD prescription patterns will differ, after controlling for potential confounders, between females and males due to the known disease phenotypic differences between the two.

3.2.2 HYPOTHESES, WITH RATIONALE, OF THE SECONDARY AIMS

MNCD prescription patterns will differ, after controlling for potential confounders, among:

- Age groups, due to the known effect of age on general prescription patterns.
- MNCD subtypes, due to the clinical indications for MNCD medications.

3.3 STUDY DESIGN

This was a population-based, retrospective cohort of patients with a recorded diagnosis of MNCD in the Clinical Practice Research Datalink (CPRD, formerly known as the Value Added Medical Products dataset from 1987-1992 and as the General Practice Research Database from 1993-2012)[391].

3.4 DATA SOURCE

The CPRD is the most validated of all databases used for pharmacoepidemiologic studies[392,393], with over 1500 resultant peer-reviewed publications[391]. Participating CPRD general practitioners (GP) have been trained to record medical information including demographic data, laboratory results, clinical measures, lifestyle variables such as body mass index (BMI) and smoking history, recorded symptoms and diagnoses using the Read coding system (a universal classification system developed in the UK and funded by the National Health Service) and prescriptions using a standard anonymous form. Other information available in the CPRD but not relevant to this thesis include clinical measures (such as blood pressure), vaccination history, pregnancy records and laboratory test results. The CPRD contains approximately 15,000,000 patient records from 700 general practitioner practices, and has been shown to be a representative sample of the UK population in terms of age, sex, ethnicity and BMI distribution[391,392]. All prescriptions issued by the GP are recorded directly in the database, making the CPRD a comprehensive and highly valid source for pharmacoepidemiologic data. Prescriptions are organized according to British National Formulary headers and codes. Date of prescription, drug substance, strength, and route of administration are available. Prescription quantity, duration and dosage instructions are poorly recorded, and prescriptions from secondary care or over-the-counter drugs are not captured.

Practices are required to meet data quality standards before they can contribute to the database. In brief, patient registration status, age and sex must meet minimum recording standards, as well as recording of events such as hospitalization and death[391]. The CPRD can be linked to other National Health Service databases, such as Hospital Episode Statistics (HES) data and Office of National Statistics (ONS) vital statistics data. However, neither of these data sources were required for the objectives of this thesis and thus records were not linked.

Furthermore, only records from England (58% of the available patients) are linkable and thus the decision to not link improves statistical precision.

The CPRD has been used in at least 6 studies of patients with MNCD[394-399]. Two of these studies concurrently validated the MNCD diagnosis in the CPRD, with 80–90% agreement between a diagnosis of MNCD in the CPRD database and diagnoses confirmed by correspondence with the patient's GP[94] or by blinded medical record review[99].

3.4.1 Context of family medicine in British healthcare system

In the UK, over 98% of the general population is registered with a GP practice[391]. The UK healthcare structure is designed such that the GP is the first professional to see a patient for their non-emergency medical needs, and coordinate referrals to and feedback from secondary care (e.g., geriatrics). The CPRD is a collection of GP patient data and care interactions that is updated monthly, that contains extensive longitudinal data[391].

When a person in the UK presents to their GP with memory-related complaints, the physician can refer to 1 of 3 specialists: an old age psychiatrist (known as a geriatric psychiatrist in Canada), a geriatrician or a neurologist. Only the specialist, who may or may not be affiliated with memory clinics[400], can formally diagnose MNCD. After diagnosis and the writing of the first prescription by a specialist, patients are referred back to their GP for follow-up[401]; thus, the study sample, while limited to GP data, should represent the MNCD experience in the UK.

3.5 Study population

I assembled an inception cohort of all patients in the CPRD with newly diagnosed with MNCD between April 1, 1997, and March 31, 2017. A total of 79 Read codes (manuscript Table S1) were used to identify MNCD; these codes included published Read code MNCD cohort definitions[318,399,402-405] cross-referenced with my independent and thorough search of the CPRD Codebook Browser.

Inclusion was restricted to patients from general practitioner practices whose data met CPRD research quality standards. Included patients were required to have at least 1 year of CPRD database history prior to MNCD diagnosis to ensure sufficient observation time to assess risk factors, confounders and new medication-user status. All patients with a previous

prescription for MNCD medications were excluded to ensure that the population was restricted to new users of MNCD therapy to avoid prevalent user bias[406]. Subjects were followed until the date of departure from the general practitioner's medical practice, last date of data collection from that practice, death, or March 31st, 2017, whichever came first.

3.6 PATIENT CHARACTERISTICS

There were three exposures under investigation in this thesis.

3.6.1 SEX

Sex is recorded as "male", "female" or "missing" in the CPRD. The CPRD uses the term "gender", while in fact the database contains information about sex, the biological and physiological characteristics of the individual. Patients with missing sex were excluded prior to downloading the data.

3.6.2 AGE

Age was defined as years of age at MNCD diagnosis. Age was categorized as 65-74 years, 75-84 years, 85-94 years and ≥95 years of age. Patients with missing age were excluded prior to downloading the data.

3.6.3 MNCD SUBTYPE

Diagnostic codes for the following 5 MNCD types were included: 1) Alzheimer's disease, including codes for both probable and possible Alzheimer's; 2) vascular MNCD; 3) non-specific MNCD, where the Read codes did not specify MNCD subtype; 4) MNCD due to multiple etiologies, defined as the combination of 2 or more codes for different MNCD subtypes on the date of diagnosis; and 5) other MNCD, including MNCD with Lewy bodies, frontotemporal MNCD and MNCD due to Parkinson's disease, which were combined due to small sample size.

In the primary analyses, diagnosis defined at baseline was fixed throughout follow-up. In sensitivity analyses, a time-varying hierarchical diagnosis definition was used, where a patient's subtype was updated throughout follow-up as an individual received additional diagnoses over time. Specifically, a person initially diagnosed with either Alzheimer's, vascular or other MNCD with a subsequent diagnostic code for a different subtype would be classified as "MNCD due to

multiple etiologies" as of the date of the second subtype diagnosis. Other time-varying diagnoses include the change from a non-specific MNCD type to any of the four specific subtypes (Alzheimer's, vascular, MNCD due to multiple etiologies or other).

3.7 MNCD MEDICATION UTILIZATION

Product codes for all relevant ChEIs and memantine prescriptions were identified through a thorough search of the CPRD Code Browser, using first the British National Formulary codes (section 4.11: Medications for dementia), and then key terms for both medication substance names (donepezil, galantamine, rivastigmine, rivastigmine tartrate and memantine) and product name (which included brand names for non-generic formulations). ChEIs and memantine (manuscript Table S2) prescriptions were assessed on each day of follow-up. Combination therapy was defined as the co-prescription of both a ChEI and memantine on the same date. Prescription information included date of prescription and medication substance prescribed; prescription duration, which is not well recorded in the CPRD, was assumed to be 30 days as most prescriptions in the CPRD for chronically used medications are for 28-30 days. Upon examination of the distribution of prescription durations for MNCD medications for which duration information was available, the estimated prescription duration of 30 days was deemed to be a reasonable assumption. Importantly, the CPRD contains prescriptions but not dispensing information.

MNCD medication utilization patterns were described as the following:

1. Treatment initiation was defined as the first MNCD medication prescribed following the first recorded MNCD diagnosis. Time to treatment initiation was defined as the number of months from diagnosis to treatment initiation; the comparator group was patients in the cohort who had not initiated MNCD treatment at that point.
2. Treatment switches were defined as the initiation with a second MNCD medication. Time to treatment switch was defined as the number of months from treatment initiation to switch; the comparator group comprised patients who used MNCD therapies but did not switch medications at that time point. Specific treatment switches under examination in this thesis were switches from:
    i. First ChEI to second ChEI;

ii. Rivastigmine oral to rivastigmine transdermal, or vice versa;
iii. Any ChEI to memantine;
iv. Memantine to any ChEI;
v. ChEI to combination therapy;
vi. Memantine to combination therapy;
vii. Combination therapy to ChEI monotherapy;
viii. Combination therapy to memantine monotherapy;
ix. A combination therapy to a second therapeutic combination.

3. MNCD treatment persistence, defined as the number of months from the patient's first prescription to first discontinuation (>60 days without prescription) of any MNCD medication.
4. MNCD treatment adherence, defined as the proportion of prescribed days' supply obtained during a specified observation period. A grace period of 30 days from the date of last day of refill exposure was added to account for biological half- life and expected issues pertaining to refill adherence. Adherence analyses were restricted to those who were persistent.

3.8 COVARIATES

The following pre-specified covariates were identified from a review of literature as potential confounders. All available look-back data were used for comorbid condition ascertainment, given the known underreporting of chronic conditions at each visit in the CPRD. Five year look-back periods were used for smoking and BMI status. Prescription drug use was measured in the year prior to baseline. Except where used in the model as a stratifying variable, all listed covariates were used for model adjustment at baseline. Covariates were tested for multicollinearity, by examining the variance inflation factor and using established guideline that values greater than 10 may merit further investigation[407].

Table 3.1 Potential confounders examined in this thesis

Variable name	Definition	Comments
Demographics		
Sex	Female, compared to male	
Age at diagnosis	Grouped as 65-74, 75-84, 85-94, 95+	
Year of diagnosis	Calendar year	
General clinical variables		

Smoking status	Ever, never, unknown	
Presence of alcohol-related disorders	Examples include alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic flexure.	Given high rates of alcohol consumption in the UK, alcohol consumption codes not informative.
Body mass index	Underweight, normal, overweight, obese (using established World Health Organization cut-points)	
Deyo-Charlson Comorbidity Index	Range of possible scores 0-25	
GP contacts in year prior to diagnosis	Number of consultations which took place in an outpatient setting	
Nursing home	GP consultations which took place in an institutional care home/long term care setting	
Prescriptions		
Total number of drugs	Using distinct British National Formulary code headers	
Prescription for antidepressants	Includes gamma-aminobutryic acid (GABA) analogs, monoamine oxidase inhibitors (MAOis), selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs)	
Prescription for anxiolytics	Examples include diazepam and buspirone	
Prescription for hypnotics	Examples include temazepam and zopiclone	
Prescription for drugs for overactive bladder control	Examples include tolterodine and solifenacin	
MNCD-specific variables		
Anticholinergic burden	Measured by Anticholinergic Cognitive Burden Scale[408]	
MNCD subtype	Defined as Alzheimer's, vascular, multiple etiologies, other and non-specific	See section 3.6.3 and manuscript table S1
Indicators of MNCD severity	Defined by Seitz et al.[409]: urinary and fecal incontinence, recorded history of falls, hip fracture, pressure ulcers and malnutrition.	
History of delirium		
History of neuropsychiatric symptoms		
Agitation/aggression		

Anxiety Depression/dysphoria Other neuropsychiatric symptoms	Presence of any of the following: aberrant motor behavior, apathy, delusions, disinhibition, euphoria, irritability or lability, hallucinations
Frailty Index	Using a modified version of the electronic Frailty Index (eFI)[410], adding 4 neuropsychiatric symptoms, hip fracture, and diagnosis of delirium.

3.9 STATISTICAL ANALYSES

Descriptive statistics were used to describe demographic and clinical characteristics, by exposure groups, at cohort entry. Categorical variables are presented as counts with corresponding proportions, and continuous variables are presented as means with standard deviations (SD). Any table cells with values less than 5 were suppressed, as per CPRD data confidentiality policies. Differences between groups for descriptive statistics were compared using standardized mean differences (SMD), calculated by dividing the effect size measure by the pooled standard deviation, to quantify the magnitude of difference in baseline variables between groups on baseline variables in a sample-size independent manner[411].

The distribution of initial MNCD treatment strategy and treatment switches were described overall, and by sex, age at diagnosis and MNCD subtype. For the initiation analyses, the study cohort contained all patients diagnosed with MNCD (i.e. at risk of drug initiation) and the underlying time axis was time from diagnosis. For the switch, adherence and persistence analyses, the study cohort was restricted to those who had ever received an MNCD drug to restrict inclusion to those patients who were at risk of the outcome; by definition, those who never initiated a drug could not switch, adhere or persist to a drug. For switches, adherence and persistence, duration of follow-up was defined as time since first drug initiation.

For each of the four outcomes, time elapsed (in months) was assessed, each by univariate (using median time to event, Kaplan-Meier curves and crude HR from Cox proportional hazard models) and multivariable analyses (using adjusted Cox proportional hazard models to compare time to initiation, switching, non-adherence and discontinuation among the 3 exposures, with HR

and corresponding 95% confidence intervals). Logistic regression was used to compare the likelihood of discontinuation after first prescription between males and females.

Adherence to MNCD medications was measured by calculating the proportion of days covered (PDC) for the time periods of 3, 6, 9, 12 and 24 months after initiation. PDC was capped at 100%, to prevent overestimation.

All statistical analyses were conducted using SAS software 9.4 (SAS Institute Inc., Cary, NC).

3.10 SENSITIVITY ANALYSES

Five sensitivity analyses were conducted to assess the robustness of results. First, to assess our assumption of a time-fixed definition of MNCD subtype, we repeated analyses using time-varying MNCD subtype definition to capture the natural trajectory of diagnoses. Second, data for the initiation analyses was restricted to patients diagnosed from 2002-2017, so as to reflect drug approval and availability (Table 1.1). Third, for both the adherence and persistence analyses, the duration of prescription length was reduced to 14 days. The CPRD does not contain consistent information about prescription duration, so a 14-day definition was chosen for a conservative estimate for the sensitivity analysis to complement the 30-day duration used in the primary analysis. Fourth, the length of the grace period in the persistence analysis was varied to 0 and 60 days. Fifth, for the persistence and adherence analyses, data were restricted to those individuals diagnosed before March 31, 2016 to allow for follow-up among those diagnosed at the end of the study observation period.

3.11 ETHICS APPROVAL

This work was approved by the Independent Scientific Advisory Committee (ISAC) of the CPRD (ISAC protocol 17_158, which will be made available to journal reviewers in accordance with CPRD policy) and the Research Ethics Committees of the West-Central Montreal Health in Montreal, Canada (Ethics Protocol CODIM-MBM-17-123). Patients and GP practices are anonymous; thus, individual patient consent was not required.

CHAPTER 4: MANUSCRIPT

To our knowledge, this is the first study to describe sex-based differences in drug utilization in major neurocognitive disorders. Two recent systematic reviews (Canevelli et al *Pharmacology Research* 2017, Mehta et al *Journal of the American Geriatrics Society 2017)* on the topic have concluded that the present study is needed.

Sex-based drug utilization differences in major neurocognitive disorders: a population-based cohort

Short running title: Sex differences in MNCD drug utilization

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ABSTRACT

Background/Objectives: Sex differences have been observed in major neurocognitive disorders (MNCD) disease prevalence, phenotypic and clinical features, and disease progression. However, little is known regarding whether MNCD drug utilization (cholinesterase inhibitors donepezil, rivastigmine and galantamine, as well as memantine) differs by sex. The objective of this study was to describe sex differences in MNCD drug utilization and to compare prescription patterns between sexes.

Design: Retrospective population-based cohort study.

Setting: General practitioner practices contributing to the Clinical Practice Research Datalink (CPRD) in the United Kingdom.

Participants: All patients aged 65+ years newly diagnosed with MNCD (n=91,025) between April 1997 and March 2017.

Measurements: Prescription patterns (initiation, switches, persistence and adherence) were described overall and by sex. Times to initiation, switch, discontinuation and non-adherence were compared between sexes using Cox proportional hazards models, adjusted for demographic and clinical characteristics.

Results: A total of 28% of patients initiated MNCD therapy, 13% of which switched to a second drug. Persistence was low (82% after first trial, 56% after 6 months, 19% after 2 years), and adherence was modest among those who were persistent (53% at 2 years). Females were less likely to initiate with oral rivastigmine (adjusted HR = 0.61, 95% CI 0.54-0.69) or memantine (adjusted HR = 0.81, 95% CI 0.75-0.87), and less likely to switch from a ChEI to memantine (adjusted HR = 0.89, 95% CI 0.79-1.00) or combination therapy (adjusted HR = 0.63, 95% CI 0.48-0.82). Female patients were also more likely to initiate, persist with and be adherent to donepezil.

Conclusion: Sex-based differences in MNCD drug utilization were observed in this primary care cohort from the UK, which may have clinical implications.

3-5 key words: sex factors, drug utilization, dementia, cholinesterase inhibitors, memantine

INTRODUCTION

Major neurocognitive disorder (MNCD, formerly dementia) is a term comprising several progressive and degenerative illness, affecting 1 in 11 patients over age 65.[1] The only disease specific drugs currently approved for MNCD are cholinesterase inhibitors (ChEIs, i.e., donepezil, galantamine, and rivastigmine [including both oral and transdermal formulations]) and the N-methyl-D-aspartate receptor antagonist memantine. These drugs are used despite limited effectiveness and common side effects. National Institute of Clinical Excellence[2] guidelines in the United Kingdom (UK) currently recommend a trial of ChEIs among patients with mild to moderate MNCD for a minimum of 6 months, with regular monitoring; American[3] and Canadian[4] guidelines are similar. While these drugs are prescribed for symptom management, only a small percentage of patients respond, and response often fails to meet pre-established levels of clinical significance. These drugs have no substantial impact on disease course and they offer no cure.

Approximately 75% of patients with MNCD are women.[5-8] This is, at least in part, due to women living longer than men on average. Prescription patterns may differ between sexes because of differences in prescribing, patient behavior, and effectiveness and safety profiles (due to metabolic differences).

The Lancet Neurology Commission issued a report in 2016 which encouraged sex-based analyses in MNCD research.[9] However, 2 systematic reviews from 2017 did not find any published literature about MNCD drug treatment reporting differences by sex.[10,11] One of these reviews specifically examined sex-specific reporting in the example of ChEIs, and concluded that sex-specific reporting should be required. Therefore, the objective of this study was to evaluate sex-differences in the prescription patterns of MNCD drugs among primary care providers in the UK.

METHODS

Data source

We assembled a population-based, retrospective cohort in the Clinical Practice Research Datalink (CPRD).[12] The CPRD is a clinical database from the UK, with over 15,000,000 patient records from 700 general practitioner practices, shown to be a representative sample of the UK.

Participating CPRD general practitioners (GP) have been trained to record medical information including demographic data, laboratory results, clinical measures, lifestyle variables such as body mass index (BMI) and smoking history, recorded symptoms and diagnoses using the Read coding system (a universal classification system developed in the UK and funded by the National Health Service) and prescriptions using a standard anonymous form and classified according to the British National Formulary. Importantly, the CPRD contains prescriptions but not dispensing information. A recorded diagnosis of MNCD in the CPRD has been shown to have a positive predictive value of 80–90%.[13,14]

Study population

We assembled a cohort of all patients with a new diagnosis with MNCD in the CPRD between April 1, 1997, and March 31, 2017. MNCD was defined by a Read code indicating its presence (Table S1), with our definition building upon previous definitions.[15-21] MNCDs were subclassified as Alzheimer's, vascular, MNCD due to multiple etiologies (defined as the presence of 2 different MNCD subtypes on the date of diagnosis), non-specific or other (MNCD due to Parkinson's disease, MNCD with Lewy bodies, and frontotemporal MNCD). We then excluded patients with less than 1 year of CPRD database history prior to MNCD diagnosis to ensure sufficient observation time to assess medical history and new drug-user status. Patients with a previous prescription for MNCD drugs were excluded to restrict the cohort to new users of MNCD therapy to avoid prevalent user bias.[22] Patients were followed from the date of their MNCD diagnosis until the date of departure from the general practitioner's medical practice, last date of data collection from that practice, death, or March 31st, 2017, whichever came first. This study was approved by the Independent Scientific Advisory Committee (ISAC) of the CPRD (ISAC protocol 17_158) and the Research Ethics Committees of the West-Central Montreal Health in Montreal, Canada (Ethics Protocol CODIM-MBM-17-123). The CPRD contains anonymized records and individual patient consent was therefore not required.

Drug utilization

ChEIs and memantine prescriptions (Table S2) were assessed on each day of follow-up. Combination therapy was defined as the co-prescription of both a ChEI and memantine written on the same date. Given the clinical contraindication of a combination of ChEIs, prescriptions for

multiple ChEIs (0.03% of prescriptions) on the same date were assumed to be monotherapy and were adjudicated according to National Institute for Health and Care Excellence clinical guidelines.[2] Prescription information included date of prescription and drug substance. Prescription duration, which is frequently missing in the CPRD, was assumed to be 30 days. A grace period of 30 days for non-overlapping prescriptions was used to define periods of continuous treatment, and was added to account for biological half- life and expected issues pertaining to refill adherence.

We investigated sex-differences in treatment initiation, switching, adherence and persistence. Treatment initiation was defined as the first MNCD drug prescribed following the first recorded MNCD diagnosis. Switches were defined as initiation of a second drug and included switches from: 1) first ChEI to second ChEI, 2) any ChEI to memantine, 3) memantine to any ChEI, 4) ChEI to combination therapy and 5) memantine to combination therapy. Persistence was defined as the number of days from the patient's first prescription to first discontinuation (>60 days without prescription) of any MNCD drug. Adherence was defined as the proportion of prescribed days' supply obtained during a specified observation period. Adherence was assessed by calculating the proportion of days covered (PDC) for the time periods of 3, 6, 9, 12 and 24 months after drug initiation, with analyses restricted to patients who had been persistent until that time point. Adherence was defined as PDC $\geq$ 0.80,[23] with PDC < 0.80 classified as non-adherent; PDC was capped at 100% to prevent overestimation. Prescription repeat writings were assumed to suggest the continued use of the medication.

Potential confounders

We measured several pre-specified baseline demographic and clinical characteristics to adjust for variables that the existing literature indicates are potential confounders. These covariates included: age and year of MNCD diagnosis, smoking status, history of alcohol-related disorders, BMI using WHO-established cut points, MNCD subtype, Charlson-Deyo Comorbidity Index,[24] indicators of MNCD severity in prior year,[25] prior prescriptions, Anticholinergic Cognitive Burden Scale,[26] frailty severity category (measured using an MNCD-adapted version of the electronic Frailty Index),[27] number of general practitioner visits, and history of neuropsychiatric symptoms. Comorbidities were assessed any time prior to cohort entry, while GP visits (in community and nursing home) and drugs were assessed in the year before cohort

entry. Covariates were tested for multicollinearity, by examining the variance inflation factor (VIF) and using established guidelines that values greater than 10 may merit further investigation.

Statistical analyses

We described baseline demographic and clinical characteristics of our cohort by sex. Categorical variables are presented as counts with corresponding proportions, and continuous variables are presented as means with standard deviations (SD). Differences between groups were compared using standardized mean differences (SMD), with a difference of 10% or more considered to be statistically important.[28]

The distribution of the initial MNCD treatment strategy and treatment switches were described overall and by sex. For the initiation analyses, analyses included all patients diagnosed with MNCD and the underlying time axis was time from diagnosis. For the switching, adherence and persistence analyses, analyses were restricted to those who initiated an MNCD drug (i.e., those who were at risk of the outcome). For switches, adherence and persistence, duration of follow-up was defined as time since initiation of first MNCD drug. Kaplan-Meier curves were constructed to describe time to event, and Cox proportional hazard models were used to estimate hazard ratios (HR) and corresponding 95% confidence intervals (CI) of the times to initiation, switch and discontinuation between males and females. Logistic regression was used to compare the likelihood of discontinuation after first prescription between males and females. Models were adjusted for the pre-specified covariates described above.

Sensitivity analyses

We conducted sensitivity analyses to examine the robustness of our results. First, a time-varying dementia subtype definition was used, to capture the natural trajectory of diagnoses, in which diagnoses were updated to reflect the most recent diagnosis subtype recorded before or at initiation. Second, for the initiation analysis, data were restricted to those diagnosed from 2002 onwards, to reflect the year at which all drugs were approved and available. Third, for both the adherence and persistence analyses, the estimated prescription duration was reduced to 14 days to provide more conservative estimates and increased to 60 days to provide more liberal estimates. Fourth, the length of the grace period was varied to produce reduced and prolonged

estimates of treatment duration. Specifically, 0 and 60 days for our primary analysis (30-day prescription duration), 0 and 28 days for the 14-day prescription duration, and 0 and 120 days for the 60-day prescription duration sensitivity analyses. Fifth, cohort entry was terminated at March 31, 2016 to allow for up to 1-year of follow-up among those more recently diagnosed. All analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Our cohort included 91,025 patients with MNCD (Figure S1), of which 58,342 (64%) were female and 32,683 (36%) were male. Compared to males, female patients were older at diagnosis (84 versus 81 years, SMD=43%), had fewer comorbidities (mean 2.5 versus 2.9, SMD=23%), and were more likely to be underweight (6% versus 2%, SMD=29%), but did not differ substantially in other demographic and clinical features (Table 1 and Table S3). Using time-fixed and time-varying definitions of MNCD diagnosis, sex-based differences in prevalence of "other MNCD" were noted (5% male versus 2% female) using both disease definitions. No other sex-based subtype differences were found (Table S4).

Treatment initiation

MNCD pharmacotherapy was initiated in 28% of the cohort. Importantly, there was no difference (SMD=0%) in the proportion of males (28%) or females (27%) who initiated MNCD therapy at any point after diagnosis (Table 1). ChEIs, memantine, and combination therapy contributed to 87%, 13% and <1% of prescriptions, respectively (Table 2).

Among the 25,071 patients who received at least 1 MNCD drug during follow-up, there were no sex differences in the proportion who received a ChEI or memantine monotherapy. After adjustment for demographic and clinical characteristics, as compared to males, female patients were significantly more likely to be prescribed ChEIs (HR = 1.05, 95% CI 1.02-1.09) and significantly less likely to receive memantine (HR = 0.81, 95% CI 0.75-0.87). Specifically, females were less likely to be prescribed oral rivastigmine (HR = 0.61, 95% CI 0.54-0.69), yet more likely to be prescribed donepezil (HR = 1.10, 95% CI 1.07-1.14) and galantamine (HR = 1.09, 95% CI 1.01-1.19) (Table 2).

Overall, median time from diagnosis to treatment initiation was 3.8 months (interquartile range 1.1-9.5), and was shorter for ChEIs (3.7 months) than memantine (4.9 months) or combination therapy (18.2 months); differences between sexes were minimal (Table S5).

Treatment switches

Treatment switches were observed in 13% of the patients who initiated therapy (Table 2). The most frequent switches were from a first to a second ChEI (49%) or from any ChEIs to memantine (41%). Switches from memantine to combination, combination to ChEI, and combination to memantine were infrequent (<10% combined; exact numbers are suppressed due to CPRD data confidentiality policies). No sex differences in the frequency of switches were observed. Overall, female patients switched a median of 1.7 months earlier than males; females switched sooner for each specific switch as well (Table S5). No sex difference was noted in the instantaneous risk of switching from a first to second ChEI. However, the risk of switching from ChEIs to combination therapy was 37% lower in females (adjusted HR = 0.63, 95% CI 0.48-0.82), and progression from ChEI monotherapy to combination therapy was 11% lower in females (adjusted HR = 0.89, 95% CI 0.79-0.998) (Table 2).

Treatment persistence

The duration of MNCD drug persistence was short (Figure 1). The median persistence with treatment was 7.4 months (interquartile range 2.8-19.2 months), with females remaining on treatment approximately 0.5 months longer than men (7.6 versus 7.1 months respectively) (Table S5). Eighteen percent of individuals prescribed an MNCD drug did not have a second prescription, indicating a discontinuation after first trial. In an analysis estimating the adjusted odds of not receiving a second prescription, there was no significant difference by drug, by sex (Table S6). The proportion of patients who were persistent to treatment declined with time since initiation (from 73% at 3 months to 19% at 2 years) (Figure S2 and Table S7). Females were less likely to discontinue their ChEIs (adjusted HR = 0.94, 95% CI 0.92-0.97), specifically donepezil (adjusted HR = 0.96, 95% CI 0.93-0.99) and oral rivastigmine (adjusted HR = 0.86, 95% CI 0.76-0.97), indicating greater persistence. No sex-based differences in time to discontinuation of other ChEIs or memantine were found (Table 3).

Treatment adherence

No sex-based differences were observed in the proportion of patients classified as adherent at any of the time study time points (Figure S3). Throughout follow-up, adherence was highest to memantine in both sexes. Females had lowest adherence to rivastigmine patches, while males had similarly low adherence to both rivastigmine patch and galantamine. Overall adherence declined over time since drug initiation, using the primary definition of 30-day prescription duration and 30-day grace period, from 62% at 3 months to 53% at 2 years (Table S8). Females had a lower rate of non-adherence than males for ChEIs (adjusted HR = 0.91, 95% CI 0.87-0.95), driven primarily by donepezil (adjusted HR = 0.91, 95% CI 0.87-0.96), indicating greater adherence to donepezil but not to other drugs (Table 4).

No evidence of covariate multicollinearity was found (VIF range 1.02-2.57).

Results of sensitivity analyses

Restricting initiation analyses to those diagnosed from 2002-2017 did not result in any substantial changes in HRs (Table S7). In sensitivity analyses examining varying assumptions pertaining to prescription duration and the grace period, the relative difference in proportion of males and females who were classified as persistent (Table S8) and adherent (Table S9) to their treatments remained similar as those observed in the primary analyses. No differences were noted when restricting to individuals diagnosed before March 31, 2016 to allow for follow-up among the more recent cases (data not shown).

DISCUSSION

Sex differences in medicine are an emerging research interest. Substantial sex differences have been observed in the utilization of antidepressants, antipsychotics, antibiotics and antiarrhythmics, all drugs with high prevalence of use in older adults.[29] Furthermore, there are well-documented differences in the ways that men and women absorb, distribute, metabolize and excrete drugs.[30,31] Body weight, plasma volume, gastric emptying time, plasma protein levels, metabolizing enzymes, medication transporter function and clearance activity all differ between males and females[32-34]; each of these differences make female patients more susceptible to adverse events,[35] which could reduce adherence and persistence. In the present population-based cohort study, important differences in MNCD prescription patterns were observed between males and females. In particular, females were more likely to be prescribed ChEIs, specifically

donepezil and galantamine, and less likely to receive rivastigmine, especially the oral formulation, or memantine. These differences were not explained by age-related and other confounding variables, including disease severity and subtype. One possible explanation is that physicians preferentially prescribe donepezil for women, given the known adverse event profile associated with rivastigmine and known female susceptibility to adverse events. The lower utilization of memantine in females as compared to males is interesting to note, given that female patients are known to survive longer, making them more likely to experience severe disease where memantine is indicated for use. Given that in general, women are more likely to seek treatment for diseases earlier than men,[36] it is possible that female patients initiate MNCD treatment at an early stage of disease. As such, it is possible that our results reflect residual confounding by disease severity, or that they are a potential indication of inadequate treatment of female patients. It is worth noting that patients may begin memantine many months or years after discontinuation of their ChEI trial, but this study stopped follow-up after first episode of treatment discontinuation. If subsequent studies are able to identify the reasons for observed differences between treatment patterns of men and women, future interventions can then be designed to target them.

While females were significantly less likely to begin combination therapy or switch to memantine, there was no difference in the rate of switching from a ChEI to another ChEI. Additionally, the median time to switch for female patients was shorter, perhaps suggesting more frequent healthcare contacts, adverse events, or more treatment failure due to disease progression.

Female patients were significantly more persistent to rivastigmine and donepezil, but not to galantamine or memantine. Among those who were persistent, adherence was highest to donepezil. These findings were significant even after adjustment for known confounders such as disease subtype and severity. Patients who are persistent to their treatments are likely to have been less susceptible to the adverse events commonly associated with ChEI discontinuation. It is also possible that the persistent individuals are those who receive the greatest benefit; a responder profile has not yet been elucidated in MNCD therapies.

Previous examination of the incidence of MNCD between the 2 sexes have been inconclusive: the Canadian Study of Health and Aging did not find differences,[37] while other

international results have found women to be at higher risk.[38-40] Possible reasons for sex-related differences in MNCD incidence include biological (sex-determining genes and hormones, specifically in brain development, structure, function and biochemistry)[41] and genetic differences (higher levels of estrogen known to be an effect modifier in the apolipoprotein E4 allele-associated increased risk of the development of MNCD)[42] and lower education level.[39,43]

This study has important strengths. To the best of our knowledge, this is the largest drug utilization study (n = 91,025) of ChEIs and memantine, with data covering the entire 20-year period that these drugs have been available for use. This study used a large population-based clinical database that has been used in more than 10 MNCD studies to date. Furthermore, this is the first analysis of sex-based patterns of treatment in MNCD, and answers an identified knowledge gap reported by 2 recent systematic reviews.[10,11] Moreover, results were consistent across sensitivity analyses, suggesting their robustness.

This study also has some potential limitations. First, the CPRD records prescriptions issued by general practitioners but not those written by specialists. Consequently, there may be some misclassification of treatment status, including the date of treatment initiation and switches in the event of side effect or treatment non-response. Second, the CPRD contains prescriptions written but not dispensed or consumed. To the extent that drugs were prescribed but not taken as written, we may have overestimated initiation and adherence. Third, due to sample size limitations, only the first treatment switch was considered; future studies may consider additional switching patterns. Fourth, we cannot discount the possibility of chance findings due to the possible consequences of multiple comparisons. We did not statistically correct for this issue and leave it to the reader to consider when interpreting our results. Lastly, residual confounding remains possible from unknown or unmeasured variables. This remains an inherent limitation to all observational studies.

In conclusion, sex-based differences in primary care MNCD prescription patterns, and by consequence drug utilization, were found in this population-level inception cohort of patients with newly diagnosed MNCD in the UK. Given that MNCD drugs are associated with high risk of side effects, it will be important for future work to identify the patient-level characteristics, in particular age at diagnosis and MNCD subtype, such that physicians may preferentially prescribe MNCD drugs to those individuals who would be most likely to adhere and persist to their

treatment. This work warrants confirmation in other data sources, as sex-based differences represent an important frontier in the goal of personalizing medicine according to clinical and sociodemographic characteristics of patients.

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Conflict of Interest

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Author contributions

Andersen, Filion, Wilchesky: study concept design, data acquisition, data analysis and interpretation, manuscript preparation, critical revision of intellectual content. Kroger, Champoux: study concept design, data interpretation, critical revision of intellectual content. Reynier: data management, analysis and interpretation.

Sponsor's role

Not applicable.

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Table 1: Characteristics of MNCD patients at baseline, overall and by sex

	All (n=91,025)	Male (n=32,683, 36%)	Female (n=58,342, 64%)	Standardized mean difference (%)
Months of follow-up	20.8 (24.3)	19.8 (23.0)	21.4 (24.9)	7
Age at diagnosis	83 (7)	81 (7)	84 (7)	43
Ever received an MNCD drug	28%	28%	27%	0
MNCD sub-type diagnosis at baseline				
Alzheimer's	56%	51%	59%	0
Vascular MNCD	23%	26%	21%	0
Multiple etiologies	1%	1%	1%	0
Non-specific MNCD	18%	19%	18%	0
Other MNCD*	2%	3%	1%	0
Charlson-Deyo Comorbidity Index	2.7 (1.7)	2.9 (1.9)	2.5 (1.7)	23
Indicators of MNCD severity				
Urinary & fecal incontinence	14%	10%	16%	2
Fall(s)	20%	17%	21%	1
Hip fracture	6%	3%	8%	15
Pressure ulcers	12%	10%	13%	1
Malnutrition	12%	11%	12%	0
Diagnosis of delirium	19%	18%	19%	0
Drugs prescribed				
Antidepressants	30%	25%	33%	2
Antipsychotics	10%	9%	10%	1
Anxiolytics	5%	4%	6%	15
Hypnotics	12%	11%	13%	1
Overactive bladder control	7%	7%	7%	0
Modified Electronic Frailty Index				
Fit	25%	27%	23%	0
Mild frailty	44%	46%	44%	0
Moderate frailty	24%	22%	25%	0
Severe frailty	7%	5%	8%	5
Anticholinergic Cognitive Burden	2.1 (2.2)	2.0 (2.2)	2.2 (2.3)	9
Number of community GP visits	8.2 (9.7)	8.0 (9.7)	8.5 (9.8)	5
Seen by GP in a nursing home visit	2%	1%	2%	0
History of neuropsychiatric symptoms	51%	49%	52%	0
Agitation or aggression	5%	4%	6%	6
Anxiety	20%	14%	23%	2
Depression or dysphoria	39%	40%	38%	0
Other	6%	5%	6%	2

Presented as mean (standard deviation) or %. GP: general practitioner; MNCD: major neurocognitive disorders. *Other MNCD subtypes include MNCD due to Parkinson's disease, MNCD with Lewy bodies, and frontotemporal MNCD.

Table 2: Time to MNCD drug initiation and treatment switch, by sex

	Number of events	Patients at risk	Crude HR (95% CI)	Adjusted[±] HR (95% CI)
Time to treatment initiation				
ChEI	21,879	91,025	--	--
Females	13,944	58,342	0.97 (0.94-1.00)	1.05 (1.02-1.09)
Males	7,935	32,683	1.00 (ref)	1.00 (ref)
Donepezil	16,390	91,025	--	--
Females	10,653	58,342	1.04 (1.01-1.07)	1.10 (1.07-1.14)
Males	5,707	32,683	1.00 (ref)	1.00 (ref)
Galantamine	3,028	91,025	--	--
Females	1,966	58,342	1.02 (0.95-1.10)	1.09 (1.01-1.19)
Males	1,062	32,683	1.00 (ref)	1.00 (ref)
Rivastigmine (all)	2,491	91,025	--	--
Females	1,325	58,342	0.62 (0.57-0.67)	0.73 (0.67-0.80)
Males	1,166	32,683	1.00 (ref)	1.00 (ref)
Rivastigmine (Oral)	1,307	91,025	--	--
Females	614	58,342	0.49 (0.44-0.54)	0.61 (0.54-0.69)
Males	693	32,683	1.00 (ref)	1.00 (ref)
Rivastigmine (Patch)	1,184	91,025	--	--
Females	711	58,342	0.82 (0.73-0.92)	0.92 (0.81-1.04)
Males	473	32,683	1.00 (ref)	1.00 (ref)
Memantine	3,147	91,025	--	--
Females	1,878	58,342	0.80 (0.75-0.86)	0.81 (0.75-0.87)
Males	1,269	32,683	1.00 (ref)	1.00 (ref)
Time to treatment switch				
ChEIs → ChEI	1,559	21,879	--	--
Females	984	13,944	0.98 (0.89-1.09)	1.06 (0.95-1.18)
Males	575	7,935	1.00 (ref)	1.00 (ref)
ChEIs → memantine	1,314	21,879	--	--
Females	797	13,944	0.85 (0.76-0.95)	0.89 (0.79-1.00)
Males	517	7,935	1.00 (ref)	1.00 (ref)
ChEIs → combination	237	21,879	--	--
Females	122	13,944	0.58 (0.45-0.76)	0.63 (0.48-0.82)
Males	115	7,935	1.00 (ref)	1.00 (ref)

ChEI: cholinesterase inhibitor. CI: confidence interval. HR: hazard ratio. [±]Models were adjusted for age and year of diagnosis, lifestyle variables (smoking, alcohol-related disorders, BMI), MNCD subtype, frailty and Charlson-Deyo comorbidity score, indicators of MNCD severity (urinary & fecal incontinence, falls, hip fracture, pressure ulcers, malnutrition, delirium), drugs (total number, antidepressants, antipsychotics, anxiolytics, hypnotics, overactive bladder control agents, Anticholinergic Cognitive Burden Scale score), medical contacts (number of GP visits, nursing home residence) and neuropsychiatric symptoms.

Table 3: Time to treatment discontinuation, by sex

	Number of events	Patients at risk	Crude HR (95% CI)	Adjusted[±] HR (95% CI)
ChEIs	14,003	21,879	--	--
Females	8,763	13,944	0.98 (0.95-1.00)	0.94 (0.92-0.97)
Males	5,240	7,935	1.00 (ref)	1.00 (ref)
Donepezil	10,254	16,390	--	--
Females	6,509	10,653	0.99 (0.96-1.02)	0.96 (0.93-0.99)
Males	3,715	5,707	1.00 (ref)	1.00 (ref)
Galantamine	2,104	3,028	--	--
Females	1,359	1,966	0.99 (0.91-1.06)	0.95 (0.88-1.03)
Males	745	1,062	1.00 (ref)	1.00 (ref)
Rivastigmine (either)	1,692	2,491	--	--
Females	902	1,325	0.91 (0.84-0.98)	0.86 (0.79-0.94)
Males	790	1,166	1.00 (ref)	1.00 (ref)
Rivastigmine (oral)	857	1,307	--	--
Females	412	614	0.88 (0.79-0.99)	0.86 (0.76-0.97)
Males	445	693	1.00 (ref)	1.00 (ref)
Rivastigmine (patch)	835	1,184	--	--
Females	490	711	0.93 (0.83-1.05)	0.89 (0.78-1.01)
Males	345	473	1.00 (ref)	1.00 (ref)
Memantine	1,419	3,147	--	--
Females	818	1,878	1.00 (0.93-1.08)	1.01 (0.94-1.10)
Males	601	1,269	1.00 (ref)	1.00 (ref)

ChEI: cholinesterase inhibitor. CI: confidence interval. HR: hazard ratio. [±]Models were adjusted for age and year of diagnosis, lifestyle variables (smoking, alcohol-related disorders, BMI), MNCD subtype, frailty and Charlson-Deyo comorbidity score, indicators of MNCD severity (urinary & fecal incontinence, falls, hip fracture, pressure ulcers, malnutrition, delirium), drugs (total number, antidepressants, antipsychotics, anxiolytics, hypnotics, overactive bladder control agents, Anticholinergic Cognitive Burden Scale score), medical contacts (number of GP visits, nursing home residence) and neuropsychiatric symptoms.

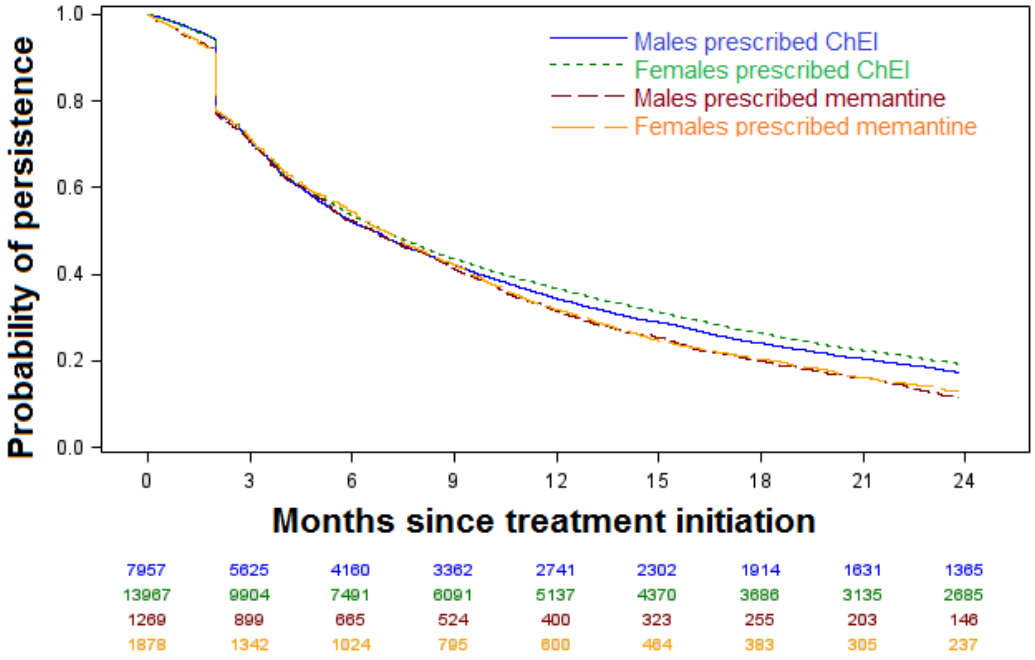
Table 4: Time to MNCD drug non-adherence, by sex

	Number of events	Patients at risk	Crude HR (95% CI)	Adjusted± HR (95% CI)
ChEIs (all)	12,904	21,879	--	--
Females	8,217	13,944	0.92 (0.88-0.95)	0.91 (0.87-0.95)
Males	4,687	7,935	1.00 (ref)	1.00 (ref)
Donepezil	9,398	16,390	--	--
Females	6,103	10,653	0.92 (0.88-0.96)	0.91 (0.87-0.96)
Males	3,295	5,707	1.00 (ref)	1.00 (ref)
Galantamine	1,813	3,028	--	--
Females	1,211	1,966	0.91 (0.83-1.01)	0.91 (0.82-1.02)
Males	602	1,062	1.00 (ref)	1.00 (ref)
Rivastigmine (either)	1,654	2,491	--	--
Females	882	1,325	0.93 (0.83-1.04)	0.91 (0.80-1.03)
Males	772	1,166	1.00 (ref)	1.00 (ref)
Rivastigmine (oral)	826	1,307	--	--
Females	386	614	0.92 (0.78-1.08)	0.94 (0.79-1.13)
Males	440	693	1.00 (ref)	1.00 (ref)
Rivastigmine (patch)	828	1,184	--	--
Females	496	711	0.90 (0.77-1.06)	0.85 (0.71-1.03)
Males	332	473	1.00 (ref)	1.00 (ref)
Memantine	2,153	3,147	--	--
Females	858	1,878	0.95 (0.84-1.07)	0.97 (0.85-1.10)
Males	1,295	1,269	1.00 (ref)	1.00 (ref)

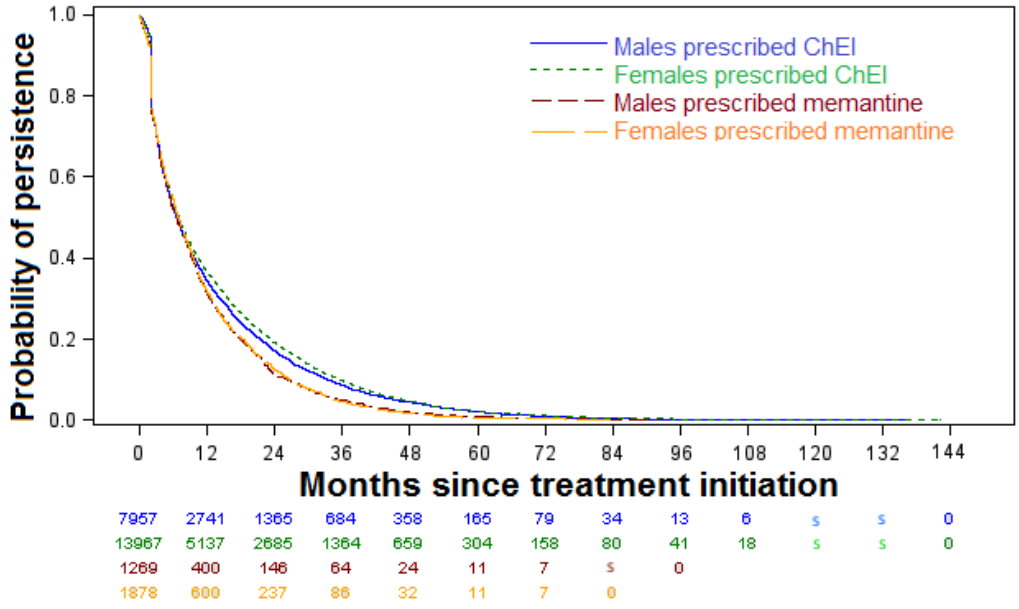
ChEI: cholinesterase inhibitor. CI: confidence interval. HR: hazard ratio. ±Models were adjusted for age and year of diagnosis, lifestyle variables (smoking, alcohol-related disorders, BMI), MNCD subtype, frailty and Charlson-Deyo comorbidity score, indicators of MNCD severity (urinary & fecal incontinence, falls, hip fracture, pressure ulcers, malnutrition, delirium), drugs (total number, antidepressants, antipsychotics, anxiolytics, hypnotics, overactive bladder control agents, Anticholinergic Cognitive Burden Scale score), medical contacts (number of GP visits, nursing home residence) and neuropsychiatric symptoms.

Figure 1: Kaplan-Meier curve describing time from cholinesterase inhibitor (ChEI) and memantine initiation to discontinuation, by sex

a. To 24 months



b. Over entire follow-up



Values less than 5 have been suppressed (s), as per CPRD data policies.

Table S1: Read codes to define MNCD diagnosis

Read code	Read term	MNCD subtype
Eu00z11	[X]Alzheimer's dementia unspec	Alzheimer's
Eu00111	[X]Alzheimer's disease type 1	Alzheimer's
Eu00013	[X]Alzheimer's disease type 2	Alzheimer's
Eu00200	[X]Dementia in Alzheimer's dis, atypical or mixed type	Alzheimer's
Eu00.00	[X]Dementia in Alzheimer's disease	Alzheimer's
Eu00000	[X]Dementia in Alzheimer's disease with early onset	Alzheimer's
Eu00100	[X]Dementia in Alzheimer's disease with late onset	Alzheimer's
Eu00z00	[X]Dementia in Alzheimer's disease, unspecified	Alzheimer's
Fyu3000	[X]Other Alzheimer's disease	Alzheimer's
Eu00011	[X]Presenile dementia,Alzheimer's type	Alzheimer's
Eu00113	[X]Primary degen dementia of Alzheimer's type, senile onset	Alzheimer's
Eu00012	[X]Primary degen dementia, Alzheimer's type, presenile onset	Alzheimer's
Eu00112	[X]Senile dementia,Alzheimer's type	Alzheimer's
F110.00	Alzheimer's disease	Alzheimer's
F110000	Alzheimer's disease with early onset	Alzheimer's
F110100	Alzheimer's disease with late onset	Alzheimer's
Eu02z11	[X] Presenile dementia NOS	Alzheimer's
Eu02z14	[X] Senile dementia NOS	Alzheimer's
Eu02z16	[X] Senile dementia, depressed or paranoid type	Alzheimer's
E001.00	Presenile dementia	Alzheimer's
E001z00	Presenile dementia NOS	Alzheimer's
E001100	Presenile dementia with delirium	Alzheimer's
E001300	Presenile dementia with depression	Alzheimer's
E001200	Presenile dementia with paranoia	Alzheimer's
E00..00	Senile and presenile organic psychotic conditions	Alzheimer's
E00..11	Senile dementia	Alzheimer's
E003.00	Senile dementia with delirium	Alzheimer's
E002100	Senile dementia with depression	Alzheimer's
E002.00	Senile dementia with depressive or paranoid features	Alzheimer's
E002z00	Senile dementia with depressive or paranoid features NOS	Alzheimer's
E002000	Senile dementia with paranoia	Alzheimer's
E00z.00	Senile or presenile psychoses NOS	Alzheimer's
E00..12	Senile/presenile dementia	Alzheimer's
E001000	Uncomplicated presenile dementia	Alzheimer's
E000.00	Uncomplicated senile dementia	Alzheimer's
Eu01.11	[X]Arteriosclerotic dementia	Vascular
Eu01300	[X]Mixed cortical and subcortical vascular dementia	Vascular
Eu01100	[X]Multi-infarct dementia	Vascular

Read code	Read term	MNCD subtype
Eu01y00	[X]Other vascular dementia	Vascular
Eu01200	[X]Subcortical vascular dementia	Vascular
Eu01.00	[X]Vascular dementia	Vascular
Eu01000	[X]Vascular dementia of acute onset	Vascular
Eu01z00	[X]Vascular dementia, unspecified	Vascular
E004.00	Arteriosclerotic dementia	Vascular
E004z00	Arteriosclerotic dementia NOS	Vascular
E004100	Arteriosclerotic dementia with delirium	Vascular
E004300	Arteriosclerotic dementia with depression	Vascular
E004200	Arteriosclerotic dementia with paranoia	Vascular
E004.11	Multi infarct dementia	Vascular
E004000	Uncomplicated arteriosclerotic dementia	Vascular
Eu02500	[X]Lewy body dementia	Other
F116.00	Lewy body disease	Other
Eu02000	[X]Dementia in Pick's disease	Other
F118.00	Frontotemporal dementia	Other
F111.00	Pick's disease	Other
Eu02300	[X]Dementia in Parkinson's disease	Other
F11x900	Cerebral degeneration in Parkinson's disease	Other
EU01111	[X] Predominantly cortical dementia	Non-specific
Eu02z13	[X] Primary degenerative dementia NOS	Non-specific
Eu02z00	[X] Unspecified dementia	Non-specific
Eu04100	[X]Delirium superimposed on dementia	Non-specific
Eu02.00	[X]Dementia in other diseases classified elsewhere	Non-specific
Eu02y00	[X]Dementia in other specified diseases classif elsewhere	Non-specific
Eu01111	[X]Predominantly cortical dementia	Non-specific
8BPa.00	Antipsychotic drug therapy for dementia	Non-specific
38C1300	Assessment of psychotic and behavioural symptoms of dementia	Non-specific
F11z.11	Cerebral atrophy	Non-specific
F11x.00	Cerebral degeneration in other disease EC	Non-specific
8CMZ.00	Dementia care plan	Non-specific
E041.00	Dementia in conditions EC	Non-specific
66h..00	Dementia monitoring	Non-specific
9hD1.00	Excepted from dementia quality indicators: Informed dissent	Non-specific
9hD0.00	Excepted from dementia quality indicators: Patient unsuitabl	Non-specific
3AE4.00	GDS level 5 - moderately severe cognitive decline	Non-specific
3AE5.00	GDS level 6 - severe cognitive decline	Non-specific
3AE6.00	GDS level 7 - very severe cognitive decline	Non-specific
E00y.00	Other senile and presenile organic psychoses	Non-specific
8Hla.00	Referral to dementia care advisor	Non-specific
F112.00	Senile degeneration of brain	Non-specific

Adapted from references 11-17

Table S2: Product codes used to define MNCD drugs

British National Formulary code 4.11 ("Drugs For Dementia")

Product code	Drug substance name	Substance strength	Formulation
5247	Donepezil hydrochloride	10mg	Oral
37188	Donepezil hydrochloride	10mg	Oral
35088	Donepezil hydrochloride	10mg	Oral
2931	Donepezil hydrochloride	10mg	Oral
58709	Donepezil hydrochloride	10mg	Oral
58947	Donepezil hydrochloride	10mg	Oral
59871	Donepezil hydrochloride	2mg/1ml	Oral
5400	Donepezil hydrochloride	5mg	Oral
53842	Donepezil hydrochloride	5mg	Oral
36848	Donepezil hydrochloride	5mg	Oral
35179	Donepezil hydrochloride	5mg	Oral
65534	Donepezil hydrochloride	5mg	Oral
2930	Donepezil hydrochloride	5mg	Oral
63217	Donepezil hydrochloride	5mg	Oral
60107	Donepezil hydrochloride	5mg	Oral
56600	Donepezil hydrochloride	5mg	Oral
11635	Galantamine hydrobromide	12mg	Oral
5334	Galantamine hydrobromide	12mg	Oral
14309	Galantamine hydrobromide	16mg	Oral
63405	Galantamine hydrobromide	16mg	Oral
56709	Galantamine hydrobromide	16mg	Oral
62867	Galantamine hydrobromide	16mg	Oral
63360	Galantamine hydrobromide	16mg	Oral
20140	Galantamine hydrobromide	16mg	Oral
61476	Galantamine hydrobromide	24mg	Oral
7361	Galantamine hydrobromide	24mg	Oral
60493	Galantamine hydrobromide	24mg	Oral
48015	Galantamine hydrobromide	24mg	Oral
55720	Galantamine hydrobromide	24mg	Oral
62868	Galantamine hydrobromide	24mg	Oral
61921	Galantamine hydrobromide	24mg	Oral
24088	Galantamine hydrobromide	24mg	Oral
10187	Galantamine hydrobromide	4mg	Oral
9854	Galantamine hydrobromide	4mg	Oral
7329	Galantamine hydrobromide	4mg/1ml	Oral
29288	Galantamine hydrobromide	4mg/1ml	Oral
10255	Galantamine hydrobromide	8mg	Oral
11654	Galantamine hydrobromide	8mg	Oral
48482	Galantamine hydrobromide	8mg	Oral
65573	Galantamine hydrobromide	8mg	Oral
18062	Galantamine hydrobromide	8mg	Oral
18587	Galantamine hydrobromide	8mg	Oral
37444	Rivastigmine	4.6mg/24 Hours	Transdermal

Product code	Drug substance name	Substance strength	Formulation
36976	Rivastigmine	4.6mg/24 Hours	Transdermal
62780	Rivastigmine	4.6mg/24hour	Transdermal
57627	Rivastigmine	4.6mg/24hour	Transdermal
62164	Rivastigmine	9.5mg/24hour	Transdermal
65761	Rivastigmine	9.5mg/24hour	Transdermal
57171	Rivastigmine	9.5mg/24hour	Transdermal
37957	Rivastigmine	9.5mg/24hour	Transdermal
63226	Rivastigmine	9.5mg/24hour	Transdermal
37132	Rivastigmine	9.5mg/24hour	Transdermal
63951	Rivastigmine	9.5mg/24hour	Transdermal
58780	Rivastigmine	9.5mg/24hour	Transdermal
11546	Rivastigmine hydrogen tartrate	1.5mg	Oral
4597	Rivastigmine hydrogen tartrate	1.5mg	Oral
18556	Rivastigmine hydrogen tartrate	2mg/1ml	Oral
53882	Rivastigmine hydrogen tartrate	2mg/1ml	Oral
11827	Rivastigmine hydrogen tartrate	2mg/1ml	Oral
11716	Rivastigmine hydrogen tartrate	3mg	Oral
11751	Rivastigmine hydrogen tartrate	3mg	Oral
56771	Rivastigmine hydrogen tartrate	3mg	Oral
20404	Rivastigmine hydrogen tartrate	4.5mg	Oral
55928	Rivastigmine hydrogen tartrate	4.5mg	Oral
11752	Rivastigmine hydrogen tartrate	4.5mg	Oral
5616	Rivastigmine hydrogen tartrate	6mg	Oral
9786	Rivastigmine hydrogen tartrate	6mg	Oral
57139	Memantine hydrochloride	10mg	Oral
18800	Memantine hydrochloride	10mg	Oral
39363	Memantine hydrochloride	20mg	Oral
9966	Memantine hydrochloride	10mg/1ml	Oral
39362	Memantine hydrochloride	5mg+10mg +15mg+20mg	Oral
6225	Memantine hydrochloride	10mg	Oral
11837	Memantine hydrochloride	10mg/1ml	Oral
65333	Memantine hydrochloride	10mg/1ml	Oral
39240	Memantine hydrochloride	20mg	Oral
64982	Memantine hydrochloride	20mg	Oral
38976	Memantine hydrochloride	5mg+10mg +15mg+20mg	Oral
61385	Memantine hydrochloride	10mg	Oral
61618	Memantine hydrochloride	20mg	Oral

Figure S1: MNCD cohort assembly flow diagram

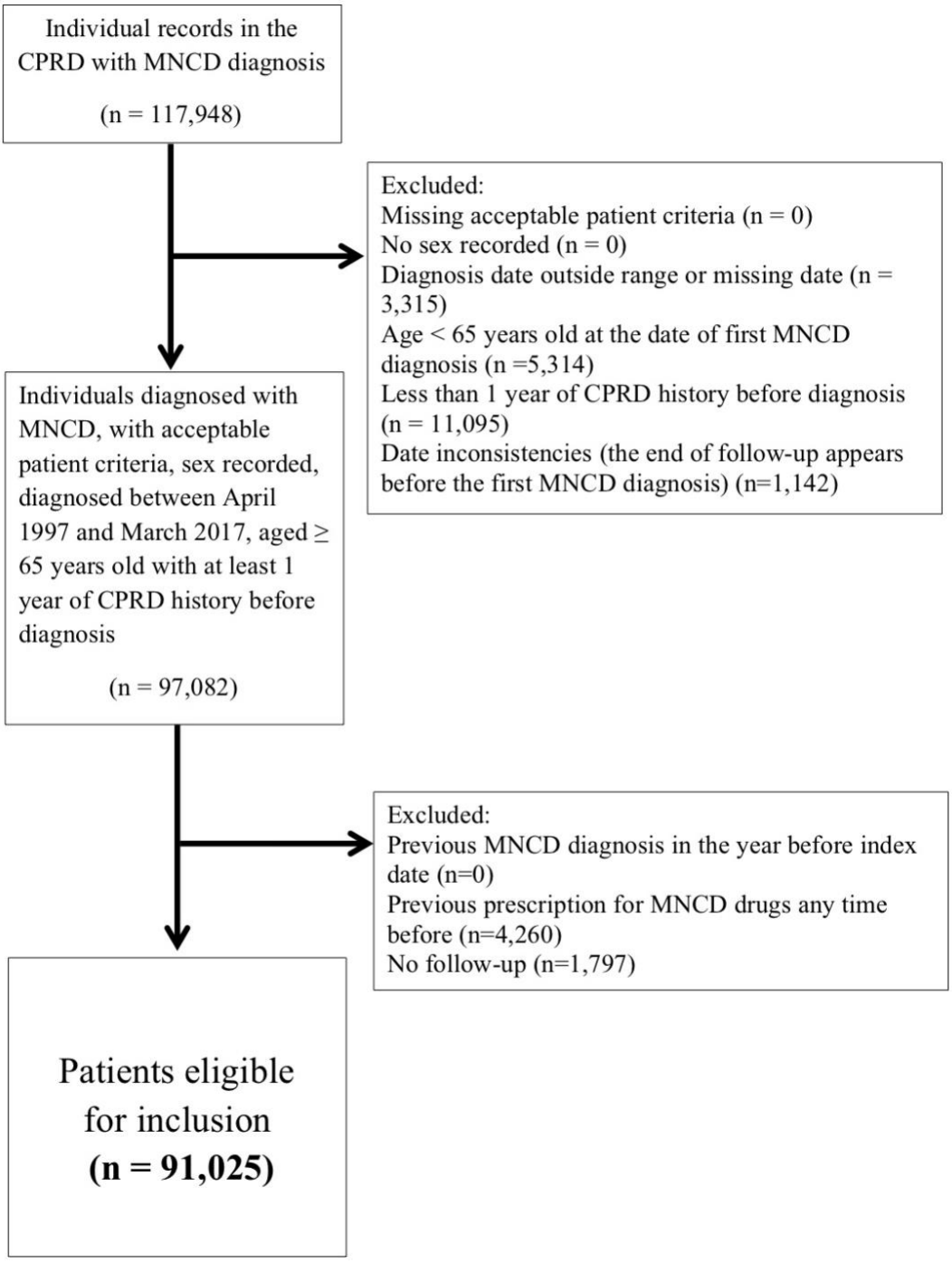


Table S3: Other patient characteristics

	All (n = 91,025)	Male (n = 32,683)	Female (n = 58,342)	Standardized mean difference (%)
Country				
England	75%	75%	75%	0
Northern Ireland	3%	3%	3%	0
Scotland	12%	12%	12%	0
Wales	10%	10%	10%	0
Year of MNCD diagnosis by 5-year periods				
1997-2001	11%	10%	11%	1
2002-2006	23%	22%	24%	0
2007-2011	32%	32%	32%	0
2012-2017	34%	36%	33%	0
Smoking status				
Ever	46%	60%	38%	1
Never	37%	26%	43%	1
Unknown	18%	14%	19%	1
Alcohol-related disorders*	7%	10%	5%	6
Body Mass Index (kg/m^2)				
< 18.5	4%	2%	6%	29
18.5 – 24.9	32%	32%	32%	0
25.0-29.9	22%	28%	19%	1
≥30	10%	11%	10%	1
Unknown	31%	27%	34%	0
Total number of distinct drugs in year prior to MNCD diagnosis				
0	3%	3%	3%	0
1-5	25%	25%	25%	0
6-10	33%	33%	33%	0
11-15	22%	21%	22%	0
≥16	18%	18%	17%	0

*Examples include alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic flexure.

Table S4: Comparison of diagnoses at baseline and at treatment initiation among those MNCD patients who received an MNCD drug

	At baseline		At treatment initiation	
	Males (n = 9,226)	Females (n = 15,845)	Males (n = 9,226)	Females (n = 15,845)
Alzheimer's	68%	75%	70%	77%
Vascular	10%	8%	9%	7%
Mixed	1%	1%	4%	3%
Non-specific	15%	14%	12%	11%
Other*	5%	2%	5%	2%

*Other MNCD subtypes include MNCD due to Parkinson's disease, MNCD with Lewy bodies, and frontotemporal MNCD.

Table S5: Median (interquartile range) months to treatment initiation, switch, and discontinuation, overall and by sex

	Overall (n = 25,071)	Male (n = 9,226)	Female (n = 15,845)
Median (interquartile range) months to treatment initiation			
Overall	3.8 (1.1-9.5)	3.9 (1.2-9.8)	3.8 (1.0-9.3)
ChEIs	3.7 (1.0-9.0)	3.8 (1.2-9.4)	3.7 (1.0-8.8)
Donepezil	3.5 (1.0-8.5)	3.7 (1.1-8.9)	3.5 (1.0-8.2)
Galantamine	4.2 (1.0-10.1)	3.9 (1.1-9.7)	4.4 (1.0-10.3)
Rivastigmine (all)	4.7 (1.4-11.1)	4.6 (1.4-11.5)	4.9 (1.6-10.7)
Oral	4.1 (1.1-10.1)	4.1 (1.0-11.1)	4.1 (1.1-9.1)
Transdermal	5.3 (2.1-12.2)	5.0 (2.0-12.5)	5.5 (2.1-11.9)
Memantine	4.9 (1.4-15.3)	4.9 (1.4-13.8)	5.0 (1.4-16.1)
Combination therapy	18.2 (6.0-48.9)	15.7 (4.1-46.8)	18.2 (6.0-68.0)
Median (interquartile range) months from treatment initiation to switch			
Overall	10.5 (3.9-24.0)	11.6 (4.6-25.9)	9.9 (3.7-23.0)
ChEIs → ChEI	5.8 (2.5-13.0)	6.6 (2.8-13.7)	5.2 (2.3-12.3)
ChEIs → memantine	18.1 (8.1-35.3)	19.8 (8.7-36.9)	17.1 (7.8-34.1)
ChEIs → combination	22.3 (12.2-37.4)	22.7 (12.4-35.0)	22.2 (10.7-39.7)
Memantine → ChEI	7.3 (3.0-14.7)	11.6 (3.4-19.0)	6.8 (2.3-11.9)
Median (interquartile range) months from treatment initiation to discontinuation			
Overall	7.4 (2.8-19.2)	7.1 (2.8-16.9)	7.6 (2.8-21.2)
ChEIs	7.5 (2.8-19.8)	7.2 (2.8-18.7)	7.7 (2.8-20.4)
Donepezil	7.5 (2.8-19.7)	7.2 (2.8-18.8)	7.7 (2.8-20.3)
Galantamine	8.2 (3.0-22.4)	7.5 (2.8-21.5)	8.5 (3.2-22.8)
Rivastigmine (either)	6.5 (2.6-17.4)	6.5 (2.7-16.7)	6.5 (2.6-18.2)
Rivastigmine (oral)	7.0 (2.8-19.1)	7.1 (2.8-18.1)	7.0 (2.9-19.9)
Rivastigmine (patch)	5.9 (2.0-16.2)	5.9 (2.0-16.2)	5.9 (2.2-16.4)
Memantine	7.0 (2.5-15.4)	6.7 (2.4-15.5)	7.2 (2.7-15.2)

ChEIs: cholinesterase inhibitor.

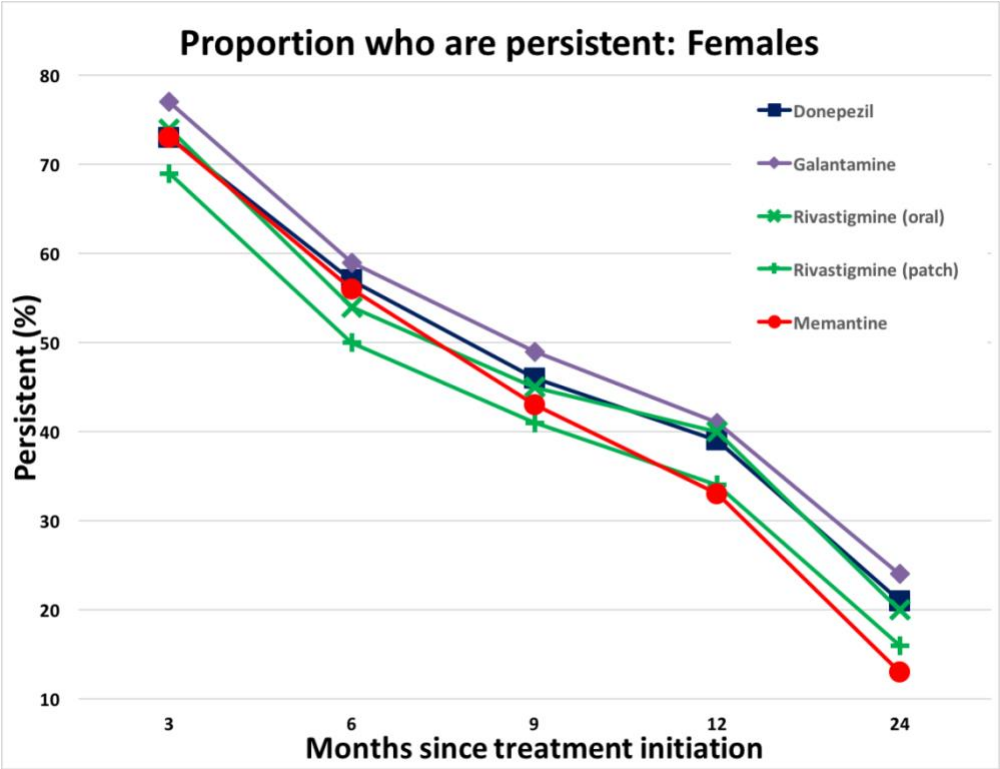
Table S6: Crude and adjusted odds ratio of discontinuation after first MNCD prescription

	Number of events	Patients at risk	Crude OR (95% CI)	Adjusted[±] OR (95% CI)
ChEIs	3,704	20,693	--	--
Females	2,340	7,508	0.97 (0.90-1.04)	0.98 (0.90-1.06)
Males	1,364	13,185	1.00 (ref)	1.00 (ref)
Donepezil	2,732	15,464	--	--
Females	1,774	10,069	0.99 (0.91-1.08)	1.00 (0.91-1.10)
Males	958	5,395	1.00 (ref)	1.00 (ref)
Galantamine	514	2,882	--	--
Females	319	1,871	0.85 (0.70-1.04)	0.87 (0.70-1.07)
Males	195	1,011	1.00 (ref)	1.00 (ref)
Rivastigmine (either)	450	2,315	--	--
Females	243	1,228	1.04 (0.84-1.27)	1.03 (0.81-1.29)
Males	207	1,087	1.00 (ref)	1.00 (ref)
Rivastigmine (oral)	213	1,223	--	--
Females	100	570	1.00 (0.74-1.34)	1.03 (0.74-1.44)
Males	113	653	1.00 (ref)	1.00 (ref)
Rivastigmine (patch)	237	1,092	--	--
Females	143	658	1.00 (0.75-1.34)	0.98 (0.71-1.37)
Males	94	434	1.00 (ref)	1.00 (ref)
Memantine	444	2,884	--	--
Females	253	1,716	0.88 (0.72-1.08)	0.89 (0.71-1.11)
Males	191	1,168	1.00 (ref)	1.00 (ref)

A total of 1,494 patients (944 females, 550 males) were censored from the cohort before 61 days of follow-up after initiation, and were removed from this analysis.

[±]Models were adjusted for age at and year of diagnosis, lifestyle variables (smoking, alcohol-related disorders, BMI), MNCD subtype, frailty and Charlson-Deyo comorbidity score, indicators of MNCD severity (urinary & fecal incontinence, falls, hip fracture, pressure ulcers, malnutrition, delirium), drugs (total number, antidepressants, antipsychotics, anxiolytics, hypnotics, overactive bladder control agents, Anticholinergic Cognitive Burden Scale score), medical contacts (number of GP visits, nursing home residence) and neuropsychiatric symptoms.

Figure S2: Proportion of patients who receive a MNCD medication that are persistent to their treatment, by sex



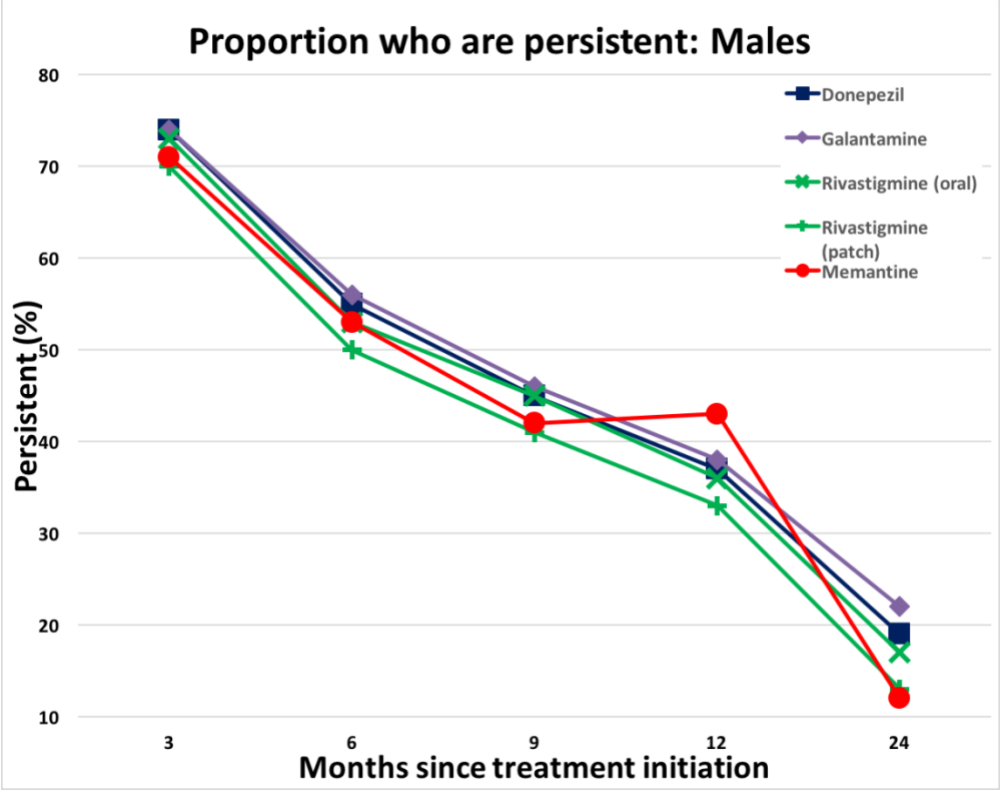
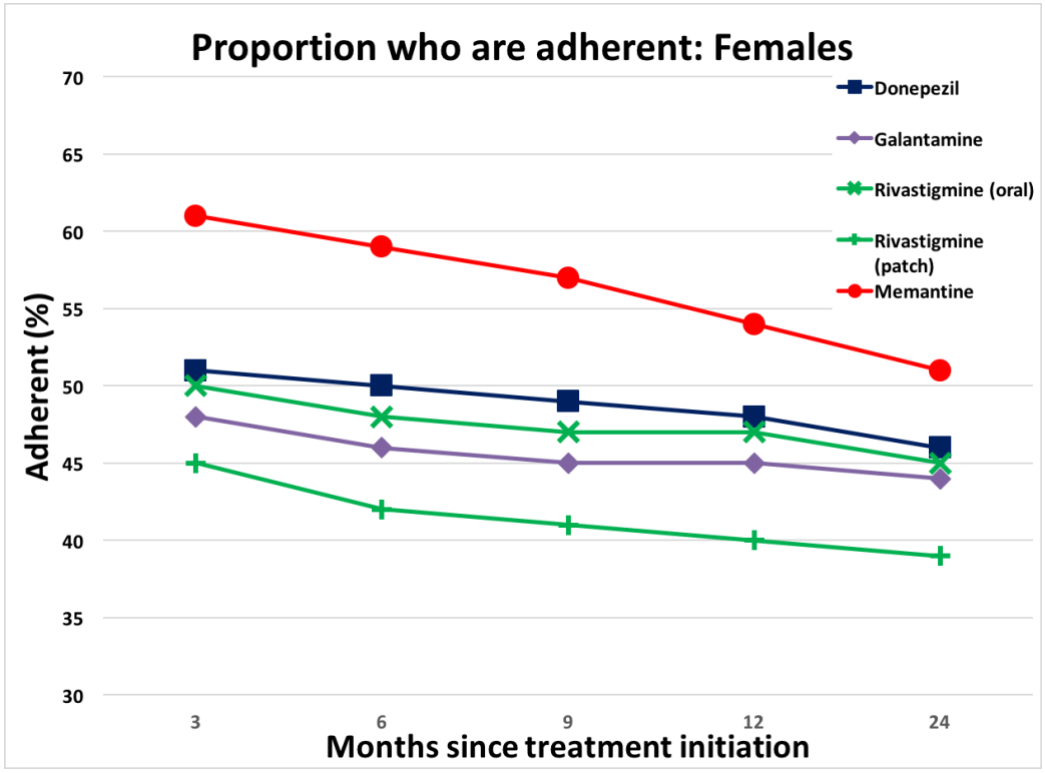


Table S7: Proportion of MNCD patients persistent to their treatment: Sensitivity analyses varying prescription duration and grace period definitions

	All (n = 25,071)	Male (n = 9,226, 37%)	Female (n = 15,845, 63%)
Using a 30-day duration and 30-day grace period, %			
3 months	73	73	74
6 months	56	55	56
9 months	45	45	46
12 months	37	36	38
24 months	19	18	20
Using a 30-day duration and 0-day grace period, %			
3 months	28	26	29
6 months	13	11	14
9 months	8	6	9
12 months	5	4	6
24 months	2	1	2
Using a 30-day duration and 60-day grace period, %			
3 months	93	93	93
6 months	69	69	69
9 months	60	70	60
12 months	52	52	52
24 months	30	29	30
Using a 14-day duration and 14-day grace period, %			
3 months	21	19	23
6 months	9	7	10
9 months	5	4	6
12 months	4	3	4
24 months	1	1	2
Using a 14-day duration and 0-day grace period, %			
3 months	4	3	4
6 months	2	2	3
9 months	2	1	2
12 months	1	1	1
24 months	<1	<1	<1
Using a 14-day duration and 28-day grace period, %			
3 months	55	53	55
6 months	38	36	39
9 months	29	28	30
12 months	23	21	24
24 months	10	9	11
Using a 60-day duration and 60-day grace period, %			
3 months	93	93	93
6 months	74	74	74
9 months	64	65	64
12 months	57	57	57
24 months	34	34	35

Using a 60-day duration and 0-day grace period, %			
3 months	73	73	74
6 months	56	55	56
9 months	45	45	46
12 months	37	36	38
24 months	19	18	20
Using a 60-day duration and 120-day grace period, %			
3 months	93	93	93
6 months	80	79	80
9 months	69	69	69
12 months	61	61	61
24 months	39	39	39

Figure S3: Proportion of patients who are adherent to MNCD drug, by sex



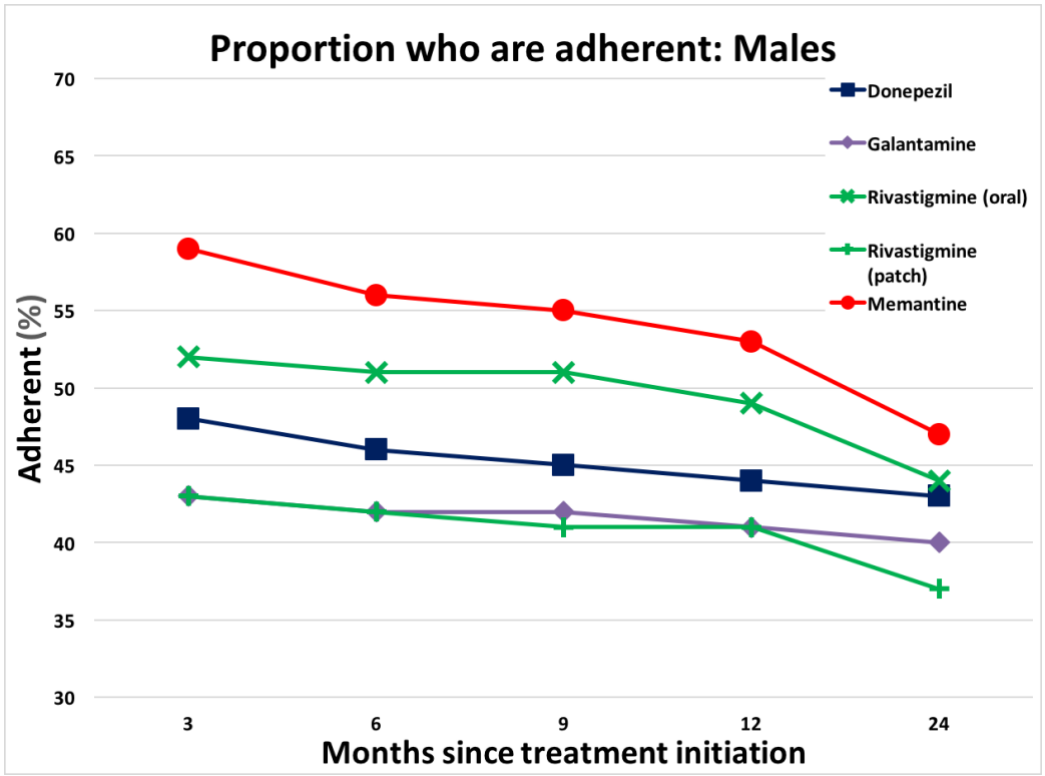


Table S8: Proportion of MNCD patients adherent to their treatment: Sensitivity analyses varying prescription duration and grace period definitions

	All (n = 25,071)	Male (n = 9,226)	Female (n = 15,845)
Using a 30-day duration and 30-day grace period, %			
3 months	62	61	63
6 months	57	55	58
9 months	55	53	56
12 months	54	52	56
24 months	53	51	55
Using a 30-day duration and 0-day grace period, %			
3 months	63	62	64
6 months	58	56	60
9 months	56	54	58
12 months	56	53	57
24 months	54	52	56
Using a 30-day duration and 60-day grace period, %			
3 months	100	100	100
6 months	88	89	88
9 months	85	86	85
12 months	84	85	84
24 months	82	83	82
Using a 14-day duration and 14-day grace period, %			
3 months	61	59	61
6 months	56	54	57
9 months	54	52	55
12 months	53	51	54
24 months	52	49	53
Using a 14-day duration and 0-day grace period, %			
3 months	8	7	9
6 months	8	6	9
9 months	8	6	8
12 months	8	6	8
24 months	8	7	8
Using a 14-day duration and 28-day grace period, %			
3 months	79	79	79
6 months	72	71	73
9 months	69	68	70
12 months	68	67	69
24 months	65	63	66
Using a 60-day duration and 60-day grace period, %			
3 months	100	100	100
6 months	97	97	97
9 months	95	96	95
12 months	92	92	92
24 months	84	84	83

Using a 60-day duration and 0-day grace period, %			
3 months	62	61	63
6 months	57	55	58
9 months	55	53	56
12 months	54	52	56
24 months	53	51	55
Using a 60-day duration and 120-day grace period, %			
3 months	100	100	100
6 months	100	100	100
9 months	95	94	95
12 months	91	92	91
24 months	87	87	86

Table S9: Time to MNCD drug initiation, by sex: Sensitivity analyses to restrict to patients diagnosed from 2002-2017

	Number of events	Patients at risk	Crude HR (95% CI)	Adjusted± HR (95% CI)
Time to treatment initiation				
ChEI	21,099	81,470	--	--
Females	13,455	51,986	0.99 (0.96-1.01)	1.06 (1.03-1.09)
Males	7,654	29,439	1.00 (ref)	1.00 (ref)
Donepezil	15,778	81,470	--	--
Females	10,283	51,986	1.06 (1.03-1.10)	1.11 (1.07-1.15)
Males	5,495	29,439	1.00 (ref)	1.00 (ref)
Galantamine	2,920	81,470	--	--
Females	1,893	51,986	1.03 (0.96-1.11)	1.09 (1.00-1.18)
Males	1,027	29,439	1.00 (ref)	1.00 (ref)
Rivastigmine (all)	2,401	81,470	--	--
Females	1,269	51,986	0.62 (0.57-0.67)	0.73 (0.67-0.80)
Males	1,132	29,439	1.00 (ref)	1.00 (ref)
Rivastigmine (Oral)	1,220	81,470	--	--
Females	559	51,986	0.47 (0.42-0.53)	0.59 (0.52-0.67)
Males	661	29,439	1.00 (ref)	1.00 (ref)
Rivastigmine (Patch)*	1,168	65,283	--	--
Females	701	41,334	0.85 (0.76-0.96)	0.92 (0.81-1.04)
Males	467	23,949	1.00 (ref)	1.00 (ref)
Memantine	3,122	81,470	--	--
Females	1,860	51,986	0.81 (0.75-0.87)	0.81 (0.75-0.88)
Males	1,262	29,439	1.00 (ref)	1.00 (ref)

ChEI: cholinesterase inhibitor. CI: confidence interval. HR: hazard ratio.

±Models were adjusted for age at diagnosis, year of diagnosis, lifestyle variables (smoking, alcohol-related disorders, BMI), MNCD subtype, frailty and Charlson-Deyo comorbidity score, indicators of MNCD severity (urinary & fecal incontinence, falls, hip fracture, pressure ulcers, malnutrition, delirium), drugs (total number, antidepressants, antipsychotics, anxiolytics, hypnotics, overactive bladder control agents, Anticholinergic Cognitive Burden Scale score), medical contacts (number of GP visits, nursing home residence) and neuropsychiatric symptoms.

CHAPTER 5: ADDITIONAL RESULTS

A total of 117,948 patients with a diagnosis for a MNCD were identified in the cohort, among whom 26,923 (23%) of patients did not meet inclusion and data quality criteria (see manuscript Figure S1). The most frequent reasons for exclusion were less than 1 year of follow-up prior to MNCD diagnosis (n=11,095), which was necessary to measure confounders and establish the incident cohort, and age less than 65 at diagnosis (n=5,314), which indicates early-onset disease that is clinically distinct from MNCD of older age. There were 4,260 patients who were excluded due to the evidence of a ChEI or memantine prescription before the recorded diagnosis date, which could possibly represent patients who had unrecorded established disease or, more likely, off-label use of drugs; there are no approved indications for either drug class other than MNCD.

A total of 91,025 patients diagnosed with MNCD were included in the base cohort (See manuscript Table 1). The mean duration of follow-up was 20.8 months. History of comorbidities as assessed using all-available lookback data, and prescriptions were measured in year prior to diagnosis (see section 3.8). As expected, the group was predominantly female (64%), with a mean age of 83 years, and the majority lived in England. Diagnoses were well distributed over calendar time. Lifestyle variable distributions are representative of the CPRD dataset, and the larger UK population, with 46% current or past smokers, 7% history of alcohol-related disorders, 32% overweight or obese[391]. The mean Charlson-Deyo comorbidity score was 2.7, suggesting an average of 1 or 2 additional serious comorbidities as dementia is a Charlson-Deyo item. Given that the cohort was restricted to older adults with dementia, it is not surprising that a history of incontinence (14%), falls (20%) and delirium (20%) was common. Polypharmacy, defined by Clegg as ≥5 distinct drugs[410], was observed, with patients taking an average of 9 (standard deviation=8) medications at baseline; use of antidepressants (30%), antipsychotics (10%), anxiolytics (5%) and hypnotics (12%) was noted. Antimuscarinics, for the symptomatic control of overactive bladder syndrome were used in 7%. Using our version of the Electronic Frailty Index that was adapted for dementia, 25% were classified as fit, 44% mild frailty, and 24% and 7% as moderately and severely frail, respectively. In the year prior to MNCD diagnosis, patients saw their GP an average of 8.2 times, and 2% were seen by their GP in a nursing home. Neuropsychiatric symptoms

before MNCD diagnosis were common (51%), most often depression or dysphoria (39%) or anxiety (20%).

Among the base cohort of identified MNCD cases, 25,071 (28%) received at least 1 MNCD prescription during follow-up and contributed to the study cohort (Table 5.1). The treated and untreated groups were similar, except those who received a drug were on average younger (81 versus 84 years) and a larger proportion lived in Northern Ireland (6% versus 2%).

Table 5.1: Characteristics of MNCD patients at baseline, by MNCD drug status

	No drug (n=65,954)	At least 1 drug (n=25,071)	Standardized mean difference
Months of follow-up, mean (SD)	25.5 (25.7)	8.7 (14.0)	0.73
Female, (%)	64%	63%	0.00
Age at MNCD diagnosis, mean (SD)	84 (7)	81 (6)	0.43
Country, n (%)			
England	76%	72%	0.00
Northern Ireland	2%	6%	0.29
Scotland	11%	14%	0.01
Wales	11%	8%	0.02
Smoking status, (%)			
Ever	45%	48%	0.00
Never	35%	40%	0.00
Unknown	20%	11%	0.02
Alcohol-related disorder, (%)	7%	7%	0.00
Body Mass Index (kg/m^2), (%)			
< 18.5	5%	4%	0.01
18.5 – 24.9	31%	35%	0.04
25.0-29.9	20%	26%	0.01
≥30	10%	11%	0.01
Unknown	35%	23%	0.01
MNCD sub-type diagnosed at baseline, (%)			
Alzheimer's	50%	73%	0.00
Vascular MNCD	28%	8%	0.05
MNCD due to multiple etiologies	<1%	1%	0.00
Other MNCD*	2%	3%	0.16
Non-specific MNCD	20%	15%	0.01
Charlson-Deyo Comorbidity Index, mean (SD)	2.7 (1.8)	2.5 (1.6)	0.01
Indicators of MNCD severity, (%)			

	No drug (n=65,954)	At least 1 drug (n=25,071)	Standardized mean difference
Urinary & fecal incontinence	15%	13%	0.01
Fall(s)	21%	15%	0.01
Hip fracture	7%	4%	0.07
Pressure ulcers	13%	10%	0.01
Malnutrition	12%	12%	0.00
Diagnosis of delirium, (%)	21%	12%	0.02
History of neuropsychiatric symptoms, (%)	50%	53%	0.00
Agitation or aggression	6%	3%	0.12
Anxiety	19%	22%	0.00
Depression or dysphoria	38%	41%	0.00
Other neuropsychiatric symptoms‡	6%	6%	0.00
Modified Electronic Frailty Index			
Fit	23%	28%	0.00
Mild frailty	44%	46%	0.00
Moderate frailty	25%	21%	0.00
Severe frailty	7%	5%	0.04
Total number of distinct drugs, (%)			
0	3%	2%	0.16
1-5	24%	29%	0.00
6-10	32%	35%	0.00
11-15	22%	20%	0.00
≥ 16	19%	14%	0.01
Drugs prescribed, (%)			
Antidepressants	30%	30%	0.00
Antipsychotics	12%	5%	0.08
Anxiolytics	5%	5%	0.00
Hypnotics	13%	10%	0.01
Overactive bladder control	7%	7%	0.00
Anticholinergic Cognitive Burden Scale, mean (SD)	2.2 (2.3)	1.8 (2.1)	0.18
Number of community GP visits, mean (SD)	8.2 (10.1)	8.3 (8.9)	0.01
Seen by GP in nursing home, (%)	2%	1%	0.00

GP: general practitioner; MNCD: major neurocognitive disorders; SD: standard deviation. *Other MNCD subtypes include MNCD due to Parkinson's disease, MNCD with Lewy bodies, and frontotemporal MNCD. ‡ Other neuropsychiatric symptoms include aberrant motor behavior, apathy, delusions, disinhibition, euphoria, irritability or lability, and hallucinations. Comorbid conditions were assessed using all available lookback data. Prior drug use was assessed in the year prior to major neurocognitive disorder diagnosis. Cells with values less than 5 have been suppressed (s), as per CPRD data regulations.

OVERALL MNCD MEDICATION UTILIZATION

Figure 5.1 presents the total numbers of prescription per complete year from 1997 to 2016; 2017 was excluded because the observation period ended on March 31. Prescription volume peaked in 2014. ChEIs make up the majority of prescriptions for each year under examination (Figure 5.1). From 2001-2012, each of the ChEIs, specifically donepezil > galantamine > rivastigmine, were more commonly prescribed than memantine. In 2013, the following changes are noted: the number of galantamine and rivastigmine prescriptions were approximately equivalent, and memantine overtook both of them to become the second most common MNCD medication.

Figure 5.1: Total MNCD prescriptions per year, by drug, from 1997-2016

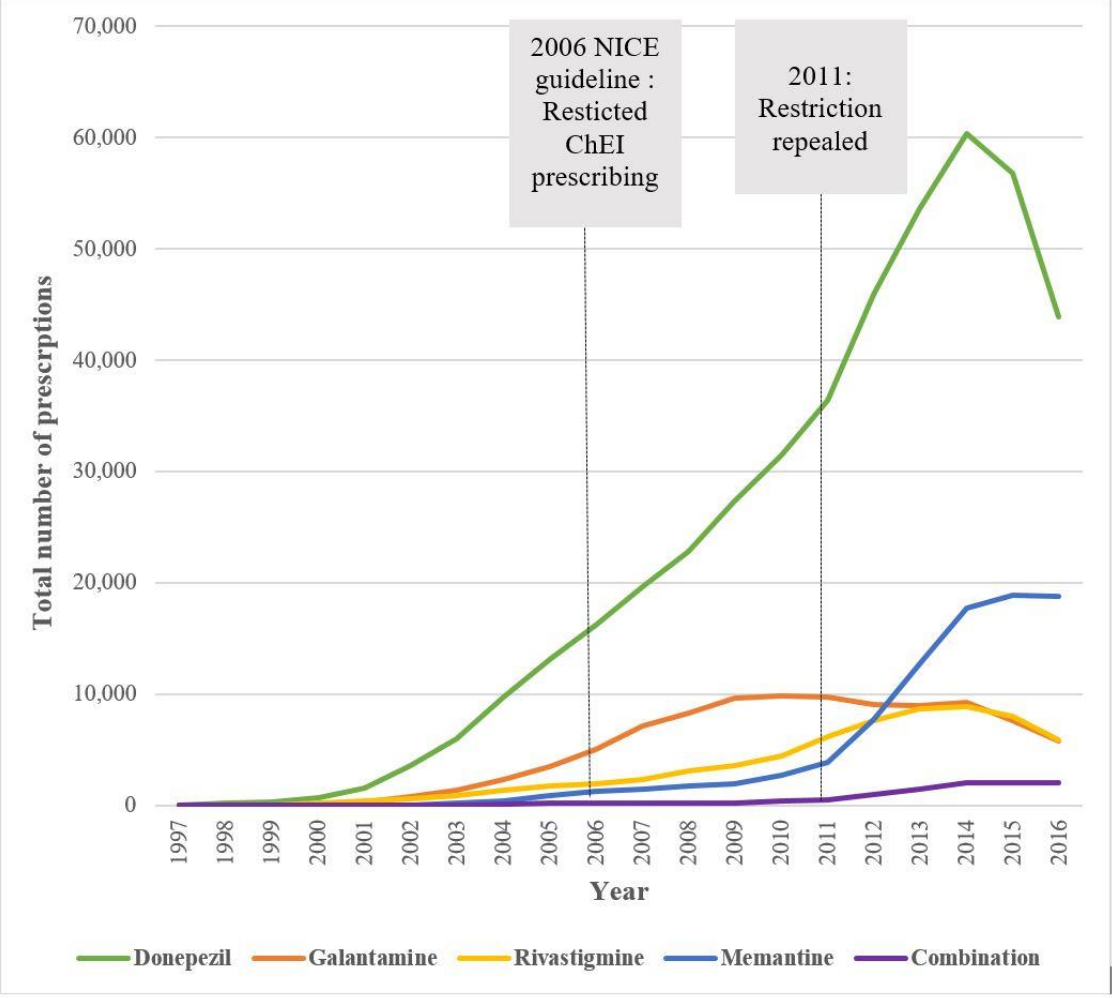
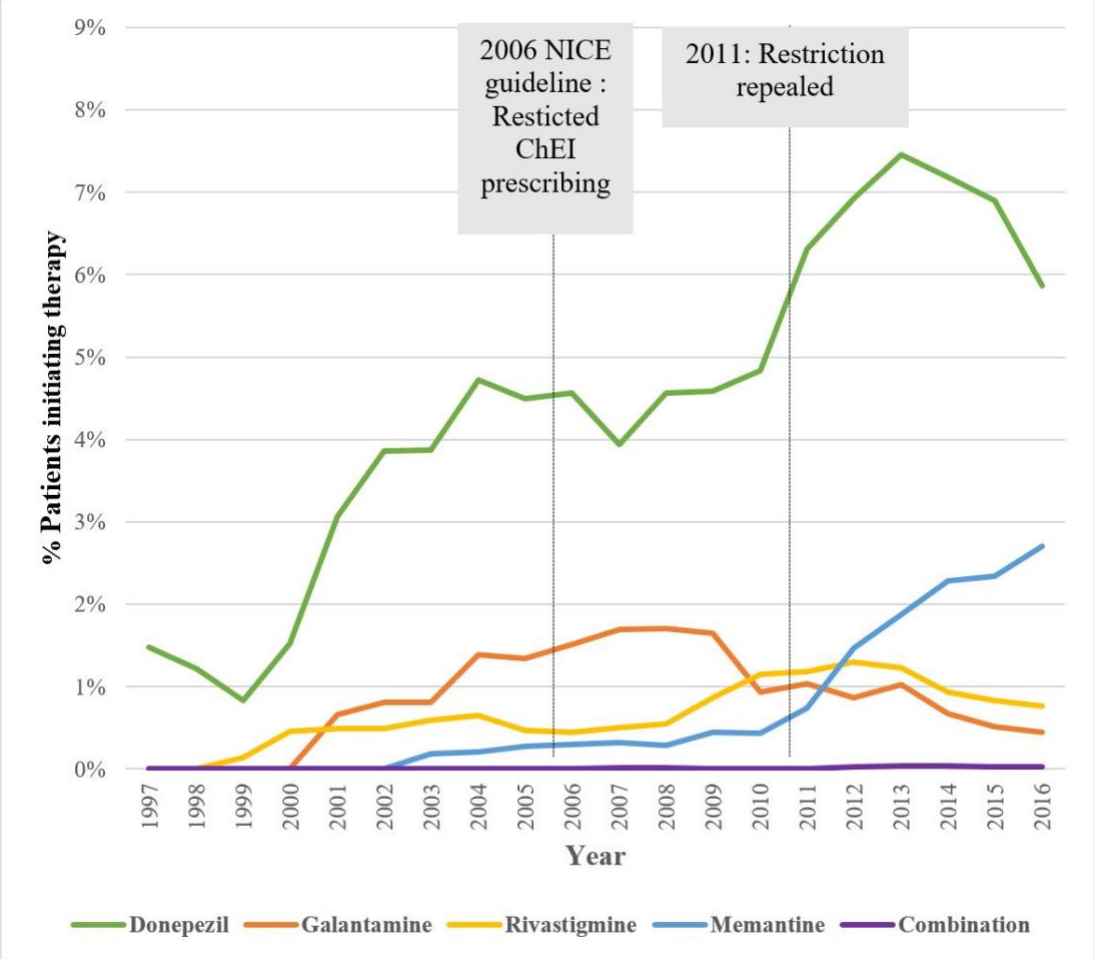


Figure 5.2 illustrates the proportion of patients who initiate MNCD medication therapy among those with follow-up data during the calendar year; similarly, data are restricted to 1997-2016. Initiation incidence rose from 1999 to 2006, then stagnated from 2006-2010; trends which reflect the uptake and then restricted use periods (indicated with vertical dashed lines) imposed by the NICE guidelines (see section 2.4.1). After the guidelines were revised to allow more liberal use in 2011, initiation rates increased to a peak in 2013. At each year, donepezil was the most frequently initiated drug among those at risk of initiation. Galantamine was initially more frequently utilized than the other ChEI option, rivastigmine, but was overtaken in 2010. Memantine initiation has become more common since 2011. Combination therapy uptake was very low, reflecting the non-approval of the treatment strategy in the UK.

Figure 5.2: Proportion of patients who initiate MNCD drug therapies among those with follow-up data during the calendar year: by drug and year



Except where the stratifying variable, all models were adjusted for age at and year of diagnosis, lifestyle variables (smoking, alcohol-related disorders, BMI), MNCD subtype, frailty and Charlson-Deyo comorbidity score, Indicators of MNCD severity (urinary & fecal incontinence, falls, hip fracture, pressure ulcers, malnutrition, delirium), drugs (total number, antidepressants, antipsychotics, anxiolytics, hypnotics, overactive bladder control agents, Anticholinergic Cognitive Burden Scale score), medical contacts (number of GP visits, nursing home residence) and neuropsychiatric symptoms. Drugs were assessed in year prior to diagnosis, and comorbidities were assessed using all-available lookback data prior to MNCD diagnosis.

MNCD MEDICATION UTILIZATION PATTERNS, BY AGE AT DIAGNOSIS

For the subtype and age analyses, a 30-day prescription duration and 30-day grace period definitions were used. Age at diagnosis was estimated using January 1 on the year of birth; for data confidentiality reasons, the CPRD does not share the month or date of birth. For the purpose of analysis, age groups of 65-74, 75-84, 85-94 and 95+ were formed.

With increasing age groups, an increase in the prevalence of females, indicators of dementia severity, frailty and nursing home utilization was found; decreases were noted in smoking and alcohol-related disorder history, as well as overweight and obesity. There were no differences in distributions of dementia subtype, polypharmacy (≥6 drugs), anticholinergic burden, or neuropsychiatric symptoms by age category (Table 5.2).

Table 5.2: Baseline characteristics (at date of MNCD diagnosis), overall and by age group

	All (n=91,025)	65-74 (n=10,276)	75-84 (n=38,499)	85-94 (n=37,664)	≥95 (n=4,586)
Months of follow-up, mean (SD)	20.8 (24.3)	26.5 (31.2)	22.3 (25.7)	18.5 (20.7)	15.1 (16.4)
Female, (%)	64%	52%	60%	70%	80%
Country, (%)					
England	75%	73%	74%	75%	80%
Northern Ireland	3%	4%	3%	3%	2%
Scotland	12%	14%	12%	11%	8%
Wales	10%	10%	10%	11%	10%
Smoking status, (%)					
Ever	46%	55%	50%	41%	28%
Never	37%	31%	34%	39%	46%
Unknown	18%	14%	16%	19%	26%
Alcohol-related disorders, (%)	7%	12%	8%	5%	3%
Body Mass Index (kg/m^2), (%)					
< 18.5	4%	4%	4%	5%	6%
18.5 – 24.9	32%	29%	32%	33%	27%
25.0-29.9	22%	26%	25%	19%	12%
≥30	10%	17%	12%	7%	3%
Unknown	31%	25%	27%	35%	53%
MNCD sub-type diagnosed at baseline, (%)					
Alzheimer's	56%	53%	56%	57%	58%
Vascular MNCD	23%	20%	23%	23%	19%
MNCD due to multiple etiologies	1%	1%	1%	1%	<1%
Non-specific MNCD	18%	22%	18%	18%	22%
Other MNCD	2%	4%	2%	1%	1%
Charlson-Deyo Comorbidity Index, mean (SD)	1.4 (0.8)	1.4 (0.8)	1.4 (0.8)	1.4 (0.8)	1.3 (0.7)
Indicators of MNCD severity, (%)					
Urinary & fecal incontinence	14%	11%	13%	15%	16%
Fall(s)	20%	10%	16%	24%	32%

	All (n=91,025)	65-74 (n=10,276)	75-84 (n=38,499)	85-94 (n=37,664)	≥95 (n=4,586)
Hip fracture	6%	2%	4%	8%	13%
Pressure ulcers	12%	7%	10%	14%	18%
Malnutrition	12%	11%	12%	12%	11%
Diagnosis of delirium, (%)	19%	12%	17%	22%	29%
History of neuropsychiatric symptoms, (%)	51%	53%	52%	50%	46%
Agitation or aggression	5%	5%	5%	5%	8%
Anxiety	20%	24%	21%	18%	15%
Depression or dysphoria	39%	40%	40%	38%	31%
Other neuropsychiatric symptoms‡	6%	5%	5%	6%	7%
Modified Electronic Frailty Index Ratio					
Fit	25%	40%	28%	20%	18%
Mild frailty	45%	43%	46%	45%	143%
Moderate frailty	24%	14%	21%	28%	30%
Severe frailty	6%	3%	5%	8%	9%
Total number of distinct drugs, (%)					
0	3%	4%	3%	3%	2%
1-5	25%	32%	26%	23%	22%
6-10	33%	31%	33%	33%	32%
11-15	22%	18%	21%	23%	24%
>16	18%	15%	17%	18%	20%
Drugs prescribed, (%)					
Antidepressants	30%	38%	31%	27%	26%
Antipsychotics	10%	10%	9%	10%	14%
Anxiolytics	5%	7%	5%	5%	5%
Hypnotics	12%	11%	11%	13%	16%
Overactive bladder control	7%	6%	7%	7%	5%
Anticholinergic Cognitive Burden Scale total score, mean (SD)	2.1 (2.2)	2.1 (2.4)	2.1 (2.3)	2.1 (2.2)	2.0 (2.1)
Number of community GP visits, mean (SD)	8.2 (9.7)	7.2 (9.2)	7.8 (9.7)	8.8 (9.9)	8.6 (9.8)
Seen by GP in nursing home, (%)	2%	<1%	2%	2%	6%

GP: general practitioner; MNCD: major neurocognitive disorders; SD: standard deviation. *Other MNCD subtypes include MNCD due to Parkinson's disease, MNCD with Lewy bodies, and frontotemporal MNCD. ‡ Other neuropsychiatric symptoms include aberrant motor behavior, apathy, delusions, disinhibition, euphoria, irritability or lability, and hallucinations. Comorbid conditions were assessed using all available lookback data. Prior drug use was assessed in the year prior to major neurocognitive disorder diagnosis.

Treatment initiation

An increase in age was significantly associated with less ChEI and more memantine prescriptions (linear test for trend, χ^2 $p<0.001$) (Table 5.3). These results were not surprising, given that age-related comorbidity may produce confounding by contraindication related to ChEI safety (see section 2.1.3), and that memantine is more often prescribed for advanced disease which is in turn associated with increased age (see section 2.2).

With increasing age, median time to first treatment initiation decreased from the 65-74, 75-84 and 85-94 groups, but paradoxically increased slightly in the 95+ groups for galantamine and rivastigmine, especially the transdermal formulation (Table 5.4). As compared to the youngest group, the 85-94 (adjusted HR=0.67, 95% CI 0.64-0.70) and 95+ group (adjusted HR=0.25, 95% CI 0.23-0.28) were significantly less likely to receive an MNCD medication (Table 5.5), indicating a decreased instantaneous risk of treatment utilization at each point in follow-up time.

Table 5.3: Distribution of initial MNCD treatment, by age group at baseline

Age group	All	ChEI, any	Donepezil	Galantamine	Rivastigmine	Rivastigmine, oral	Rivastigmine, transdermal	Memantine	Combination therapy
65-74	3,901	91%	66%	13%	12%	7%	5%	9%	<1%
75-84	12,636	88%	65%	13%	10%	6%	5%	12%	<1%
85-94	8,194	85%	66%	11%	8%	4%	4%	15%	<1%
95+	340	72%	61%	5%	6%	2%	3%	28%	0%

A total of 65,954 patients (72%) never received an MNCD drug, and were excluded from this analysis.

Table 5.4: Median (interquartile range) time in months from diagnosis to first treatment initiation, by age group at baseline

Age group	All	ChEI, any	Donepezil	Galantamine	Rivastigmine	Rivastigmine, oral	Rivastigmine, transdermal	Memantine	Combination therapy
65-74	4.5 (1.3-11.1)	4.3 (1.2-10.2)	4.1 (1.2-9.6)	4.9 (1.2-11.6)	5.3 (1.9-12.3)	5.1 1.3-12.1)	5.6 (2.5-12.4)	7.1 (1.8-24.7)	52.6 (25.5-68.0)
75-84	4.0 (1.2-10.4)	3.9 (1.1-9.7)	3.7 (1.1-9.3)	4.3 (1.0-10.5)	4.9 (1.5-11.7)	4.2 (1.1-10.4)	5.8 (2.3-13.2)	5.8 (1.8-17.8)	18.2 (6.4-48.9)
85-94	3.4 (1.0-8.0)	3.3 (0.9-7.6)	3.1 (0.9-7.2)	3.9 (1.1-9.1)	4.1 (1.2-9.2)	3.7 (1.0-8.2)	4.6 (1.6-9.9)	4.0 (1.1-10.7)	5.2 (1.0-15.9)
95+	2.6 (0.7-6.2)	2.6 (0.9-6.1)	2.6 (0.7-5.5)	4.3 (1.2-9.0)	4.2 (1.1-9.4)	2.2 (1.2-4.8)	7.2 (0.9-15.5)	2.5 (0.4-8.2)	---

*Other MNCD subtypes include MNCD due to Parkinson's disease, MNCD with Lewy bodies, and frontotemporal MNCD. A total of 65,954 patients (72%) never received an MNCD drug, and were excluded from this analysis.

Table 5.5: Instantaneous risk of receiving any MNCD medication, by age group at baseline

	Crude HR (95% CI)	Adjusted HR (95% CI)
65-74	1.00 (ref)	1.00 (ref)
75-84	0.91 (0.88-0.94)	0.96 (0.93-1.00)
85-94	0.63 (0.61-0.66)	0.67 (0.64-0.70)
95+	0.23 (0.21-0.26)	0.25 (0.23-0.28)

Treatment switches

Frequency of switching by age groups roughly represent the distribution of the age groups in the cohort (Table 5.6). Median time to switch was 10.5 months, and was shorter for a switch from a first to a second ChEI than for a ChEI to memantine (Table 5.7). With increasing age, a decreased hazard of switching is noted in a dose-response type fashion (Table 5.8).

Table 5.6: Frequency of prescription switches, by age group at baseline

	Overall	First ChEI to another ChEI	ChEI to memantine	ChEI to combination
Overall	3,212	49%	41%	7%
65-74	24%	23%	25%	s
75-84	54%	53%	53%	s
85-94	22%	24%	21%	s
95+	<1%	<1%	1%	s

ChEI: cholinesterase inhibitor. The following have been excluded from this analysis: 65,954 patients (72%) never received an MNCD drug and 21,859 (24%) did not switch. Cells with values less than 5 have been suppressed (s), as per CPRD data regulations.

Table 5.7: Median (interquartile range) months from first treatment initiation to first switch, by age group at baseline

	Overall	First ChEI to another ChEI	ChEI to memantine	ChEI to combination
Overall	3,212	49%	41%	7%
65-74	13.6 (5.2-30.8)	7.4 (3.1-15.9)	23.5 (11.0-41.2)	-
75-84	11.0 (4.1-24.9)	5.8 (2.4-13.4)	19.3 (8.9-37.3)	-
85-94	7.2 (3.2-15.9)	4.9 (2.2-10.4)	11.5 (5.5-24.0)	-
95+	4.1 (1.4-8.4)	2.1 (1.2-3.7)	8.4 (4.5-15.0)	-

ChEI: cholinesterase inhibitor; MNCD: major neurocognitive disorders. *Other MNCD subtypes include MNCD due to Parkinson's disease, MNCD with Lewy bodies, and frontotemporal MNCD. The following have been excluded from this analysis: 65,954 patients (72%) never received an MNCD drug and 21,859 (24%) did not switch.

Table 5.8: Rate of switching MNCD medication, by age group at baseline

	Crude HR (95% CI)	Adjusted HR (95% CI)
65-74	1.00 (ref)	1.00 (ref)
75-84	0.75 (0.69-0.81)	0.72 (0.66-0.79)
85-94	0.55 (0.50-0.61)	0.51 (0.46-0.57)
95+	0.32 (0.19-0.55)	0.28 (0.17-0.48)

A total of 65,954 patients (72%) never received an MNCD drug and were excluded from this analysis.

Treatment persistence

There were no significant age group differences in the adjusted likelihood to discontinue after first drug trial of ChEI or memantine (Table 5.9). While the crude proportion of persistent patients age 95+ was lower at each time point (Figure 5.3), these differences were tested and were not significant (χ^2 $p>0.05$ for trend). For each drug, median time to discontinuation (i.e. persistence) decreased with increasing age group (Table 5.10). Sensitivity analyses to restrict to patients diagnosed before 2016, thereby allowing up to 1 year of follow-up among those diagnosed at the end of the study, yielded similar results (data not shown).

Table 5.9: Likelihood of drug discontinuation after first treatment trial, by age group at baseline

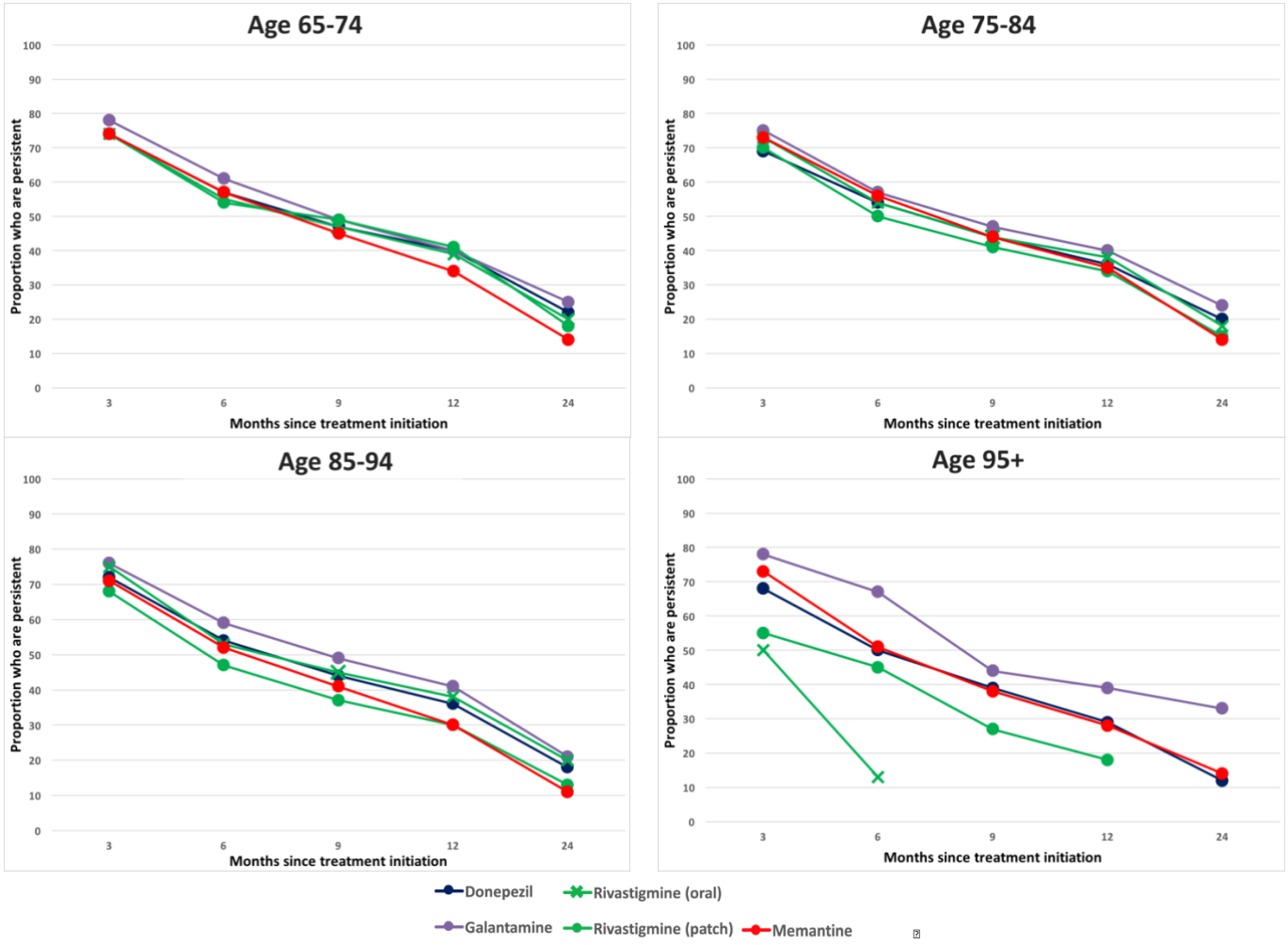
	ChEIs, overall Adjusted OR (95% CI)	Memantine Adjusted OR (95% CI)
65-74	1.00 (ref)	1.00 (ref)
75-84	0.94 (0.85-1.04)	1.06 (0.75-1.49)
85-94	0.97 (0.87-1.09)	0.98 (0.68-1.40)
95+	1.20 (0.85-1.70)	0.76 (0.35-1.63)

Table 5.10: Median (interquartile range) time from drug initiation to discontinuation, by age group at baseline

Age group	ChEIs, overall	Donepezil	Galantamine	Rivastigmine, either	Rivastigmine, oral	Rivastigmine, patch	Memantine
65-74	7.9 (2.9-21.3)	7.9 (2.9-21.3)	8.6 (3.3-24.0)	7.7 (2.9-20.5)	7.7 (2.9-20.8)	7.8 (2.8-20.0)	7.5 (2.9-15.5)
75-84	7.8 (2.9-20.5)	7.8 (2.9-20.5)	7.8 (2.9-23.0)	6.5 (2.6-16.9)	6.9 (2.8-18.2)	6.1 (2.3-16.2)	7.4 (2.6-16.5)
85-94	7.0 (2.7-18.5)	7.0 (2.7-18.5)	8.4 (3.1-20.6)	5.8 (2.6-16.9)	7.2 (3.0-20.7)	5.4 (2.0-14.9)	6.3 (2.4-13.9)
95+	5.8 (2.0-14.8)	5.8 (2.0-14.8)	7.9 (5.0-24.0)	3.4 (2.0-8.1)	3.0 (2.0-5.1)	4.4 (2.0-11.3)	6.1 (2.8-13.8)

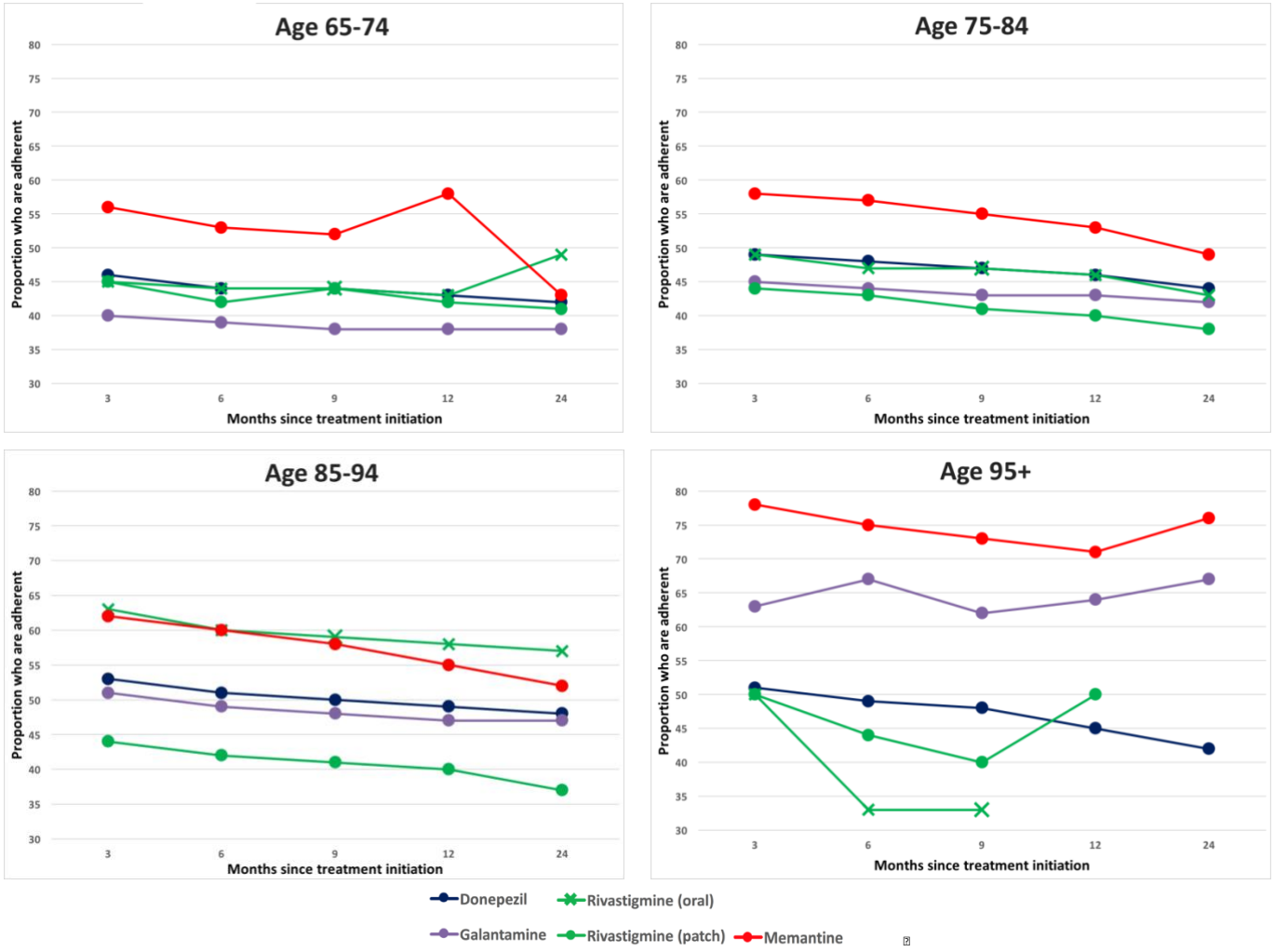
A total of 65,954 patients (72%) never received an MNCD drug and were excluded from this analysis.

Figure 5.3: Proportion of patients classified as persistent, by age group at baseline



Treatment adherence

Figure 5.4: Proportion of patients classified as adherent, by age group at baseline



As compared to the youngest group, no significant differences in time to non-adherence were found for the 75-84 or the 85-94 groups (Table 5.11). The oldest group had a shorter time to non-adherence (i.e. less adherence) to ChEIs overall, especially donepezil and rivastigmine, but neither galantamine nor memantine.

Table 5.11: Adjusted HR for time to non-adherence, by age group at baseline

Age group	ChEIs	Donepezil	Galantamine	Rivastigmine, either	Rivastigmine, oral	Rivastigmine, patch	Memantine
65-74	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
75-84	1.00 (0.95-1.06)	0.99 (0.93-1.06)	0.98 (0.85-1.12)	1.09 (0.94-1.27)	1.07 (0.87-1.32)	1.16 (0.91-1.48)	0.96 (0.79-1.16)
85-94	1.07 (1.00-1.14)	1.08 (1.00-1.16)	1.07 (0.91-1.25)	0.99 (0.83-1.19)	0.84 (0.64-1.11)	1.15 (0.88-1.51)	1.05 (0.85-1.28)
95+	1.31 (1.08-1.60)	1.28 (1.03-1.59)	0.73 (0.34-1.57)	4.63 (2.28-9.39)	11.97 (4.12-34.74)	3.01 (1.13-8.06)	0.79 (0.47-1.30)

MNCD MEDICATION UTILIZATION PATTERNS, BY MNCD SUBTYPE

MNCD subtype was described both using a time-fixed definition, where the first diagnosis was used throughout the observation period, and a time-varying definition, where the most recent diagnosis before initiation was used for analysis. Using the time-fixed definition, the most common MNCD subtype was Alzheimer's (73%), followed by non-specific (15%), vascular (8%), other MNCD (3%, which includes MNCD due to Parkinson's disease, MNCD with Lewy bodies and frontotemporal MNCD) and multiple etiologies (1%, formerly referred to as "mixed dementia") (see Table 5.12). Using the time-varying disease subtype definition, 1,500 patients had received an updated MNCD diagnosis prior to drug initiation, most commonly from non-specific MNCD to either Alzheimer's or to multiple etiologies. Of these 1,500, 19 patients had their diagnosis updated twice (indicating a progression from non-specific MNCD, to a specific category, to multiple etiologies).

The majority of patients were diagnosed with either Alzheimer's (56%) or non-specific (18%) MNCD subtypes; clinically, these two groups were similar with respect to baseline characteristics (Table 5.12). Vascular MNCD patients were more likely to be male, have a history of smoking and alcohol-related disorders, had more polypharmacy, comorbidities and frailty than the rest of the cohort, together indicating a profile of patients who were less healthy. Patients classified as having "other MNCD" were substantially more male, younger, had higher rates of antipsychotic medication utilization and were more frail.

Table 5.12: Baseline characteristics, overall and MNCD subtype

	All (n=91,025, 100%)	Alzheimer's (n=51,230, 56%)	Vascular (n=20,656, 23%)	Multiple etiologies (n=558, <1%)	Other MNCD* (n=1,815, 2%)	Non-specific (n=16,766, 18%)
Months of follow-up, mean (SD)	20.8 (24.3)	19.3 (23.6)	24.0 (24.1)	15.9 (23.0)	15.2 (21.2)	22.6 (26.2)
Female, (%)	64%	67%	58%	62%	43%	62%
Age (years) at MNCD diagnosis, mean (SD)	83 (7)	83 (7)	83 (7)	82 (6)	79 (7)	83 (7)
Country, (%)						
England	75%	75%	73%	s	79%	73%
Northern Ireland	3%	s	s	s	s	s
Scotland	12%	11%	15%	s	9%	11%
Wales	10%	10%	10%	s	10%	11%
Smoking status, n (%)						
Ever	46%	42%	53%	56%	45%	48%
Never	37%	37%	36%	37%	38%	37%
Unknown	18%	21%	11%	6%	17%	15%
Alcohol-related disorders, n (%)	7%	5%	9%	11%	7%	8%
Body Mass Index (kg/m^2), n (%)						
< 18.5	4%	4%	4%	6%	5%	5%
18.5 – 24.9	32%	32%	33%	34%	31%	31%
25.0-29.9	22%	21%	25%	23%	24%	22%
≥30	10%	9%	13%	16%	11%	11%
Unknown	31%	35%	25%	21%	29%	31%
Charlson-Deyo Comorbidity Index, mean (SD)	2.7 (1.7)	2.5 (1.6)	3.2 (1.9)	2.9 (1.9)	2.3 (1.6)	2.7 (1.8)
Indicators of MNCD severity, (%)						
Urinary & fecal incontinence	14%	13%	16%	13%	17%	15%
Fall(s)	20%	17%	23%	20%	24%	21%
Hip fracture	6%	6%	6%	6%	6%	7%
Pressure ulcers	12%	11%	13%	10%	10%	12%
Malnutrition	12%	11%	12%	15%	11%	12%
Diagnosis of delirium, (%)	19%	18%	21%	18%	22%	19%

	All	Alzheimer's	Vascular	Multiple etiologies	Other MNCD*	Non-specific
History of neuropsychiatric symptoms, (%)	51%	47%	58%	63%	58%	53%
Agitation or aggression	5%	5%	5%	4%	5%	6%
Anxiety	20%	19%	20%	22%	24%	20%
Depression or dysphoria	39%	35%	47%	54%	39%	40%
Other neuropsychiatric symptoms‡	6%	5%	6%	7%	17%	6%
Modified Electronic Frailty Index Ratio						
Fit	25%	29%	15%	22%	18%	23%
Mild frailty	44%	45%	44%	42%	47%	45%
Moderate frailty	24%	21%	30%	26%	28%	25%
Severe frailty	7%	5%	11%	10%	7%	7%
Total number of distinct drugs, (%)						
0	3%	4%	1%	2%	1%	2%
1-5	25%	30%	16%	23%	18%	22%
6-10	33%	33%	32%	32%	34%	33%
11-15	22%	20%	26%	24%	25%	23%
>16	18%	14%	25%	19%	21%	20%
Drugs prescribed, (%)						
Antidepressants	30%	28%	34%	30%	30%	31%
Antipsychotics	10%	10%	9%	5%	16%	10%
Anxiolytics	5%	5%	5%	5%	7%	6%
Hypnotics	12%	11%	13%	11%	16%	13%
Overactive bladder control	7%	6%	8%	8%	11%	7%
Anticholinergic Cognitive Burden, mean (SD)	2.1 (2.2)	1.9 (2.2)	2.5 (2.4)	2.2 (2.3)	2.5 (2.4)	2.2 (2.3)
Number of community GP visits, mean (SD)	8.2 (9.7)	7.0 (8.7)	10.4 (11.1)	10.0 (9.3)	10.0 (10.3)	8.7 (10.5)
Seen by GP in nursing home, (%)	2%	2%	2%	<1%	2%	2%

GP: general practitioner; MNCD: major neurocognitive disorders; SD: standard deviation. *Other MNCD subtypes include MNCD due to Parkinson's disease, MNCD with Lewy bodies, and frontotemporal MNCD. ‡ Other neuropsychiatric symptoms include aberrant motor behavior, apathy, delusions, disinhibition, euphoria, irritability or lability, and hallucinations. Cells with values less than 5 have been suppressed (s), as per CPRD data regulations.

Treatment initiation

ChEIs were the predominant treatment initiation class for each MNCD subtype (Table 5.13), especially in Alzheimer's (89%) and "other MNCD" subtypes (94%). The initiation with a ChEI (77%) and memantine (23%) in patients with vascular MNCD was observed, despite the fact that neither class is approved for use in vascular MNCD. Initiation with memantine was lower in "other MNCD", in line with guidelines. Patterns remained similar after the time-varying definition for MNCD diagnosis was applied. Using both the time-fixed and time-varying definitions, after adjustment and as compared to non-specific MNCD, Alzheimer's, multiple etiologies and "other MNCD" subtypes were significant more likely to receive an MNCD medication while patients diagnosed with vascular MNCD were less likely (Table 5.14). Median time to treatment initiation was shorter for "other MNCD" (2.9 months), and higher for non-specific and vascular MNCD (4.7 and 5.7 months, respectively). Median time to initiation was the shortest with donepezil for Alzheimer's and vascular MNCD, and with oral rivastigmine for both other and non-specific MNCD (Table 5.15). Time to initiation with memantine was shortest for patients diagnosed with multiple etiologies MNCD, which might reflect increasing disease severity or complexity. Using the time-varying definition, time to initiation was shorter, especially for memantine.

Table 5.13: Distribution of initial MNCD treatment strategy, by MNCD subtype

	All	ChEI	Donepezil	Galantamine	Rivastigmine	Rivastigmine, oral	Rivastigmine, transdermal	Memantine	Combination therapy
	25,071	87%	65%	12%	10%	5%	5%	13%	<1%
MNCD diagnosis at baseline									
Alzheimer's	18,189	89%	69%	12%	7%	3%	4%	11%	s
Vascular	2,121	77%	53%	13%	11%	5%	5%	23%	s
Multiple etiologies	267	86%	60%	14%	12%	7%	5%	14%	s
Other MNCD*	822	94%	28%	5%	61%	41%	20%	5%	s
Non-specific	3,672	84%	63%	11%	11%	6%	5%	16%	s
Time-varying diagnosis									
Alzheimer's	18,749	89%	69%	13%	7%	4%	3%	11%	s
Vascular	1,841	76%	53%	13%	10%	5%	5%	24%	s
Multiple etiologies	896	83%	56%	13%	14%	6%	8%	17%	s
Other MNCD*	813	95%	28%	5%	62%	21%	42%	16%	s
Non-specific	2,772	84%	63%	10%	11%	5%	6%	16%	s

*Other MNCD subtypes include MNCD due to Parkinson's disease, MNCD with Lewy bodies, and frontotemporal MNCD. Cells with values less than 5 have been suppressed (s), as per CPRD data regulations. A total of 65,954 patients (72%) never received an MNCD drug, and were excluded from this analysis.

Table 5.14: Instantaneous risk of receiving any MNCD medication, by MNCD subtype

	Crude HR (95% CI)	Adjusted HR (95% CI)
MNCD diagnosis at baseline		
Alzheimer's disease	1.78 (1.71-1.84)	2.04 (1.97-2.11)
Vascular MNCD	0.44 (0.42-0.47)	0.43 (0.41-0.46)
Multiple aetiologies	2.70 (2.39-3.06)	2.35 (2.07-2.66)
Other MNCD*	2.59 (2.41-2.80)	2.37 (2.19-2.55)
Non-specific MNCD	1.00 (ref)	1.00 (ref)
Time-varying diagnosis		
Alzheimer's disease	1.71 (1.65-1.77)	1.95 (1.89-2.02)
Vascular MNCD	0.42 (0.40-0.45)	0.41 (0.39-0.43)
Multiple etiologies	1.87 (1.74-2.02)	2.08 (1.93-2.24)
Other MNCD*	2.53 (2.35-2.73)	2.26 (2.10-2.44)
Non-specific MNCD	1.00 (ref)	1.00 (ref)

*Other MNCD subtypes include MNCD due to Parkinson's disease, MNCD with Lewy bodies, and frontotemporal MNCD.

Table 5.15: Median (interquartile range) months from diagnosis to first treatment initiation, by MNCD subtype

	All	ChEI	Donepezil	Galantamine	Rivastigmine	Rivastigmine oral	Rivastigmine transdermal	Memantine	Combination therapy
MNCD diagnosis at baseline, median (interquartile range)									
Alzheimer's disease	3.7 (1.0-8.8)	3.5 (1.0-8.4)	3.3 (0.9-7.9)	4.0 (1.0-9.6)	5.2 (1.7-11.4)	5.0 (1.3-10.9)	5.3 (2.1-12.2)	4.4 (1.4-13.0)	23.4 (8.9-51.9)
Vascular MNCD	5.7 (1.7-15.4)	5.5 (1.7-13.7)	5.2 (1.6-13.2)	5.2 (1.4-14.0)	7.6 (3.0-14.6)	7.6 (2.5-15.3)	7.7 (3.5-14.5)	6.6 (1.7-23.8)	---
Multiple etiologies	3.1 (0.8-6.9)	3.1 (0.9-7.0)	2.7 (0.8-6.3)	5.0 (1.2-9.7)	3.7 (2.7-10.3)	3.6 (1.0-6.7)	7.3 (3.3-12.8)	2.6 (0.4-6.5)	---
Other MNCD*	2.9 (0.8-7.0)	2.8 (0.8-6.9)	2.7 (1.0-7.8)	4.9 (0.5-11.2)	6.5 (2.8-17.6)	2.5 (0.7-6.4)	3.2 (0.6-6.5)	3.7 (1.4-8.9)	---
Non-specific MNCD	4.7 (1.4-11.2)	4.6 (1.4-10.6)	4.4 (1.4-9.9)	4.8 (1.5-12.2)	5.3 (1.6-13.1)	4.2 (1.0-10.4)	6.3 (3.0-16.6)	5.7 (1.4-19.0)	---
Time-varying diagnosis, median (interquartile range)									
Alzheimer's disease	3.6 (1.0-8.5)	3.5 (0.9-8.2)	3.3 (0.9-7.7)	3.9 (0.9-9.5)	5.0 (1.6-11.2)	4.9 (1.1-10.5)	5.1 (1.9-12.0)	4.3 (1.2-12.2)	---
Vascular MNCD	4.6 (1.2-4.6)	4.4 (1.2-11.2)	4.1 (1.0-10.7)	4.0 (1.0-11.7)	6.6 (2.5-12.5)	5.5 (1.7-12.3)	7.1 (3.0-12.5)	5.9 (1.3-20.3)	---
Multiple etiologies	2.7 (0.7-7.1)	2.6 (0.7-6.9)	2.4 (0.6-6.4)	2.7 (0.7-8.2)	3.6 (1.0-9.9)	3.0 (0.7-16.2)	5.9 (1.4-12.1)	2.8 (0.5-7.3)	---
Other MNCD*	2.7 (0.8-6.4)	2.6 (0.7-6.4)	2.6 (0.9-6.8)	2.8 (0.6-11.2)	2.6 (0.7-6.1)	2.4 (0.7-5.9)	3.2 (0.6-6.4)	3.3 (1.4-7.9)	---
Non-specific MNCD	3.6 (0.9-8.8)	3.5 (0.9-8.5)	3.4 (0.9-8.3)	3.3 (0.8-8.6)	4.1 (1.1-9.5)	3.5 (0.8-7.4)	5.2 (2.1-12.6)	4.2 (0.9-13.5)	---

*Other MNCD subtypes include MNCD due to Parkinson's disease, MNCD with Lewy bodies, and frontotemporal MNCD. A total of 65,954 patients (72%) never received an MNCD drug, and were excluded from this analysis.

Treatment switches

Treatment switching frequencies represented the relative distribution of MNCD subtypes in the study cohort (switchers were 70% Alzheimer's, 15% non-specific, 9% vascular, 5% other, 1% mixed) (Table 5.16). Switches from first to a second ChEI (49%) and a ChEI to memantine (41%) were most common; other switches outlined in section 3.7 are not described by subtype as CPRD data regulations prohibit publishing results where cells have values of 5 or less. Median time to switch was 10.5 months, and was shorter for a switch from a first to a second ChEI than from a ChEI to memantine (Table 5.17). After adjustment for relevant confounders and compared to non-specific MNCD, only the "other MNCD" subtypes were significantly more likely to switch MNCD medication (HR=1.40, 95% CI 1.17-1.69) (Table 5.18). When using the time-varying definition, Alzheimer's patients were significantly less likely to switch (adjusted HR=0.86, 95% CI 0.75-0.98).

Table 5.16: Frequency of prescription switching, by MNCD subtype

	Overall	First ChEI to another ChEI	ChEI to memantine	ChEI to combination
n =	3,212	49%	41%	7%
MNCD diagnosis at baseline				
Alzheimer's disease	70%	68%	74%	s
Vascular MNCD	9%	9%	8%	s
Multiple etiologies	1%	1%	1%	s
Other MNCD*	5%	8%	1%	s
Non-specific MNCD	15%	15%	16%	s
Time-varying diagnosis				
Alzheimer's disease	72%	70%	76%	s
Vascular MNCD	7%	7%	7%	s
Multiple etiologies	4%	5%	3%	s
Other MNCD*	5%	7%	1%	s
Non-specific MNCD	12%	11%	13%	s

ChEI: cholinesterase inhibitor; MNCD: major neurocognitive disorders. *Other MNCD subtypes include MNCD due to Parkinson's disease, MNCD with Lewy bodies, and frontotemporal MNCD. The following have been excluded from this analysis: 65,954 patients (72%) never received an MNCD drug and 21,859 (24%) did not switch. Cells with values less than 5 have been suppressed (s), as per CPRD data regulations.

Table 5.17: Median months from initiation to first switch, by MNCD subtype

	Overall	ChEI to ChEI	ChEI to memantine	ChEI to combination
n =	3,212	49%	41%	7%
MNCD diagnosis at baseline				
Alzheimer's disease	10.8 (4.0-24.8)	5.8 (2.5-13.2)	18.1 (8.3-35.7)	s
Vascular MNCD	9.2 (3.7-23.8)	4.8 (2.1-11.3)	18.0 (8.1-34.6)	s
Multiple etiologies	8.0 (4.8-13.9)	6.7 (4.3-8.5)	17.3 (6.6-26.2)	s
Other MNCD*	9.4 (3.2-17.8)	7.6 (3.1-15.5)	16.6 (10.2-32.3)	s
Non-specific MNCD	10.9 (4.4-25.2)	5.7 (2.6-12.0)	17.9 (7.6-34.4)	s
Time-varying diagnosis				
Alzheimer's disease	10.7 (4.0-24.8)	5.8 (2.5-12.7)	18.1 (8.3-35.5)	s
Vascular MNCD	9.1 (3.6-23.1)	5.1 (2.1-12.8)	17.8 (6.0-32.8)	s
Multiple etiologies	9.4 (3.8-20.4)	5.5 (3.2-10.4)	22.8 (12.9-42.0)	s
Other MNCD*	9.4 (3.1-16.9)	7.4 (2.9-15.0)	17.8 (10.4-37.3)	s
Non-specific MNCD	11.3 (4.3-25.1)	5.7 (2.5-13.1)	17.1 (7.5-32.0)	s

ChEI: cholinesterase inhibitor; MNCD: major neurocognitive disorders. *Other MNCD subtypes include MNCD due to Parkinson's disease, MNCD with Lewy bodies, and frontotemporal MNCD. The following have been excluded from this analysis: 65,954 patients (72%) never received an MNCD drug and 21,859 (24%) did not switch. Cells with values less than 5 have been suppressed (s), as per CPRD data regulations.

Table 5.18: Rate of MNCD medication switches, by MNCD subtype

	Crude HR (95% CI)	Adjusted HR (95% CI)
MNCD diagnosis at baseline		
Alzheimer's disease	0.88 (0.80-0.97)	0.91 (0.83-1.00)
Vascular MNCD	1.03 (0.89-1.19)	1.00 (0.86-1.16)
Multiple etiologies	1.00 (0.70-1.42)	0.93 (0.65-1.33)
Other MNCD*	1.60 (1.34-1.92)	1.40 (1.17-1.69)
Non-specific MNCD	1.00 (ref)	1.00 (ref)
Time-varying diagnosis		
Alzheimer's disease	0.84 (0.75-0.94)	0.86 (0.75-0.98)
Vascular MNCD	0.98 (0.83-1.15)	1.00 (0.82-1.22)
Multiple etiologies	1.04 (0.85-1.28)	1.08 (0.85-1.39)
Other MNCD*	1.53 (1.27-1.84)	1.28 (0.98-1.66)
Non-specific MNCD	1.00 (ref)	1.00 (ref)

MNCD: major neurocognitive disorders. *Other MNCD subtypes include MNCD due to Parkinson's disease, MNCD with Lewy bodies, and frontotemporal MNCD. A total of 65,954 patients (72%) never received an MNCD drug and were excluded from this analysis.

Treatment persistence

Vascular MNCD patients were significantly more likely to discontinue their memantine treatment after first trial, using both the time-fixed (adjusted HR = 1.63, 95% CI 1.14-2.32) and time-varying (adjusted HR = 1.69, 95% CI 1.13-2.51) MNCD subtype definitions. No other subtype-specific differences were noted (Table 5.19).

Table 5.19: Likelihood of drug discontinuation after first trial, by MNCD subtype

	ChEIs, overall Adjusted OR (95% CI)	Memantine Adjusted OR (95% CI)
MNCD diagnosis at baseline		
Alzheimer's	1.00 (0.90-1.11)	1.20 (0.90-1.60)
Vascular	1.02 (0.87-1.20)	1.63 (1.14-2.32)
Mixed	1.19 (0.84-1.69)	1.02 (0.34-3.05)
Other MNCD*	1.03 (0.83-1.29)	0.50 (0.15-1.68)
Non-specific	1.00 (ref)	1.00 (ref)
Time-varying diagnosis		
Alzheimer's	0.97 (0.86-1.09)	1.28 (0.92-1.79)
Vascular	0.99 (0.83-1.19)	1.69 (1.13-2.51)
Mixed	1.06 (0.85-1.32)	1.56 (0.91-2.66)
Other MNCD*	1.04 (0.83-1.30)	0.38 (0.09-1.66)
Non-specific	1.00 (ref)	1.00 (ref)

Treatment persistence decreased over time within each MNCD subtype (Figure 5.6), with similar patterns observed across the drugs. Evidence suggests that galantamine may result in greater persistence in some subtypes, particularly Alzheimer's and multiple etiology MNCD. Median persistence for drugs among subtypes was similar (Table 5.20), though patient with mixed dementia had shorter persistence to donepezil and longer persistence to galantamine (Figure 5.20); trends were similar to the primary analysis after applying time-varying definitions.

Figure 5.6: Proportion of patients classified as persistent, by MNCD subtype

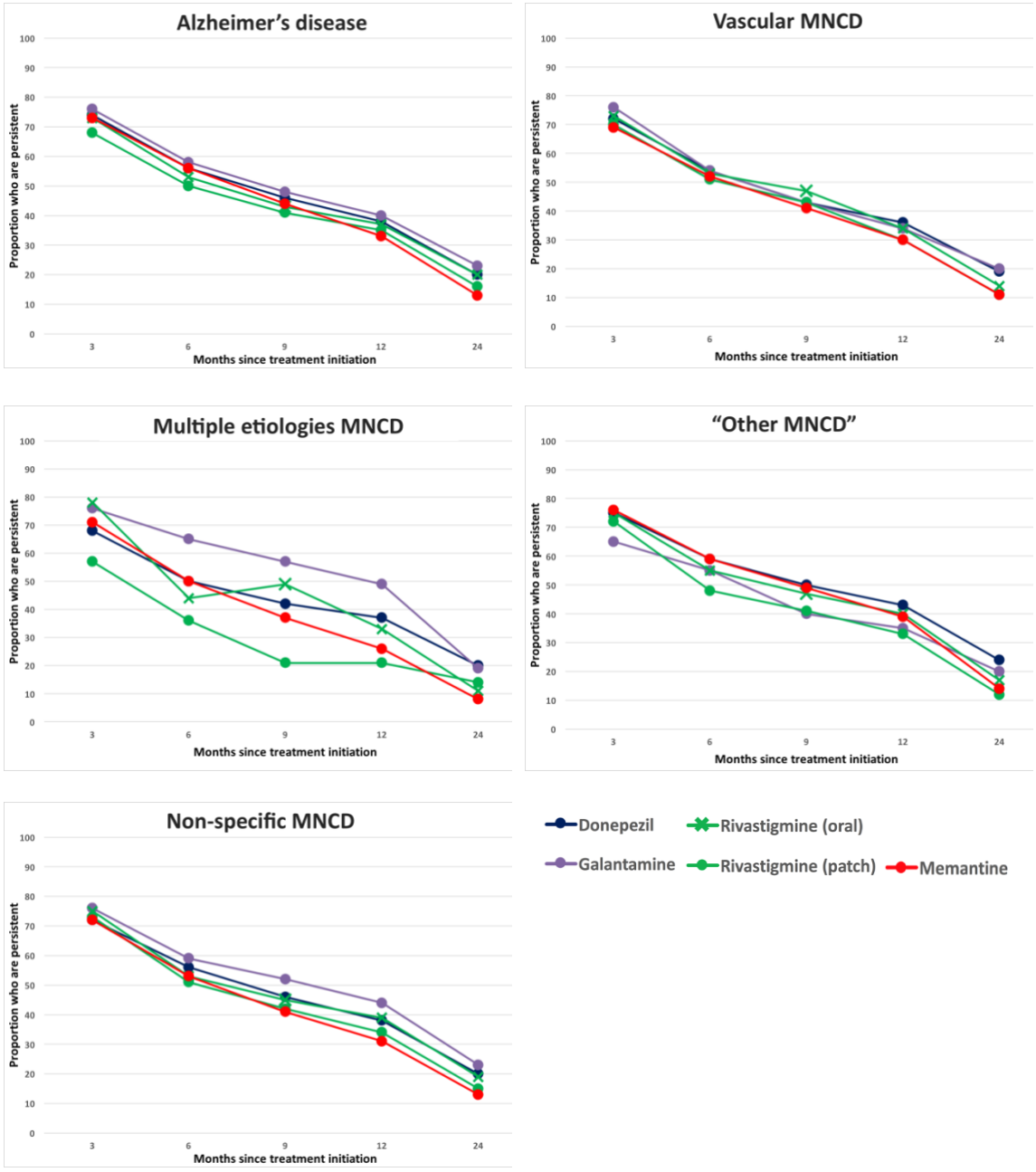


Table 5.20: Median time from drug initiation to discontinuation, by time-fixed and time-varying MNCD subtypes

	ChEIs, overall	Donepezil	Galantamine	Rivastigmine, either	Rivastigmine, oral	Rivastigmine, patch	Memantine
MNCD diagnosis at baseline							
Alzheimer's	7.6 (2.8-20.1)	7.6 (2.8-19.8)	8.2 (3.1-22.7)	6.3 (2.2-17.8)	6.8 (2.7-20.7)	5.9 (2.0-16.7)	7.3 (2.7-15.7)
Vascular	7.0 (2.8-17.6)	7.0 (2.7-18.0)	7.1 (3.0-17.6)	6.8 (2.7-16.4)	7.4 (2.9-16.5)	6.4 (2.5-15.9)	6.4 (2.0-14.2)
Mixed	6.3 (2.3-18.6)	5.8 (2.2-19.0)	11.7 (3.6-22.6)	4.3 (2.1-15.9)	5.1 (3.0-17.3)	3.5 (2.0-7.9)	5.9 (2.5-13.0)
Other MNCD*	7.5 (2.9-19.2)	8.7 (3.1-23.6)	6.7 (2.0-18.5)	7.1 (2.9-16.9)	7.9 (3.0-18.2)	5.5 (2.6-15.6)	8.7 (3.0-15.0)
Non-specific	7.5 (2.7-20.0)	7.4 (2.7-19.9)	9.4 (3.1-22.8)	6.6 (2.7-18.4)	6.9 (2.8-20.4)	6.4 (2.7-16.1)	6.6 (2.7-15.3)
Time-varying diagnosis							
Alzheimer's	7.6 (2.9-20.1)	7.7 (2.9-19.9)	8.2 (3.1-22.8)	6.3 (2.2-17.8)	6.8 (2.7-20.8)	5.9 (2.0-16.5)	7.3 (2.7-15.8)
Vascular	7.0 (2.8-17.8)	7.1 (2.8-18.0)	7.5 (3.5-18.0)	6.4 (2.6-15.9)	6.8 (2.9-16.5)	6.0 (2.0-15.0)	6.6 (2.0-14.6)
Mixed	6.5 (2.5-17.3)	6.9 (2.6-18.4)	7.4 (2.0-17.3)	5.5 (2.5-14.9)	5.5 (2.2-14.9)	4.8 (2.5-14.9)	5.0 (2.0-13.2)
Other MNCD*	7.6 (2.8-19.2)	8.3 (3.1-22.6)	6.9 (2.0-17.7)	7.3 (2.8-17.6)	7.9 (2.9-18.4)	5.7 (2.6-15.9)	8.4 (3.2-14.5)
Non-specific	7.3 (2.7-19.6)	7.1 (2.5-19.5)	10.1 (3.1-22.4)	7.1 (3.1-19.4)	8.4 (3.6-21.6)	6.1 (2.8-16.0)	6.5 (2.7-14.5)

MNCD: major neurocognitive disorders. *Other MNCD subtypes include MNCD due to Parkinson's disease, MNCD with Lewy bodies, and frontotemporal MNCD. A total of 65,954 patients (72%) never received an MNCD drug and were excluded from this analysis.

Treatment adherence

For each subtype, persistence to memantine was higher than each of the ChEIs at almost all time points (Figure 5.7). No differences in time to non-adherence to each drug were found for Alzheimer's and other MNCD subtypes using both the time-fixed and the time-varying definitions, compared to non-specific MNCD. In vascular MNCD, only the risk of memantine non-adherence using the time-fixed definition was significant (adjusted HR = 1.27, 95% CI 1.02-1.56). In mixed MNCD, only the risk of rivastigmine non-adherence (driven by the oral formulation) using the time-varying definition was significant (adjusted HR = 1.68, 95% CI 1.11-2.53) (Table 5.21).

Figure 5.7: Proportion of patients classified as adherent, by MNCD diagnosis

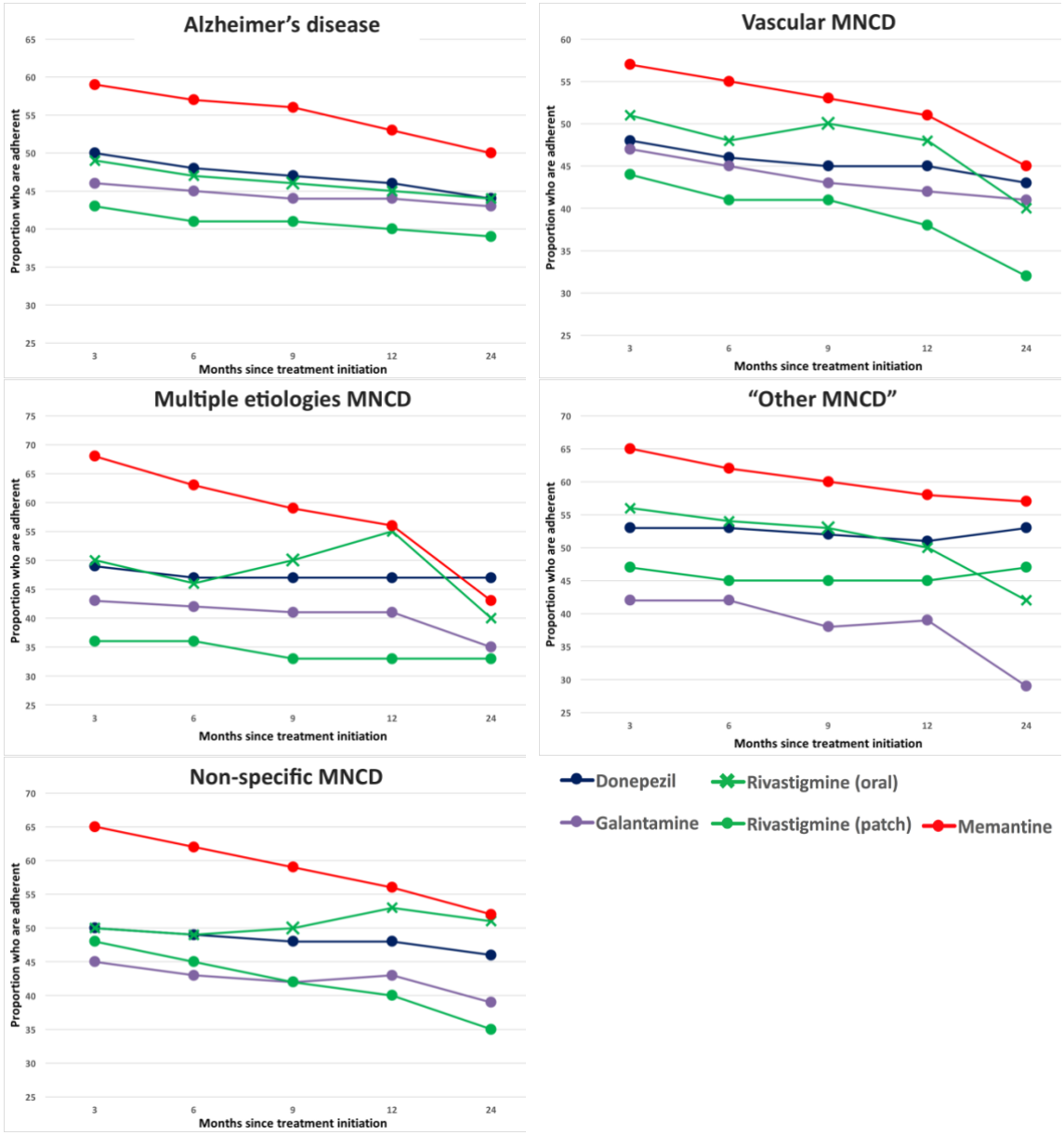


Table 5.21: Instantaneous risk of non-adherence to treatment, by time-fixed and time-varying MNCD subtypes: Adjusted hazard ratios (95% CI)

	ChEIs, overall	Donepezil	Galantamine	Rivastigmine, either	Rivastigmine, oral	Rivastigmine, patch	Memantine
MNCD diagnosis at baseline							
Alzheimer's	1.01 (0.95-1.06)	1.00 (0.94-1.07)	1.03 (0.89-1.20)	1.06 (0.90-1.25)	0.91 (0.72-1.15)	1.10 (0.86-1.40)	1.12 (0.95-1.33)
Vascular	1.08 (0.99-1.17)	1.06 (0.96-1.18)	1.11 (0.90-1.37)	1.13 (0.89-1.44)	1.05 (0.73-1.50)	1.19 (0.84-1.69)	1.27 (1.02-1.56)
Mixed	1.07 (0.88-1.30)	1.05 (0.83-1.34)	1.11 (0.70-1.74)	1.19 (0.69-2.05)	1.41 (0.67-3.01)	1.09 (0.48-2.49)	1.20 (0.63-2.29)
Other MNCD*	1.02 (0.90-1.15)	0.93 (0.76-1.14)	1.26 (0.80-1.97)	0.99 (0.81-1.21)	0.85 (0.65-1.11)	1.22 (0.88-1.69)	0.97 (0.56-1.67)
Non-specific	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Time-varying diagnosis							
Alzheimer's	0.99 (0.93-1.05)	0.96 (0.89-1.03)	1.01 (0.85-1.20)	1.13 (0.94-1.36)	1.01 (0.77-1.32)	1.14 (0.87-1.50)	1.02 (0.85-1.23)
Vascular	1.04 (0.95-1.15)	1.03 (0.91-1.15)	1.06 (0.83-1.36)	1.19 (0.91-1.56)	1.15 (0.77-1.71)	1.24 (0.84-1.82)	1.13 (0.90-1.42)
Mixed	1.10 (0.97-1.23)	1.03 (0.89-1.19)	1.09 (0.81-1.47)	1.42 (1.05-1.91)	1.68 (1.11-2.53)	1.14 (0.72-1.83)	1.33 (0.98-1.81)
Other MNCD*	1.02 (0.90-1.15)	0.94 (0.77-1.16)	1.26 (0.82-1.93)	1.06 (0.85-1.32)	0.96 (0.71-1.30)	1.24 (0.88-1.75)	0.89 (0.49-1.62)
Non-specific	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)

MNCD: major neurocognitive disorders. *Other MNCD subtypes include MNCD due to Parkinson's disease, MNCD with Lewy bodies, and frontotemporal MNCD. A total of 65,954 patients (72%) never received an MNCD drug and were excluded from this analysis.

CHAPTER 6: DISCUSSION

MAIN FINDINGS

In this thesis, I aimed to describe the patient-level factors associated with MNCD drug treatment initiation, switches, adherence and persistence, with a primary focus on sex and a secondary focus on age at diagnosis and MNCD subtype.

Sex-based differences in treatment were observed in this large, population-based cohort of MNCD patients treated in a primary care setting. In particular, females were more likely to be prescribed ChEIs, specifically donepezil and galantamine, and less likely to receive rivastigmine, especially the oral formulation, or memantine. These differences persisted after adjustment for age-related and other disease severity-related confounding variables. While females were significantly less likely to begin combination therapy or switch from a ChEI to memantine, there was no difference in the rate of switching from an initial ChEI to another ChEI. Additionally, the median time to switch for female patients was shorter, perhaps suggesting more frequent healthcare contacts, adverse events, or more treatment failure due to disease progression. Female patients were significantly more persistent to rivastigmine and donepezil, but not to galantamine or memantine. Among those who were persistent, adherence was high, especially to donepezil.

Prescription patterns were also examined by age at MNCD diagnosis. As compared to younger groups, those aged 95+ were significantly less likely to initiate MNCD therapy, perhaps due to their shortened life expectancy (and therefore, perceived benefit), baseline polypharmacy and comorbidities, as well as concerns about serious adverse events. This group was also less likely to switch MNCD therapy, and more likely to become non-adherent. However, it is important to consider the possibility of rightward truncation, due to the competing risk of death and increased likelihood of institutionalization. Furthermore, this cohort was primarily community-dwelling and, with many individuals aged 95+ years in the general population institutionalized, the generalizability of our findings in this age group to all individuals aged 95+ years is

unclear. Furthermore, given these selection processes, comparisons between the different age groups should be made with caution given the predominantly community-dwelling nature of our cohort.

In addition to demographic stratification, prescription patterns by MNCD subtypes were examined. Diagnoses were defined using a time-fixed approach (i.e. at baseline) in primary analyses. In sensitivity analyses, a time-varying approach was used, in which the diagnosis was hierarchically updated if there was a second diagnosis code identified before drug initiation. As expected, the use of updated diagnoses resulted in an increase in the prevalence of MNCD due to multiple etiologies (reflecting the natural disease progression where signs of more than 1 MNCD become apparent with time).

I was surprised by the unexpectedly high prevalence of ChEI use among patients with vascular MNCD, as this represents off-label prescribing for this class of drugs. It is possible that UK general practitioners are unaware that vascular MNCD is not listed as an indication for ChEI treatment. Given that this unexpected observation could have been due to heterogeneity within the diagnoses included in my vascular MNCD definition, I investigated this phenomenon further by performing a sub-analysis by individual vascular dementia diagnosis code. ChEI use was more predominant in patients diagnosed with "mixed cortical and subcortical vascular dementia" (44%) and "other vascular dementia" (26%). Given the non-trivial amount of off-label use, these results may indicate the need for knowledge translation and communication strategies to help general practitioners in the UK prescribe according to approved indications.

The only difference that was found in time to non-adherence by MNCD subtype pertained to patients with vascular MNCD to memantine. It should be noted, however, that the lower confidence bound was close to unity, and that the effect size was small. This finding, therefore, warrants further investigation, as this result may be a chance finding as the result of multiple testing.

IMPACT OF THESIS

Despite the first MNCD drug (donepezil) being approved over 20 years ago and the known presence of sex differences in disease presentation, there were no large-scale drug utilization studies available to describe the real-world use of these drugs by sex and other patient-level characteristics. There is an increasing shift in medicine towards personalizing therapies to the individual based on evidence of their predicted benefits and harms. Consequently, sex- and/or gender-based analyses were identified by the Canadian Institutes of Health Research as an important component of modern research, and now mandates that all research proposals incorporate sex- or gender-based analyses, or to justify why not.

Pharmacoepidemiology includes drug utilization, effectiveness, and safety studies. While perhaps less recognized than the landmark efficacy and safety studies that lead to drug approval, drug utilization studies are important because they provide real-world evidence of how drugs are being used in clinical practice. RCTs of MNCD therapies have included relatively healthy patients with few comorbidities, presenting with mild to moderate disease. Participating RCT centers and physicians are also not necessarily representative of real world practice, and RCTs often involve highly protocolized treatment. However, in the real-world setting, patients with MNCD seen in clinical practice often have more complex medical illness and are, arguably, at greater risk for side effects and pharmacologic interactions than those included in RCTs. Multiple studies have shown that MNCD RCT populations do not represent real-world populations, given their multiple comorbidities, older age and rates of institutionalization[389,390]. While females are well-represented in the published MNCD drug RCT literature, information pertaining to treatment utilization differences by sex have remained, until now, an identified information gap[412]. This thesis directly addresses this identified gap. Furthermore, describing the determinants of drug exposure in an unselected patient population seeks to inform future work in this substantive area. Indeed, the results of this thesis will inform sex, age-related and subtype considerations in future drug safety studies planned to examine rates of adverse events in MNCD patients. Lastly,

it may help clinicians in planning treatment for their patient population, and perhaps inform future treatment guidelines.

STRENGTHS & LIMITATIONS

To the best of our knowledge, this was the largest drug utilization study (n=91,025) of ChEIs and memantine. Additionally, the exclusion of prevalent users by the inception cohort design reduces important sources of bias related to drug tolerability; without an inception cohort, it is possible that those who were most susceptible to discontinuation would have self-selected themselves out of the cohort and thus the prevalent users, who inherently had higher tolerability to the drugs of interest, would be overrepresented. Furthermore, results were consistent across sensitivity analyses, suggesting robustness of results.

This thesis has some potential limitations. First, the CPRD captures prescriptions issued by general practitioners but not those written by specialists. Consequently, there may be some misclassification of time to treatment, including the time of initial treatment initiation and switch. Second, the CPRD contains prescriptions written, and does not contain information on prescriptions filled or on doses taken. This could introduce bias if the patients never filled a prescribed medication, did not take the medication as prescribed, or if there were subsequent alterations to the prescription that were not recorded in the CPRD (i.e. modifications over the phone or fax with a pharmacy). Third, there is the possibility of residual confounding from unknown or unmeasured variables. This remains an inherent limitation to all observational studies. Fourth, different MNCD drugs entered the market at different times in the study period (Table 1.1), which may have impacted time to initiation and time to switching analyses. Sensitivity analyses restricted to the period of time where all drugs were available produced results that were consistent with those of our primary analysis, suggesting that while there may have been some immortal time (i.e., time before the drug was approved, and therefore patients were not at risk of the outcome), there was no immortal time bias.

Lastly, this thesis involved the use of a UK database. As previously discussed, the CPRD is a gold-standard worldwide for pharmacoepidemiology studies in a primary care

setting. While several Canadian databases are available, many have important limitations, including relatively small sample sizes (e.g., Manitoba, Saskatchewan, maritime provinces), and long data access delays (e.g., Quebec, British Columbia). While there are certain system-level differences between the UK and Canada and formulary restrictions may impact some results, the overall results of this thesis are likely generalizable to similar (i.e. socialized) healthcare systems.

AREAS FOR FUTURE RESEARCH

Further work is needed to confirm these results in other populations, outside the UK, and in other settings (i.e. nursing homes). Additionally, to address time-dependent confounding, future studies should consider linking to cognitive function assessment scores to more fully tease out if treatment switches occur in response to progression to a more advanced stage in the disease. Furthermore, the duration of follow-up was shorter among those who did, versus did not, receive a drug. Linkage to the hospitalization and death statistics would be helpful to understand whether this shorter follow-up duration was reflective of hospitalization, institutionalization or death, representing potential sources of informative censoring. Finally, the use of multiple imputation for missing covariate data would have been ideal, but goes beyond the scope of this thesis.

The treatment gaps identified in this thesis warrant future research to better understand which factors are driving the observed differences. One possible explanations is residual confounding, given that these differences persisted after adjusting for disease severity and other confounding variables. A second possible explanation is physician prescribing preference, where clinicians may preferentially prescribe one drug over another based on their prior experience. The CPRD does not share practice or physician identifiers, so there is no way for the present study to assess this possibility. Lastly, patient behavior may influence adherence and persistence. It is possible that healthier patients were more likely to seek out medical treatment, and be both persistent with and adherent to their MNCD drugs. This phenomenon has been observed in several settings, including a 2009 study which showed a healthy-user effect in those adherent to statins. Such patients were associated with lower risks of motor vehicle and car accidents, associations most likely to be due to other health-seeking behaviors than true causal

effects of statin adherence[413]. When interpreting the results of this thesis, it is important to consider that the observed drug utilization patterns can be influenced by physician and patient behavior in addition to the effects of the drugs themselves. This work warrants confirmation in other data sources, as sex, age and MNCD subtype-based differences represent an important frontier in the goal of personalizing medicine according to clinical and sociodemographic characteristics of patients.

CHAPTER 7: CONCLUSIONS

In this population-based inception cohort, the largest MNCD primary care drug utilization study conducted to date, MNCD drug utilization varied by sex, age and MNCD subtype. Compared to male patients, female patients were more likely to initiate treatment with donepezil, less likely to discontinue treatment with donepezil and less likely to become non-adherent to donepezil treatment. Additionally, female patients were less likely to be initiated with memantine, and less likely to switch from a ChEI to memantine. As compared to patients diagnosed at age 65-74, those diagnosed over age 95 were more frequently prescribed memantine, less likely to switch medications, were less persistent and had a higher rate of non-adherence. There were observed differences among the 5 dementia subtypes with respect to MNCD treatment initiation, switches and persistence but not adherence. Our findings remained highly consistent across several sensitivity analyses to vary the duration and grace period applied to prescriptions, meant to address possible sources of bias, suggesting robustness of results. This thesis provides insight into MNCD drug utilization in a primary care setting in the UK over the period from 1997-2017.

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APPENDIX: ETHICS APPROVAL FOR PROTOCOL

ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING CPRD DATA

FEEDBACK TO APPLICANTS

CONFIDENTIAL			***by e-mail***
PROTOCOL NO:	17_158		
PROTOCOL TITLE:	Alzheimer's treatment and the risk of serious adverse events		
APPLICANT:	Samy Suissa, Director, Centre for Clinical Epidemiology, Jewish General Hospital, samy.suissa@mcgill.ca		
APPROVED ☐	**APPROVED WITH COMMENTS (resubmission not required)** ☒	**REVISION/ RESUBMISSION REQUESTED** ☐	**REJECTED** ☐

INSTRUCTIONS:

Protocols with an outcome of 'Approved' or 'Approved with comments' do not require resubmission to the ISAC.

REVIEWER COMMENTS:

Please address the following comments, revising the protocol as necessary:

Reviewer 1-
Lay Summary
The following sentence is incomplete "With an aging population and increasing use of these medications, there is thus an urgent need to evaluate their."
Exposures, Outcomes and Covariates
Please clarify how treatment persistence, switching and treatment discontinuation will be operationalised in the CPRD.
Comments:
A well-considered and very detailed protocol that have taken care to address many of the important issues in the therapeutic/disease area. Some details required to clarify how treatment persistence, switching and treatment discontinuation will be operationalised in the CPRD.
Reviewer 2 -
Lay Summary
"There is thus an urgent need to evaluate their" Appears some words are missing, I believe it would be "safety", please amend this.
Exposures, Outcomes and Covariates

Please consider the issue of COPD exacerbation/ acute COPD hospitalisation. How do you define the first-time recorded occurrence? Patients with COPD are likely to have many episodes of "recurrence", "exacerbation" and "acute hospitalisation".

APPLICANT FEEDBACK:

The above protocol is approved.

DATE OF ISAC FEEDBACK:	03/08/17
DATE OF APPLICANT FEEDBACK:	

Centre intégré universitaire de santé et de services sociaux du Centre-Ouest-de-l'Île-de-Montréal
Québec
Hôpital général juif

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CENTRE D'HÉBERGEMENT ST-MARGARET RESIDENTIAL CENTRE
CENTRE MIRIAM HOME AND SERVICES
CENTRE DE RÉADAPTATION CONSTANCE-LETHBRIDGE REHABILITATION CENTRE
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Integrated Health and Social Services University Network for West-Central Montreal

BUREAU DE L'EXAMEN DE LA RECHERCHE
RESEARCH REVIEW OFFICE

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August 9, 2017

Dr. Samy Suissa
Centre for Clinical Epidemiology
Jewish General Hospital
Contact: Marisa Mancini

SUBJECT: **Ethics Protocol:** CODIM-MBM-17-123
Title: "Treatment for Alzheimer's Disease and Related Disorders and the Risk of Serious Events"
Sponsor: N/A

Dear Dr. Suissa,

Thank you for responding to the MBM/FLP Research Ethics Committee's concerns and for forwarding the following revised documents to the Research Review Office for review:

- Protocol (08 August 2016 version 1.0
- ISAC Evaluation of Protocols for Research Involving CPRD Data – Approval (03/08/2017)

The Research Ethics Committees of the West-Central Montreal Health (Federalwide Assurance Number: 0796) are designated by the province (MSSS) and follows the published guidelines of the TCPS 2 - Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2014), in compliance with the "Plan d'action ministériel en éthique de la recherche et en intégrité scientifique" (MSSS, 1998), the membership requirements for Research Ethics Boards defined in Part C Division 5 of the Food and Drugs Regulations; acts in conformity with standards set forth in the United States Code of Federal Regulations governing human subjects research, and functions in a manner consistent with internationally accepted principles of good clinical practice.

As this study involves no more than minimal risk in accordance with TCPS 2 article 6.12, this protocol received a delegated research ethics review. We are pleased to inform you that the above-mentioned documents are granted Delegated Approval for the period of one year.

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For your information, the above-mentioned protocol will be presented for corroborative approval at the next meeting of the MBM Research Ethics Committee to be held on September 15, 2017.

Please note that it is the Investigator's responsibility to ensure that all necessary final approval letters (Feasibility) are granted before the study can be initiated at our site.

Delegated Approval Date:	**August 9, 2017**
Expiration date of Delegated Approval:	**August 8, 2018**

Your "Continuing Review Application" must be received by the Research Review Office one month before the expiration date above in order to ensure timely review. Otherwise, the study will be terminated.

Respectfully,

Dr. Vasiliki Bessy Bitzas, N, PhD, CHPCN(C)
Chair, Medical/Biomedical Research Ethics Committee

Resource person for this project:
Mrs. Kathleen Blagrave, MBM Research Ethics Coordinator
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