OPTIMISING PSYCHOTROPIC MEDICATION USE IN OLDER ADULTS AND PEOPLE WITH DEMENTIA

Trong Hieu Le

B. Pharm (Hons)

A thesis submitted to fulfil requirements for the degree of

Master of Philosophy

2025

School of Pharmacy

Faculty of Medicine and Health

University of Sydney

STATEMENT OF ORIGINALITY

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

30th June 2025

Trong Hieu Le, BPharm (Hons)

The University of Sydney

ACKNOWLEDGEMENT OF GENERATIVE AI USE

No content produced by generative AI tools has been used in the preparation of this thesis.

AUTHORSHIP ATTRIBUTION STATEMENT

This thesis comprises two research papers: Chapter 2, Section 2.2, and Chapter 3, Section 3.2. The former has been **accepted for publication** in Drugs & Aging, while the latter is currently **under second review** in Alzheimer's & Dementia.

I, Harry Le, was responsible for the work compiled in this thesis, accomplished under the supervision of **Dr Edwin Tan, Professor Christine Lu, Professor Lee-Fay Low, and Associate Professor Tuan Anh Nguyen**. My contributions to all the publications and work presented in this thesis involved the following authorship attribution statements in accordance with the Contributor Roles Taxonomy (CRedIT) for each content chapter in this thesis.

Chapter 2: The candidate's role was methodology, software, data collection and curation, validation, formal analysis, investigation, resources, writing- original draft and editing, visualisation.

Chapter 3: The candidate's role was conceptualisation, methodology, software, data collection and curation, validation, formal analysis, investigation, resources, writing- original draft and editing, visualisation, project administration.

30th June 2025

Trong Hieu Le, BPharm (Hons)

The University of Sydney

As primary supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Supervisor name: Dr Edwin Tan

Date: 30 June 2025

SUPERVISORY TEAM

Primary supervisor: Dr. Edwin C.K. Tan, BPharm (Hons), PhD, FHEA

Dementia Australia Research Foundation Mid-Career Research Fellow and Senior Lecturer in Pharmacy.

Senior Lecturer, School of Pharmacy, Faculty of Medicine and Health, The University of Sydney.

Co-supervisor: Professor Christine Lu, BPharm (Hons), MSc, PhD UNSW

Chair of Clinical Pharmacy, Northern Sydney Local Health District.

Professor, School of Pharmacy, Faculty of Medicine and Health, University of Sydney.

Co-supervisor: Professor Lee-Fay Low, BSc Psych (Hons) UNSW; PhD ANU

Professor in Ageing and Health, Faculty of Medicine and Health, University of Sydney.

Chair, Sydney Dementia Network Executive Committee

Co-supervisor: Professor Tuan Anh Nguyen, BPharm (Hons), PhD UNSW

Principal Research Fellow, National Ageing Research Institute.

Associate Professor, School of Health Sciences, Swinburne University of Technology.

ACKNOWLEDGEMENT

First and foremost, I would like to express my sincere gratitude to my primary supervisor, **Dr. Edwin Tan**, for his unwavering support, guidance, and encouragement throughout my MPhil journey. His expertise and mentorship were instrumental in helping me stay focused and navigate the challenges of this research. I have been especially impressed by his optimism and calm under pressure—qualities I deeply admire and aspire to adopt, as I am not always quite as positive!

I would also like to thank my co-supervisors, **Associate Professor Tuan Anh Nguyen, Professor Christine Lu, and Professor Lee-Fay Low**, for their thoughtful advice and continuous guidance. Their input has shaped the direction of my research and helped me develop a deeper understanding of the field.

My heartfelt thanks also go to **Professor Sarah Hilmer** and **Professor Yun-Hee Jeon** for their generous feedback and expert insights, which greatly enhanced the quality of my work and publications.

A big thanks to **PhD candidate Edward Lau** for your generous support throughout my candidature—you often answered my questions before I even had the chance to ask them. To the **Stocker team** at Room S327: thank you for mentally adopting me and offering a safe haven throughout my MPhil, especially during those thesis-induced moments of existential crisis. The warmth of our little corner—complete with snacks, quiet productivity, and even a Christmas tree—made the stress a little more bearable and the journey a lot less lonely.

To **Benson, Kevin, TJ** and my other new friends at the Pharmacy School—thank you for being such kind, fun, and supportive companions along the way. I'm lucky to have crossed paths with you all.

And thank you to my supervisors in Vietnam, **Associate Professor Thanh Hai** and **Dr. Ba Hai**. Without your early guidance and unwavering support, I wouldn't be where I am today. I truly hope to collaborate with you in the future and contribute to improving healthcare in Vietnam through our research. To all my Vietnamese friends—thank you for always being there. I miss you all dearly… truly, crying.

Last but definitely not least, I want to thank my amazing family for their unconditional support and love. Maybe it's best I write this part in Vietnamese: *Con cảm ơn bố mẹ, cháu cảm ơn ông bà và cô cậu đã giúp cháu có được ngày hôm nay. Con hứa sẽ tiếp tục cố gắng để làm cả nhà tự hào ạ. Kính gửi gia đình cô Hà chú Tuấn Anh, cháu cảm ơn cô chú đã định hướng và đưa ra những lời khuyên hữu ích cho cháu trong quá trình làm nghiên cứu ạ.*

30th June 2025

Harry (Hiếu)

THESIS ABSTRACT

With the global acceleration of population ageing, dementia has emerged as a leading contributor to disease burden among older adults. Psychotropic medications are frequently used to manage mental health conditions in this population; however, their use is associated with substantial risks. Notably, these medications have been linked to serious adverse outcomes, including cerebrovascular events and mortality, with antipsychotics posing the highest level of concern. This master's thesis investigates the prescribing patterns and determinants of psychotropic use in older adults, with a particular emphasis on individuals living with dementia, and explores strategies for optimising the safe and appropriate use of these medications.

Chapter 1 introduces the clinical challenges and public health significance of psychotropic prescribing in dementia and ageing populations. It outlines the pharmacological classes of psychotropic medications, age-related pharmacokinetic and pharmacodynamic changes, and the elevated risks of drug-related problems (DRPs) in older adults. Particular attention is given to people with dementia, and the use of antipsychotics in behaviours and psychological symptoms of dementia (BPSD), highlighting the need for safer and more individualised treatment approaches. To address these issues, the thesis pursues two key objectives: (1) exploring the current use and associated factors of psychotropic medication among Australian older adults and people with dementia, and (2) investigating treatment modifiers and predictors associated with antipsychotic use in people with dementia – a case study of risperidone.

Chapter 2 presents one of the most comprehensive studies to date evaluating the use of all psychotropic subclasses among the Australian older population. It used nationally linked data from the 2021 Census and the Pharmaceutical Benefits Scheme (PBS) to examine psychotropic prescribing patterns in a cohort of 3.85 million Australians aged 65 years and older. Approximately one-third were prescribed at least one psychotropic medication, with antidepressants, opioids, and benzodiazepines being the most common. Moreover, psychotropic polypharmacy affected 8.4% of this population. This chapter also identified significant variation in use across clinical and sociodemographic subgroups, including those with dementia, Aboriginal and Torres Islander people, culturally and linguistically diverse (CALD) populations and people living in non-private dwellings—underscoring potential gaps in the quality use of these high-risk medications. The findings highlight not only the widespread use of psychotropics in older adults but also striking disparities across vulnerable groups, reinforcing the urgent need for targeted, evidence-based strategies to optimise their safe and equitable use.

Chapter 3 presents the first study to employ advanced methodologies aimed at informing personalised antipsychotic use in people with dementia. It investigated the therapeutic response to risperidone in people with BPSD, using individual participant data from six clinical trials. Results showed that risperidone was effective for alleviating psychosis, aggression, and anxiety/phobias, but not for affective, activity and sleep disturbances. Subgroup analysis identified several treatment modifiers—such as sex, body mass index (BMI), endocrine disease, and race—potentially linked to pharmacokinetic and pharmacodynamic pathways. Early response at week 2 emerged as a strong predictor of later treatment outcomes, supporting its use as a clinical decision point for ongoing treatment. These findings offer key insights to support more

individualised antipsychotic prescribing and identify early intervention markers that could improve treatment efficacy in dementia care.

Chapter 4 brings together the key findings from earlier chapters to reflect on the broader implications of psychotropic medication use in older adults, particularly focusing on antipsychotic prescribing in people with dementia. While personalised antipsychotic prescribing remains complex due to clinical variability and system-level constraints, it is both necessary and increasingly feasible. Drawing from the evidence generated in this thesis—especially the identification of treatment modifiers and early response predictors—a stepwise framework is proposed to guide the development of predictive models for individualised treatment decisions. The chapter concludes by acknowledging the overarching limitations of the thesis, including the absence of integrated adverse outcome analysis, limited generalisability across psychotropic drug classes, and the need for real-world validation of proposed strategies.

In conclusion, this thesis highlights the high prevalence of and disparities in psychotropic use among older adults, particularly those with dementia and from vulnerable populations. While it offers a foundation for optimising antipsychotic use, broader efforts across clinical, cultural, and systemic levels are essential to improve the safety, appropriateness, and equity of these high-risk medications in aged care.

LIST OF PUBLICATIONS

Published

Le, H.T., Lau, E.C.Y., Chen, W. et al. Prevalence and Risk Factors for Psychotropic Medication Use in Older Adults in Australia: A Nationwide Data Linkage Study. Drugs Aging 42, 755–769 (2025). https://doi.org/10.1007/s40266-025-01220-6 **(Chapter 2)**

Accepted for publication

Hieu T. Le, Edward C.Y. Lau, Christine Y. Lu, Sarah N Hilmer, Yun-Hee Jeon, Lee-Fay Low, Tuan A. Nguyen, and Edwin C.K. Tan (2025). Treatment Modifiers and Predictors of Risperidone Response in Dementia: An Individual Participant Meta-Analysis of Six Randomised Controlled Trials. Alzheimer's and Dementia **(Chapter 3)**

Additional publications not related to this thesis

Le HT, Lau ECY, Ali MA, et al. Potentially High-Risk Antipsychotic Use in People With Dementia: A National Data Linkage Study. J Am Med Dir Assoc. Published online August 4, 2025. doi:10.1016/j.jamda.2025.105750

Tan TJD, Lau ECY, **Le TH**, Lu CY, Hilmer SN, Jeon YH, Low LF, Tan ECK. Predictors and Moderators of Hospitalisation and Mortality in People with Dementia Using Antipsychotics: Systematic Review. Drugs Aging. 2025 May;42(5):381-394. doi: 10.1007/s40266-025-01202-8.

LIST OF PRESENTATIONS

Accepted Abstracts for Oral Presentations

Hieu T. Le, Edward C.Y. Lau, Weisi Chen, Christine Y. Lu, Tuan A. Nguyen, Lee-Fay Low, Sarah N Hilmer, Yun-Hee Jeon and Edwin C.K. Tan. Prevalence and risk factors for psychotropic medication use in older adults in Australia: a nationwide, data linkage study. ASCEPT, APFP & APSA Joint Congress, Melbourne, 2024.

Hieu T. Le, Edward C.Y. Lau, Christine Y. Lu, Sarah N Hilmer, Yun-Hee Jeon, Lee-Fay Low, Tuan A. Nguyen, and Edwin C.K. Tan (2025). Treatment Modifiers and Predictors of Risperidone Response in Dementia: An Individual Participant Meta-Analysis of Six Randomised Controlled Trials. International Pharmaceutical Federation (FIP) 83rd World Congress, Personalised and Precision Medicine section, Copenhagen, 2025.

Hieu T. Le, Edward C.Y. Lau, Mohammad Afshar Ali, Christine Y. Lu, Sarah N Hilmer, Yun-Hee Jeon, Lee-Fay Low, Tuan A. Nguyen, and Edwin C.K. Tan. Potentially high-risk antipsychotic use in people with dementia: a national data linkage study. International Pharmaceutical Federation (FIP) 83rd World Congress, Social and Administrative Pharmacy section, Copenhagen, 2025.

TABLE OF COMMONLY USED ABBREVIATIONS

Abbreviation	Definition
ABS	Australian Bureau of Statistics
AD	Alzheimer's disease
AEDs	Antiepileptic drugs
ATC	Anatomical Therapeutic Chemical
BEHAVE-AD	Behavioural Pathology in Alzheimer's Disease Rating Scale
BMI	Body mass index
BPSD	Behaviours and psychological symptoms of dementia
CALD	Culturally and linguistically diverse
cAMP	Cyclic Adenosine Monophosphate
CI	Confidence interval
CMAI	Cohen-Mansfield Agitation Inventory
DALYs	Disability-adjusted life years
DRP	Drug-related problems
DSM-5	The Diagnostic and Statistical Manual of Mental Illnesses
eGFR	Estimated Glomerular Filtration Rate
EPS	Extrapyramidal side effects
FDA	U.S. Food and Drug Administration
GABA	Gamma-aminobutyric acid
HR	Hazard ratio
IPD-MA	Individual participant data meta-analysis
IQRs	Interquartile ranges
MAOIs	Monoamine Oxidase Inhibitors
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination

NMDA	N-Methyl-D-Aspartate
NPI	Neuropsychiatric Inventory
OR	Odds ratio
PBS	Pharmaceutical Benefits Scheme
PLIDA	Person Level Integrated Data Asset
SD	Standard deviation
SMD	Standardised mean difference
SNRIs	Serotonin-Norepinephrine Reuptake Inhibitors
SSRIs	Selective Serotonin Reuptake Inhibitors
TCAs	Tricyclic Antidepressants
TGA	Therapeutic Goods Administration
VIF	Variance inflation factor
WHO	World Health Organization
YODA	Yale University Open Data Access Project

LIST OF TABLES AND FIGURES

Contents

CHAPTER 1. BACKGROUND AND LITERATURE REVIEW

1.1. Chapter overview

This chapter provides the foundational context for this thesis, outlining the clinical and public health importance of psychotropic medication use in older adults and people with dementia. It begins by exploring the demographic shift toward an ageing population and the increasing burden of mental and neurological conditions in later life. The chapter then introduces dementia, including its definition, epidemiology, aetiology, and current management strategies, followed by an in-depth examination of behaviours and psychological symptoms of dementia (BPSD)—a major driver of antipsychotic prescribing in this population. Next, the chapter discusses the role of psychotropic medications in the care of older adults, detailing the main drug classes commonly used—opioids, antiepileptics, antipsychotics, antidepressants, and benzodiazepines/Z-drugs—and their associated risks. Particular attention is given to antipsychotic use in individuals with dementia, as these medications pose the greatest risk of harm among all psychotropic drugs and offer only modest benefits, making them a critical target for prescribing optimisation. The chapter concludes by identifying gaps in the current literature, particularly in the pattern of psychotropic use among Australian older adults and personalisation of antipsychotic therapy in dementia care. This sets the stage for the thesis aims and objectives, which focus on understanding current prescribing patterns and building a foundation for safer, more individualised treatment strategies.

1.2. Older adults and dementia

1.2.1. Population aging

The World Health Organization (WHO) estimates that one in six individuals globally will be aged 60 years or older by 2030. This proportion is expected to increase significantly, with the number of people aged 60+ projected to reach 2.1 billion by 2050 [1]. In Australia, population ageing refers to individuals aged 65 years and older, who currently make up approximately 23% of the total population [2]. Ageing is a progressive and irreversible biological process characterised by a decline in cellular and tissue function, leading to an increased vulnerability to a range of age-related diseases [3]. These can include neurodegenerative, cardiovascular, metabolic, musculoskeletal, and immune system disorders [3]. Indeed, people aged 60 and over account for 23% of the total global burden of disease [4]. Older adults are also more likely to live with multiple chronic conditions, or multimorbidity. A recent systematic review found that 37.2% of older people living in the community worldwide have more than one chronic disease [5]. In 2017–18, nearly one-third of older Australians (1.1 million, 29%) were living with a single chronic condition, while over 831,000 (23%) had two, and 1.0 million (28%) experienced three or more [6].

1.2.2. Mental and neurological conditions

Mental and neurological disorders rank among the most common diseases in older adults. According to a 2023 WHO report, about 14% of people aged 60 and over are affected by a mental disorder [7], with depression and anxiety being the most prevalent. These conditions contribute to 10.6% of the total disability burden among this age group, as measured by disability-adjusted life years (DALYs) [7]. In Australia, nearly one third of adults aged 65 and over reported experiencing moderate and high levels of psychological distress in the four weeks prior to a 2017–18 survey [6]. Mental and neurological conditions

are not only highly prevalent but also major contributors to mortality. Globally, approximately 15% of deaths in people aged 60 and over are attributed to these conditions [8].

Given the substantial impact of these conditions on the health and well-being of older adults, improving mental health and addressing neurological conditions has become a central component of WHO's approach to healthy aging [7]. Effective strategies include promoting mental well-being through preventive care, increasing access to mental health services, encouraging social engagement, supporting interventions aimed at cognitive stimulation and pharmaceutical care [7]. Pharmaceutical care involves comprehensive medication reviews, monitoring for medication adherence and side effects, appropriate prescribing practices tailored to older adults, and education for patients and caregivers about the safe and effective use of psychotropic and neurological medications [7, 9]. Implementing these pharmaceutical care strategies can significantly enhance functional ability, reduce disease-related disability, and support older adults in maintaining independence and an improved quality of life as they age [9].

1.2.3. Dementia

1.2.3.1. Dementia definition

In the fifth edition of The Diagnostic and Statistical Manual of Mental Illnesses (DSM-5), the condition previously known as dementia has been reclassified as Major Neurocognitive Disorder [10]. However, the term "dementia" remains widely used in clinical practice and academic literature. It is defined by a marked deterioration in one or more cognitive domains—such as executive function, attention, memory, language, learning, perceptual-motor abilities, or social cognition—relative to the individual's prior functioning [10]. This decline must be persistent, progressive, and not solely attributable to a delirium episode. Importantly, the cognitive impairment must also interfere with the individual's capacity to carry out daily tasks. Functional assessment typically involves evaluating the person's ability to manage complex responsibilities (e.g., medication or financial management) or, in more advanced cases, basic self-care activities like dressing or eating [10]. Dementia can result from various underlying causes, with Alzheimer's disease contributing to up to 80% of cases [11]. Therefore, dementia and Alzheimer's disease are often incorrectly used interchangeably. There are other types of dementia, including vascular dementia (linked to cerebrovascular conditions), frontotemporal dementia (caused by frontotemporal degeneration), dementia with Lewy bodies (associated with Lewy body disease), Parkinson's disease dementia, and mixed-type dementia, which involves multiple concurrent pathological processes [11].

1.2.3.2. Epidemiology

Dementia represents a growing global health challenge. Recent estimates indicate that more than 55 million people are affected by dementia, with close to 10 million new diagnoses each year [12]. Alzheimer's disease and other dementias are currently the seventh leading cause of death in the world [13]. In Australia, they are the second most common cause of death overall, surpassed only by coronary heart disease, and the leading cause of death among women [14]. Provisional data also indicates that dementia may soon become the leading cause of death nationwide [14]. Meanwhile, an estimated 411,100 Australians were living with dementia in 2023, and this figure is expected to more than double by 2058 [14]. These statistics underscore the pressing demand for comprehensive support strategies to

mitigate the increasing burden of dementia on individuals, their families, and the broader healthcare system.

1.2.3.3. Aetiology

While dementia encompasses a variety of subtypes with distinct underlying causes—for example, vascular dementia is associated with cerebrovascular disease and frontotemporal dementia arises from frontotemporal degeneration—this section focuses specifically on the aetiology of Alzheimer's disease (AD), the most common form of dementia. Alzheimer's disease involves several characteristic pathological changes within the brain, notably the accumulation of two abnormal proteins: beta-amyloid and tau [15]. Beta-amyloid proteins form plaques outside neurons, disrupting communication across synapses. Simultaneously, within neurons, abnormal tau proteins develop into tangles, interfering with essential nutrient transport and neuronal function. These combined processes result in neuronal injury and cell death, commonly referred to as neurodegeneration [11]. This constellation of changes—beta-amyloid accumulation (A), tau pathology (T), and neurodegeneration (N)—is collectively recognised as the AT(N) framework in Alzheimer's disease [11]. Additionally, Alzheimer's disease triggers inflammation, driven by activated microglial cells attempting to clear these harmful protein accumulations, and leads to brain atrophy due to neuron loss. Another significant hallmark is impaired glucose metabolism, further undermining the brain's functional capacity [11, 15].

1.2.3.4. Management

The management of dementia typically requires a comprehensive and multidisciplinary approach, addressing cognitive symptoms, behaviours and psychological symptoms (BPSD), and co-morbid conditions. Alzheimer's disease, being the most common type of dementia, is the primary focus of this section, specifically addressing strategies to manage cognitive symptoms and underlying neurodegenerative processes. Several symptomatic therapies for Alzheimer's disease, primarily including cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the NMDA receptor antagonist memantine have first received approval from the U.S. Food and Drug Administration (FDA) [11, 15], and were subsequently approved by the Therapeutic Goods Administration (TGA) in Australia.

Cholinesterase inhibitors function by enhancing levels of acetylcholine, a neurotransmitter critical for memory and cognition [16]. Donepezil is administered once daily and rapidly inhibits acetylcholinesterase. Rivastigmine, available orally or transdermally, slowly inhibits both acetylcholinesterase and butyrylcholinesterase and is used for mild cognitive impairment (MCI) and mild dementia and later approved for Parkinson's disease dementia [16]. Galantamine, another rapid inhibitor approved for MCI and mild dementia, is contraindicated in severe liver or kidney disease [16]. Common side effects of these agents include gastrointestinal symptoms and cardiac conduction issues [15]. Memantine, indicated for moderate-to-severe Alzheimer's disease, blocks NMDA receptors to reduce harmful calcium influx into neurons and can be combined with cholinesterase inhibitors [16].

In line with advances in understanding the pathophysiological mechanisms of Alzheimer's disease, particularly the role of beta-amyloid accumulation and neurodegeneration as described in the AT(N) framework, recent therapeutic developments have shifted toward disease-modifying strategies that target these underlying abnormalities. Several monoclonal antibodies have been developed to reduce beta-

amyloid deposition in the brain and slow disease progression in individuals with early-stage Alzheimer's disease. Aducanumab was the first anti-amyloid agent to receive accelerated approval by FDA in July 2021, based on its ability to reduce amyloid-beta plaques [17, 18]. However, as of November 2024, the manufacturer Biogen has withdrawn the product from the market, citing reasons unrelated to its safety or effectiveness [19]. Lecanemab, approved by the FDA in July 2023, demonstrated a statistically significant 27% reduction in cognitive decline in its phase III clinical trial among patients with early symptomatic Alzheimer's disease [17, 20]. Another agent, donanemab, a recently approved monoclonal antibody (FDA approval: July 2024), demonstrated a statistically significant reduction in cognitive decline over 76 weeks [17, 21]. Alongside donanemab, several investigational agents—including remternetug, solanezumab, and gantenerumab—are currently undergoing advanced clinical evaluation [17]. These amyloid-targeting therapies are primarily indicated for individuals with MCI or early-stage Alzheimer's dementia, with confirmed amyloid pathology through positron emission tomography imaging or cerebrospinal fluid biomarkers [17]. Nonetheless, the safety and effectiveness of these monoclonal antibodies remain subjects of ongoing debate, and none were approved in Australia until recently [22]. On 22 May 2025, donanemab became the first to receive approval from the Therapeutic Goods Administration (TGA) [23]. A notable safety concern associated with this therapeutic class is amyloid-related imaging abnormalities (ARIA), which may manifest as vasogenic oedema or cerebral microhemorrhages, necessitating regular MRI surveillance during treatment [15]. **Table 1** summarises the current pharmacological therapy for Alzheimer's disease. In parallel with anti-amyloid approaches, research efforts are expanding toward disease-modifying strategies targeting additional pathological features of Alzheimer's disease, such as tau protein aggregation, neuroinflammation, and dysregulated neuronal metabolism.

In addition, non-pharmacological interventions continue to play an important supportive role in the holistic care of individuals with Alzheimer's disease [15]. Although these interventions do not address the biological underpinnings of the disease, they aim to sustain cognitive functioning, enhance quality of life, and preserve the capacity for daily living activities. These approaches can include structured physical activity programs, cognitive stimulation therapies (e.g., memory training and orientation exercises), and creative therapies involving music and art, which have demonstrated beneficial effects on emotional well-being and engagement [15].

Table 1. Pharmacological Therapies for Alzheimer's Disease

Treatment type	Drug class	Mechanism of action	Example drugs	First Regulatory Approval	Indication
Symptomatic Therapies	Cholinesterase Inhibitors	Selectively inhibit acetylcholinesterase (and in some cases, butyrylcholinesterase), thereby preventing the breakdown of acetylcholine and enhancing cholinergic neurotransmission in the cerebral cortex and hippocampus [16]	Donepezil [16, 24]	FDA approval: 1996 TGA approval: 1998	Mild to moderate Alzheimer's disease. A 23 mg/day dosage has been approval for use in people with

					moderate to severe AD [16].
			Rivastigmine [16, 24]	FDA approval: 2000 TGA approval: 2000	Mild to moderate Alzheimer's disease and Parkinson's-related dementia [16].
			Galantamine [16, 24]	FDA approval: 2001 TGA approval: 2004	Mild to moderate Alzheimer's disease [16].
	Partial N-Methyl D-Aspartate (NMDA) antagonists	Acts as a low to moderate-affinity uncompetitive antagonist of NMDA receptors, inhibiting sustained excitatory glutamate activity and limiting calcium-mediated excitotoxicity that contributes to neuronal degeneration [16]	Memantine [16, 24]	FDA approval: 2003 TGA approval: 2009	Moderate to severe Alzheimer's disease [16].
Disease Modifying Therapies	Monoclonal antibodies	Bind to aggregated amyloid-beta species (e.g., fibrils or oligomers) to facilitate their clearance via microglial phagocytosis, thereby reducing amyloid plaque burden and potentially modifying disease progression [17]	Aducanumab [17, 18]	FDA approval: June 2021*	Mild cognitive impairment or mild dementia due to Alzheimer's disease [18]
			Lecanemab [17, 20]	FDA approval: July 2023	Mild cognitive impairment or mild dementia due to AD [17]
			Donanemab [17, 21, 23]	FDA approval: July 2024 TGA approval: May 2025	Mild cognitive impairment or mild dementia due to AD [17]

			Remternetug [17]	Ongoing phase-3 trials	
			Solanezumab [17]	Ongoing phase-3 trials	
			Gantenerumab [17]	Ongoing phase-3 trials	
FDA, The U.S. Food and Drug Administration; TGA, Therapeutic Goods Administration; AD, Alzheimer's disease					
*Aducanumab has been discontinued by its manufacturer (Biogen) since November 2024					

Beyond medications aimed at slowing down cognitive decline, people with dementia frequently require pharmacological management for comorbidities and behaviours and psychological symptoms of dementia (BPSD) [25]. Because agents such as cholinesterase inhibitors and memantine have limited efficacy in alleviating BPSD [26], psychotropic medications are frequently used to manage acute episodes. These may include opioids for pain, antidepressants for depressive symptoms, and antipsychotics for psychosis-related manifestations such as paranoia and hallucinations [27]. The therapeutic use and clinical implications of psychotropic medications in dementia are discussed in detail in section 1.3.

1.2.4. Behaviours and psychological symptoms of dementia (BPSD)

1.2.4.1. Definition

Behaviours and psychological symptoms of dementia (BPSD) encompass a spectrum of non-cognitive disturbances that frequently occur in individuals with dementia and contribute to functional decline, increased caregiver burden, and reduced quality of life [28]. These neuropsychiatric symptoms can include delusions, hallucinations, depression, anxiety, apathy, agitation, disinhibition, and aggression. BPSD shares clinical features with various psychiatric disorders and can complicate both the prognosis and management of dementia. For clinical clarity, BPSD may be grouped into five domains: (1) cognitive/perceptual disturbances (e.g., hallucinations, delusions); (2) motor behaviours (e.g., wandering, pacing, physical aggression); (3) verbal behaviours (e.g., shouting, repetitive speech, verbal aggression); (4) emotional symptoms (e.g., anxiety, depression, euphoria, apathy); and (5) vegetative disturbances (e.g., diurnal disturbances or appetite patterns) [28].

1.2.4.2. Epidemiology

BPSD is highly prevalent among individuals living with dementia. It is estimated that up to 90% of people with dementia will experience at least one BPSD symptom during the course of their illness [29]. While the prevalence of specific symptoms varies, features such as apathy, depression, agitation, sleep disturbances, and irritability are frequently reported [29, 30]. In Australia, the most recent study in 2014 reported BPSD in 61–88% of community-dwelling individuals with dementia, 29–90% of residents in aged care facilities, and up to 95% of patients hospitalised in long-term acute care settings [31]. Meanwhile, BPSD can place a substantial burden on people living with dementia, their families, and caregivers. These symptoms are associated with increased hospital admissions, earlier entry into residential care, caregiver stress, and reduced functional independence for the individual [32].

1.2.4.3. Aetiology

The underlying causes of BPSD are multifactorial and not fully understood [33]. Rather than arising from a singular pathological process, BPSD is best explained through a biopsychosocial framework, which considers the complex interplay between neurobiological changes, individual life history, psychological resilience, and environmental factors [34]. Neuroimaging studies have linked symptoms such as agitation, disinhibition, and psychosis to structural and functional abnormalities in brain regions responsible for emotional regulation and perception—including the orbitofrontal cortex, dorsolateral prefrontal cortex, anterior cingulate, insula, and temporal lobes. In addition, disruptions in multiple neurotransmitter systems—namely cholinergic, serotonergic, dopaminergic, noradrenergic, and glutamatergic pathways—have been implicated in the development of BPSD, particularly in individuals with Alzheimer's disease [35]. These neurochemical alterations partly inform current pharmacological treatment approaches. Beyond biological factors, BPSD may also arise from unmet physical, psychological, or social needs, as well as co-existing medical conditions, sensory impairments, or environmental stressors [34]. Importantly, the clinical presentation of BPSD can overlap with pre-existing or emerging psychiatric conditions, complicating differential diagnosis and management, particularly as dementia progresses. Thus, understanding BPSD requires a holistic, person-centred approach that considers both intrinsic and extrinsic contributors to behaviour changes in dementia.

1.2.4.4. Assessment

Several standardised assessment tools have been developed and validated to assess and evaluate BPSD, particularly in research and clinical settings. The Neuropsychiatric Inventory (NPI) and the Behavioural Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) are widely utilised instruments that rely on structured interviews with caregivers [36]. Both tools have demonstrated comparable effectiveness in capturing global changes in BPSD. The NPI assesses a broad spectrum of symptoms, including delusions, hallucinations, agitation, aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor activity, sleep disturbances, and appetite or eating disorders. Caregivers rate each symptom domain based on its frequency, severity, and associated caregiver distress over a specified period [36]. Meanwhile, the BEHAVE-AD focuses on key behavioural domains such as delusions, hallucinations, activity disturbances, aggression, diurnal rhythm disturbances, tearfulness, depression, and anxiety [36, 37]. It incorporates symptom severity ratings over the preceding two weeks, a global severity score, and the identification of the most distressing symptom from the caregiver's perspective. Additionally, the Cohen-Mansfield Agitation Inventory (CMAI) is a specialised tool designed to quantify agitation [38]. It categorises behaviours into four types: physically aggressive, physically non-aggressive, verbally aggressive, and verbally non-aggressive, offering detailed insight into agitation profiles.

1.2.4.5. Management

The management of BPSD follows a structured, stepwise approach that prioritises both patient and caregiver needs, with interventions aimed at enhancing patient comfort and reducing caregiver stress being essential [39]. Best practice involves addressing physical and mental health, social support, and behavioural symptoms through integrated, multicomponent interventions aimed at optimising overall well-being and reducing neuropsychiatric distress [40]. Before initiating BPSD-specific interventions, it is crucial to assess the appropriate care setting and address any underlying discomfort that may be

contributing to these symptoms [34]. Ensuring patient safety, especially in cases of delirium or severe risk to self or others, and relieving factors such as pain, constipation, or environmental discomfort, are foundational steps in effective BPSD management [34]. Then, non-pharmacological interventions are recommended as first-line strategies, especially for mild symptoms, and should be integrated alongside pharmacological treatment when needed [39]. Although evidence from randomised controlled trials remains limited, music therapy and massage have shown benefits in alleviating BPSD and depression [39, 41]. Caregiver training has demonstrated effectiveness in reducing symptom severity and improving caregiver well-being by promoting strategies to manage behaviours related to unmet needs or discomfort [39, 41]. Other non-drug interventions, including aromatherapy, bright light therapy, multisensory stimulation, reminiscence therapy, and task-based activities (e.g., folding laundry or using sensory quilts), may offer individualised benefits with minimal risk [34].

When non-pharmacological strategies prove insufficient and BPSD pose a risk to the individual or others, pharmacological treatment may be considered [34, 39]. Medications used in this context are typically prescribed off-label and are based on their efficacy in managing similar symptoms in other psychiatric or neurological conditions. Antipsychotic agents are commonly used to address severe agitation, aggression, and psychotic features such as hallucinations, while antidepressants may be indicated for symptoms of depression and apathy [34]. In cases where pain is suspected to contribute to behaviour disturbances, empirical treatment with analgesics—including paracetamol, opioids, or agents for neuropathic pain—may be initiated [34]. The use of these medications requires careful consideration of potential risks, particularly in older adults, and should be guided by ongoing monitoring and evaluation of treatment response.

1.3. Psychotropic medication use in older adults and people with dementia

Psychotropic medications are substances that can influence neurotransmitters in the brain, thereby affecting mood, cognition, behaviour, and perception. They act primarily on the central nervous system and are commonly prescribed for the management of mental health conditions and neurological disorders. The following section provides an overview of psychotropic classes frequently used in older adults, including their classifications, pharmacology and therapeutic indications, and the risk of use in older adults.

1.3.1. Psychotropic medication commonly used in older adults

1.3.1.1. Opioids

Pain is a common and significant concern in older adults, often leading to reduced function and quality of life [42]. Among the various analgesic options, opioids are frequently prescribed for the management of moderate to severe pain in this population. Opioids are a class of substances—whether natural, semisynthetic, or synthetic—that exert morphine-like effects by binding to opioid receptors throughout the central and peripheral nervous systems [43]. While their primary therapeutic role is to relieve pain, they also influence mood, consciousness, and various physiological functions.

Opioid activity is mediated through three major types of G protein–coupled receptors: the mu (μ), kappa (κ), and delta (δ) receptors [43, 44]. These receptors are primarily located in the brain, spinal cord, and peripheral tissues. Mu receptors are primarily responsible for the analgesic and euphoric effects of opioids,

as well as adverse effects like respiratory depression and dependence. Kappa receptors contribute to spinal analgesia and may also cause dysphoria and hallucinations. Delta receptors are less well understood but are believed to modulate mood and peripheral analgesia. Upon activation, these receptors inhibit adenylyl cyclase, reduce intracellular cyclic Adenosine Monophosphate (cAMP) levels, decrease calcium influx, and promote potassium efflux. These actions lead to neuronal hyperpolarisation and reduced neurotransmitter release, resulting in diminished pain transmission [44].

Based on their receptor activity, opioids are commonly classified into full agonists, partial agonists, mixed agonist-antagonists, and antagonists [43, 44]. Full agonists, such as morphine and fentanyl, fully activate opioid receptors and are typically used for moderate to severe pain. Partial agonists, like tramadol, activate receptors to a lesser extent and are less likely associated with respiratory depression. Mixed agonist-antagonists, such as buprenorphine, exhibit agonist activity at one receptor subtype and antagonist activity at another. Opioid antagonists, such as naloxone and naltrexone, are used to reverse opioid effects, particularly in overdose situations [43, 44].

Therapeutic indications of opioids can include the management of acute pain (e.g., trauma, surgery), chronic non-malignant or malignant pain (e.g., palliative care), and adjunct treatment in anaesthesia (e.g., fentanyl, remifentanil) [44]. Certain opioids, such as methadone and buprenorphine, are also utilised in opioid dependence treatment programs. Other agents, like codeine and hydrocodone, are used as antitussives, while drugs like loperamide and diphenoxylate are prescribed for the management of diarrhea [44].

1.3.1.2. Antiepileptics

Epilepsy is a prevalent neurological disorder, with a prevalence of approximately 6% in people over 65 years old [45]. While up to 10% of the population may experience at least one seizure in their lifetime, epilepsy is not a single disease but rather a group of syndromes characterised by recurrent, unprovoked seizures due to abnormal, synchronous neuronal activity [44]. In older adults, seizures may result from stroke, neurodegeneration, metabolic disturbances, or medication effects, and may be more difficult to diagnose due to atypical presentations.

Antiepileptic drugs (AEDs), also known as antiseizure medications, form the mainstay of epilepsy management. These agents do not cure epilepsy but work to suppress the occurrence of seizures through a range of neurophysiological mechanisms [44]. AEDs may act by inhibiting voltage-gated sodium or calcium channels, stimulating gamma-aminobutyric acid (GABA)'s activity—the main inhibitory neurotransmitter in the central nervous system—or reducing excitatory glutamatergic transmission [44]. Some agents have multiple sites of action, while the exact mechanism for others remain partially understood.

AEDs can be broadly grouped into two generations. First-generation drugs include older agents such as phenytoin, carbamazepine, phenobarbital, and valproic acid, which have established efficacy but may pose higher risks for drug–drug interactions and adverse effects, particularly in older adults [46]. Second-generation AEDs, such as lamotrigine, levetiracetam, gabapentin, and lacosamide, have been introduced since the 1990s and often offer more favourable pharmacokinetic profiles, including fewer hepatic drug interactions and more predictable absorption [44]. Despite initial optimism, evidence has not consistently

shown that newer agents are more effective or better tolerated than older drugs. Therefore, AED selection is typically individualised based on seizure type, comorbidities, side-effect profiles, and patient-specific factors such as age and polypharmacy [44]. In clinical practice, AEDs are used not only for epilepsy but also for other neurological and psychiatric conditions, particularly in older populations [46]. These include neuropathic pain (e.g., gabapentin, pregabalin), mood disorders (e.g., valproate, lamotrigine), and migraine prophylaxis (e.g., topiramate). The choice of agent must be balanced against the increased sensitivity to side effects in older adults, including sedation, cognitive impairment, hyponatremia, and gait instability.

1.3.1.3. Antipsychotics

Antipsychotics, often referred to as neuroleptics or major tranquilizers, are mainly used to treat schizophrenia and other psychotic disorders. They are also employed in managing acute mania, delirium, and behavioural symptoms linked to dementia [15]. In older adults, antipsychotics are often used cautiously due to the increased susceptibility to adverse effects. While they do not cure the underlying disease process, antipsychotics can alleviate distressing symptoms such as hallucinations, delusions, and agitation, thus improve functional outcomes and quality of life when use appropriately.

Antipsychotic drugs exert their therapeutic effects mainly by modulating neurotransmitter activity in the brain, particularly dopamine and serotonin [44, 47]. They are broadly classified into first-generation (typical) and second-generation (atypical) antipsychotics. First-generation agents act predominantly as dopamine D_2 receptor antagonists in the mesolimbic pathway, which is associated with their efficacy in treating positive symptoms of schizophrenia such as hallucinations and delusions. However, this mechanism also underlies their higher risk of extrapyramidal side effects (EPS), especially with high-potency agents like haloperidol [44, 47]. Second-generation antipsychotics, by contrast, are characterised by their dual activity—antagonism of both dopamine D_2 and serotonin 5-HT2A receptors [44, 47]. This dual mechanism may contribute to a lower incidence of EPS and modest benefits for negative symptoms, such as social withdrawal and blunted affect. Agents like risperidone, olanzapine, and aripiprazole exhibit varying degrees of receptor affinity, which influence both their clinical efficacy and side effect profiles [47]. Notably, second-generation agents are more commonly associated with metabolic complications, including weight gain, diabetes, and dyslipidaemia. Beyond their antipsychotic action, these medications can affect a wide range of neurotransmitter systems, including cholinergic, histaminergic, and adrenergic pathways [44, 47]. This receptor binding diversity contributes to adverse effects such as sedation, orthostatic hypotension, anticholinergic symptoms (e.g., dry mouth, constipation), and hyperprolactinaemia. Some antipsychotics also possess antiemetic properties due to D_2 receptor blockade in the chemoreceptor trigger zone, although this is not a primary indication for second-generation drugs.

Antipsychotics are indicated for schizophrenia, schizoaffective disorder, acute psychosis, bipolar mania, and behavioural symptoms in dementia—though caution is urged in the latter due to increased mortality risks [47]. Older antipsychotics like prochlorperazine are also used for severe nausea and vomiting. In certain cases, these agents may be employed for adjunctive management of agitation, chronic pain with comorbid anxiety, Tourette disorder, or behaviour symptoms associated with autism spectrum disorder [44].

1.3.1.4. Antidepressants

Depression is a common mental health condition in older adults, often presenting with symptoms such as persistent sadness, anhedonia, changes in appetite or sleep, fatigue, and cognitive impairment [7]. It can be accompanied by anxiety, psychomotor agitation or retardation, and in some cases, suicidal ideation. Due to its multifactorial aetiology and impact on overall health and functioning, the timely and appropriate use of antidepressant medications is a key component of treatment in late-life depression.

Most antidepressants act by enhancing monoaminergic neurotransmission, particularly through increasing the synaptic availability of serotonin and/or norepinephrine [44]. This foundational concept, known as the biogenic amine hypothesis, posits that depression is linked to reduced activity of these neurotransmitters at central synapses [44]. Although immediate effects on neurotransmitter levels are observed following administration, the therapeutic benefits typically emerge over a period of 2–4 weeks, suggesting that downstream receptor and neuroplastic changes play a critical role in clinical improvement.

Antidepressants are classified into several pharmacological classes based on their mechanisms of action [44]:

- *Selective Serotonin Reuptake Inhibitors (SSRIs):* These drugs selectively inhibit the serotonin transporter, leading to increased serotonin levels in the synaptic cleft. SSRIs, such as fluoxetine, sertraline, and escitalopram, are considered first-line treatments due to their favourable safety profile, particularly in overdose, and low anticholinergic burden. They are commonly used in older adults with depression and are also effective in anxiety disorders and obsessive-compulsive disorder.
- *Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs):* Agents such as venlafaxine and duloxetine inhibit the reuptake of both serotonin and norepinephrine. These dual-action antidepressants are often considered when SSRIs are ineffective, especially in cases of depression with comorbid chronic pain syndromes such as neuropathic pain or fibromyalgia.
- *Tricyclic Antidepressants (TCAs):* TCAs, including amitriptyline, nortriptyline, and imipramine, inhibit the reuptake of serotonin and norepinephrine but are associated with a broad range of off-target effects due to antagonism at muscarinic, histaminergic, and adrenergic receptors. As a result, TCAs carry a higher risk of anticholinergic side effects, sedation, orthostatic hypotension, and cardiotoxicity, making them less suitable for routine use in older adults. Nevertheless, they remain useful in selected cases such as chronic pain and migraine prophylaxis.
- *Monoamine Oxidase Inhibitors (MAOIs):* MAOIs, including phenelzine and tranylcypromine, inhibit the enzyme monoamine oxidase responsible for the degradation of serotonin, norepinephrine, and dopamine. Due to their risk of serious food and drug interactions (e.g., hypertensive crisis with tyramine-containing foods), MAOIs are generally reserved for treatment-resistant depression or atypical depression.
- *Other antidepressants:* This heterogeneous group includes agomelatine, mianserin, mirtazapine, reboxetine, and vortioxetine. Each agent has a distinct mechanism—for example, melatonin receptor agonism and 5HT2C antagonism (agomelatine), alpha2-adrenergic blockade (mianserin, mirtazapine), noradrenaline reuptake inhibition (reboxetine), and multimodal serotonergic

modulation (vortioxetine). These drugs may be preferred in patients with specific tolerability concerns—for instance, mirtazapine in individuals with insomnia and weight loss.

Antidepressants are primarily indicated for the treatment of major depressive disorder. However, they are also effective in managing other conditions frequently encountered in older adults, including generalised anxiety disorder, panic disorder, post-traumatic stress disorder, chronic pain syndromes, and insomnia (in the case of sedating agents like doxepin or mirtazapine) [44]. Choice of agent should consider patient-specific factors such as comorbidities, risk of drug interactions, cognitive function, and overall tolerability. In older adults, SSRIs and SNRIs are generally preferred due to their more favourable side effect profiles [48].

1.3.1.5. Benzodiazepine and Z-drugs

Anxiety disorders are one of the most common mental health conditions in older adults [7], often presenting with both psychological symptoms (such as excessive worry or restlessness) and somatic manifestations (e.g., tachycardia, sweating, and insomnia). When persistent and functionally impairing, pharmacological treatment may be warranted, particularly in cases of generalised anxiety disorder, panic disorder, or sleep disturbances. Anxiolytic and hypnotic agents are commonly prescribed for the symptomatic relief of these conditions, with benzodiazepines and Z-drugs (non-benzodiazepine hypnotics) being the most frequently used classes in clinical practice.

Benzodiazepines

Benzodiazepines are commonly prescribed due to their ability to reduce anxiety, promote sleep, relax muscles, and control seizures [44]. Their pharmacological action is mediated through modulation of the γ-aminobutyric acid $GABA_A$ receptor complex—the principal inhibitory neurotransmitter system in the central nervous system. Benzodiazepines bind to specific high-affinity sites on the $GABA_A$ receptor at the interface between the α and γ subunits [44]. This binding amplifies GABA's action by promoting more frequent opening of chloride channels, resulting in neuronal hyperpolarisation and decreased excitability. The pharmacodynamic profile varies slightly among agents based on their affinity for subtypes of the $GABA_A$ receptor, particularly those containing the α1 (associated with sedation and amnesia) and α2 (associated with anxiolysis) subunits [44]. Importantly, benzodiazepines do not exert antipsychotic or analgesic effects and should not be used in place of other drug classes for those indications.

Benzodiazepines are indicated for acute management of anxiety disorders (including generalised anxiety disorder, panic disorder, and social anxiety disorder), insomnia, procedural sedation, alcohol withdrawal, muscle spasms, and certain seizure disorders [44]. Their use in older adults is associated with increased risks, including sedation, falls, cognitive impairment, and dependence. For this reason, short-acting or intermediate-acting agents such as lorazepam or oxazepam are generally preferred over longer-acting agents (e.g., diazepam) due to reduced accumulation risk.

Z-drugs (non-benzodiazepine hypnotics)

Z-drugs—such as zolpidem and zopiclone—are structurally unrelated to benzodiazepines but act on the same $GABA_A$ receptor complex, with higher selectivity for receptors containing the α1 subunit [44]. This specificity contributes to their hypnotic effects with minimal anxiolytic, anticonvulsant, or muscle relaxant

properties. Z-drugs are often preferred for the short-term treatment of insomnia due to their rapid onset and shorter half-lives, which reduce the likelihood of next-day sedation—a critical consideration in older adults. Zolpidem is widely used and has an extended-release formulation available. Zopiclone has a longer half-life than zolpidem, which may increase the likelihood of residual drowsiness the following day. All Z-drugs have a lower potential for tolerance and dependence compared to benzodiazepines, although caution is still advised with prolonged use [44].

1.3.2. Risk of psychotropic use in older adults and people with dementia

Aging is accompanied by changes in pharmacokinetics and pharmacodynamics, including reduced hepatic and renal clearance, altered body composition, and increased sensitivity at receptor sites [3]. These alterations heighten the risk of drug accumulation and exaggerated pharmacologic effects, even at standard doses. For instance, declines in hepatic and renal function impair the metabolism and clearance of many AEDs, particularly those dependent on cytochrome P450 enzymes (e.g., phenytoin, carbamazepine) or renal excretion (e.g., gabapentin, levetiracetam) [49]. Moreover, decreased hepatic metabolism and renal excretion prolong the half-life of many long-acting benzodiazepines (e.g., diazepam, flurazepam), leading to drug accumulation and delayed toxicity [3, 50]. Additionally, aging is associated with a less efficient blood–brain barrier and increased central nervous system sensitivity, resulting in exaggerated sedation, confusion, and impaired motor coordination [50].

Meanwhile, older adults frequently present with multimorbidity and polypharmacy. The prevalence of multimorbidity in this population ranges from 4.8% to 93.1%, and polypharmacy from 2.6% to 86.6%, contributing to an elevated risk of drug–drug and drug–disease interactions [51]. Polypharmacy is not inherently inappropriate, but when combined with fragmented care or guideline-driven prescribing for individual conditions, it can lead to cumulative harm in older people. Among drugs that are commonly used for older people, psychotropic medications pose the greatest risk, especially those with anticholinergic, sedative, or cardiovascular effects [51]. Indeed, psychotropic medications are a notable contributor to drug-related problems (DRPs) in older adults. They have been associated with 2.1% (95% CI: 1.2%–3.3%) of all-cause hospitalisations and 11.3% (95% CI: 8.2%–14.8%) of adverse drug event-related hospitalisations [52]. The psychotropics most frequently implicated include antidepressants, hypnotics, sedatives, and antipsychotics. In a recent systematic review, potentially inappropriate psychotropic prescribing was consistently associated with adverse outcomes, including increased risk of falls, unplanned hospitalisations, mortality, and decreased ability to perform activities of daily living [53, 54].

When non-pharmacological interventions prove insufficient, psychotropic medications are often use in people with dementia to manage behaviours and psychological changes such as agitation, aggression, depression, apathy, delusions, and hallucinations [11, 15]. However, the use of these medications remains controversial, as the risks can be magnified in people with dementia. Psychotropic use in people with dementia can heighten risk of serious adverse outcomes such as sedation, falls, hospitalisation, and even mortality [54]. Therefore, these concerns underscore the critical need to carefully balance therapeutic benefits against potential harms when prescribing psychotropics in dementia care.

Despite these well-documented risks, psychotropic medications remain widely prescribed among individuals with dementia. In the United Kingdom, a 2015 study showed that around one third (36.6%) of

older adults with dementia were using antidepressant, and 11.4% receiving antipsychotics [55]. In the Australian context, a large-scale study of 177,809 older adults with dementia reported that 58.6% had been prescribed at least one psychotropic drug [25]. Antidepressants were the most frequently used (41%), followed by opioids (20%) and antipsychotics (13%). Additionally, psychotropic polypharmacy in people with dementia remains a major issue. A recent meta-analysis revealed that one in three nursing home residents are prescribed two or more psychotropic agents [56]. In Denmark, about one-quarter of dementia patients were found to be concurrently using two or more psychotropic medications [57]. Similarly, in Finland, 53% of people diagnosed with Alzheimer's disease had filled prescriptions for at least one psychotropic, 20% had used antipsychotics, and 18% had been exposed to polypharmacy involving two or more psychotropics within a six-year period [58]. In Australia, 23% of people with dementia had psychotropic polypharmacy [25].

Among psychotropic medications, antipsychotics pose the greatest safety concern in older adults with dementia, with evidence showing they nearly double the risk of both short- and long-term mortality [59]. Antipsychotics are consistently associated with increased risk of adverse outcomes, including sedation, cerebrovascular events, hospitalisation, and mortality [60]. Both first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) may increase mortality, with reported relative risks (RR) of 1.46 and 1.36, respectively [61]. Haloperidol has been linked to a significant elevated hazard ratio (HR) for mortality (HR = 2.43) [60]. Moreover, antipsychotic use is associated with a more than twofold increase in the odds of cerebrovascular events (HR = 2.16) [60]. A recent study showed that within 90 days of initiating antipsychotic treatment, the risk of stroke increased markedly (HR = 1.61), along with other outcomes such as myocardial infarction (HR = 1.28), heart failure (HR = 1.27), acute kidney injury (HR = 1.72), venous thromboembolism (HR = 1.62), pneumonia (HR = 2.19), and fracture (HR = 1.43) [62]. Additional risks include extrapyramidal symptoms, accelerated cognitive decline, and head injuries [60]. These risks are exacerbated by co-prescription with cardiovascular or psychotropic medications and underlying comorbidities. Indeed, the FDA have issued black box warnings on the use of antipsychotics in people with dementia [63]. Given the modest benefits and substantial harm, antipsychotic use in dementia should be reserved for severe cases and closely monitored.

Among antipsychotics, haloperidol and risperidone are both approved in the UK and several European countries for short-term management of behavioural disturbances in dementia when non-pharmacological interventions have proven ineffective [62]. In Australia, only risperidone is currently approved for this indication [64] whereas both of them are not approved in the US due to the safety concerns [64]. The recommended maximum duration of risperidone use is 6 to 12 weeks, with starting doses typically at 0.25 mg to 0.5 mg per day and titrated based on response and tolerability. In 2015, TGA revised risperidone's indication in Australia, limiting its use for BPSD to a maximum of 12 weeks and only in people with Alzheimer's disease [65]. This decision followed growing concerns about the elevated risk of stroke and other adverse events in individuals with non-Alzheimer's dementias. In addition, the recent Royal Commission into Aged Care advocated that the inappropriate use of psychotropics, in particular antipsychotics, was an area requiring significant and immediate attention [66]. Considering these evolving regulatory actions and ongoing safety concerns, a personalised approach to antipsychotic prescribing—

tailored to individual risk profiles and therapeutic needs—has become increasingly imperative to ensure safe and appropriate care for people with dementia.

1.4. Gaps in the literature

Globally, the prevalence of psychotropic medication use has been investigated, with several studies from countries like the United States [67], Scotland [68], and New Zealand [69] providing national estimates across broader populations and settings. In Australia, research has largely focused on specific subgroups, such as individuals with dementia, or aged care residents [25, 70, 71]. However, broader population-level estimates remain limited, and most existing studies are restricted to particular psychotropic classes (e.g., antipsychotics or opioids) or certain regions, such as those highlighted in the Australian Atlas of Healthcare Variation [72]. While these targeted studies are valuable, understanding the overall prevalence of psychotropic use at the population level is crucial for informing system-level interventions and monitoring trends over time. Moreover, given the substantial risks associated with psychotropic use in older adults—particularly those with multimorbidity or cognitive impairment—it is essential to identify and monitor high-risk subgroups. Some international studies have begun to examine sociodemographic and risk factors for psychotropic use [67], but such investigations remain limited in Australia and often rely on small or selective cohorts [25]. A broader, more inclusive approach to monitoring psychotropic use—along with stratified analyses to highlight vulnerable populations—can guide clinicians and policymakers in promoting safer and more targeted prescribing practices.

A recent review of the adverse outcomes of antipsychotics use in dementia concluded that no antipsychotic can be considered entirely safe for this population [60]. Given these significant and well-documented risks, there is an urgent need to personalise treatment approaches in order to improve both safety and therapeutic outcomes. Therefore, identifying potential treatment modifiers—patient characteristics or clinical factors that indicate higher likelihood of benefit or harm—is essential to develop tailored interventions and improve patient outcomes. Understanding how baseline cognitive function, genetic markers, comorbidities, or symptom profiles influence treatment effectiveness or risk can lead to more precise and safer prescribing practices. For instance, a population-based cohort study suggested that people with different baseline BPSD profiles may have varying risks of cardiovascular events when using antipsychotics [73]. Moreover, exploring predictors of therapeutic response at an individual level can support clinicians in making informed decisions about initiating, continuing, or altering treatment plans. Such insights might indicate when antipsychotics are likely to be beneficial, when they pose significant risks, and when alternative treatments may be preferable. Although aggregate-data meta-analyses [61, 74] and single-trial studies [75, 76] have been conducted in this area, these methodologies often mask individual patient differences, are prone to ecological bias, and may have limited generalisability due to narrow populations [77, 78]. In contrast, individual participant data meta-analysis (IPD-MA) enables researchers to conduct analyses that are more precise by standardising patient-level data across multiple studies [78]. IPD-MA can clarify whether observed effects apply uniformly or are modified by specific patient characteristics, thereby providing high-quality evidence on treatment modifiers and predictors of therapeutic response. Only one IPD-MA has investigated factors associated with a specific type of adverse event [79], but no IPD-MA has yet examined treatment modifiers or response predictors across various BPSD domains. This represents a significant research gap that, if addressed, could substantially enhance

clinicians' ability to personalise treatment, minimise harm, and maximise therapeutic benefits for people living with dementia.

1.5. Aims and objectives

Given the existing gaps in the literature regarding the effective use of psychotropic medications in older adults and specifically in people living with dementia, this thesis aims to optimise psychotropic medication management in these populations. Considering the heightened risk profile associated with antipsychotic medications, a key focus is placed on addressing critical knowledge gaps concerning their use. Specifically, the thesis will:

1. Explore the current use of and factors associated with psychotropic medication among Australian older adults and people with dementia (Chapter 2)

2. Explore treatment modifiers and predictors associated with antipsychotic use in people with dementia – a case study of risperidone (Chapter 3)

Reference

1. World Health Organisation. *Ageing and health*. 2024 [cited 2025 05/04/2025]; Available from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health.
2. Australian Bureau of Statistics. *National, state and territory population*. 2024 [cited 2025 05/04/2025]; Available from: https://www.abs.gov.au/statistics/people/population/national-state-and-territory-population/sep-2024.
3. Ngcobo, N.N., *Influence of Ageing on the Pharmacodynamics and Pharmacokinetics of Chronically Administered Medicines in Geriatric Patients: A Review.* Clinical Pharmacokinetics, 2025. **64**(3): p. 335-367.
4. Prince, M.J., et al., *The burden of disease in older people and implications for health policy and practice.* The Lancet, 2015. **385**(9967): p. 549-562.
5. Chowdhury, S.R., et al., *Global and regional prevalence of multimorbidity in the adult population in community settings: a systematic review and meta-analysis.* eClinicalMedicine, 2023. **57**.
6. Australian Institute of Health and Welfare. *Older Australians*. 2024 [cited 2025 05/04/2025]; Available from: https://www.aihw.gov.au/reports/older-people/older-australians/contents/health/health-disability-status.
7. World Health Organisation. *Mental health of older adults*. 2023 [cited 2025 05/04/2025]; Available from: https://www.who.int/news-room/fact-sheets/detail/mental-health-of-older-adults.
8. World Health Organisation. *Global Health Estimates*. 2019 [cited 2025 05/04/2025]; Available from: https://www.who.int/data/global-health-estimates.
9. World Health Organisation. *Medication safety in polypharmacy: technical report*. 2019 [cited 2025 05/04/2025]; Available from: https://www.who.int/publications/i/item/WHO-UHC-SDS-2019.11.
10. Sachdev, P.S., et al., *Classifying neurocognitive disorders: the DSM-5 approach.* Nat Rev Neurol, 2014. **10**(11): p. 634-42.
11. ALZHEIMER'S ASSOCIATION, *2023 Alzheimer's disease facts and figures.* Alzheimers Dement, 2023. **19**(4): p. 1598-1695.
12. World Health Organisation. *Dementia*. 2023 [cited 2025 05/04/2025]; Available from: https://www.who.int/news-room/fact-sheets/detail/dementia.
13. GBD 2019 Ageing Collaborators, *Global, regional, and national burden of diseases and injuries for adults 70 years and older: systematic analysis for the Global Burden of Disease 2019 Study.* Bmj, 2022. **376**: p. e068208.
14. Health, A.I.o. and Welfare, *Dementia in Australia*. 2024, AIHW: Canberra.
15. Kumar, A., et al., *Alzheimer Disease*, in *StatPearls*. 2025, StatPearls Publishing Copyright © 2025, StatPearls Publishing LLC.: Treasure Island (FL).
16. Marucci, G., et al., *Efficacy of acetylcholinesterase inhibitors in Alzheimer's disease.* Neuropharmacology, 2021. **190**: p. 108352.
17. Huang, L.K., et al., *Clinical trials of new drugs for Alzheimer disease: a 2020-2023 update.* J Biomed Sci, 2023. **30**(1): p. 83.
18. The U.S. Food and Drug Administration. *FDA Grants Accelerated Approval for Alzheimer's Drug*. 2021 [cited 2025 05/04/2025]; Available from: https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug.
19. ALZHEIMER'S ASSOCIATION. *Aducanumab Discontinued as an Alzheimer's Treatment*. 2024 [cited 2025 15/04/2025]; Available from: https://www.alz.org/alzheimers-dementia/treatments/aducanumab.

20. The U.S. Food and Drug Administration. *FDA Converts Novel Alzheimer's Disease Treatment to Traditional Approval*. 2023 [cited 2025 05/04/2025]; Available from: https://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval.
21. The U.S. Food and Drug Administration. *FDA approves treatment for adults with Alzheimer's disease*. 2024 [cited 2025 05/04/2025]; Available from: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-adults-alzheimers-disease.
22. Administration, T.G., *TGA confirms decision to not register lecanemab (LEQEMBI)*. 2025.
23. Therapeutic Goods Administration (TGA). *KISUNLA donanemab 350 mg/20 mL concentrated solution for intravenous infusion vial (420194)*. 2025; Available from: https://www.tga.gov.au/resources/artg/420194#artg-id-420194.
24. Australian Drug Information. *AusDI*. 2025; Available from: https://www.ausdi.com/.
25. Lau, E.C.Y., et al., *Antidementia and Psychotropic Drug Use in Older People with Dementia in Australia: A National Data Linkage Study.* J Am Med Dir Assoc, 2024. **25**(11): p. 105237.
26. Wang, F., et al., *Drug Therapy for Behavioral and Psychological Symptoms of Dementia.* Curr Neuropharmacol, 2016. **14**(4): p. 307-13.
27. Simon Bell, R.B., Sue Brennan, Malcolm, et al. *Clinical Practice Guidelines for the Appropriate Use of Psychotropic Medications in People Living with Dementia and in Residential Aged Care: Summary of Recommendations and Good Practice Statements*. 2022 [cited 2025 14/04/2025]; Available from: https://www.monash.edu/__data/assets/pdf_file/0005/3458417/Clinical-Practice-Guideline-for-the-Appropriate-Use-of-Psychotropic-Medications-in-People-Living-with-dementia-and-in-Residential-Aged-Care.pdf.
28. Bessey, L.J. and A. Walaszek, *Management of Behavioral and Psychological Symptoms of Dementia.* Curr Psychiatry Rep, 2019. **21**(8): p. 66.
29. Anantapong, K., et al., *Behavioural and psychological symptoms of people with dementia in acute hospital settings: a systematic review and meta-analysis.* Age and Ageing, 2025. **54**(1).
30. Kwon, C.Y. and B. Lee, *Prevalence of Behavioral and Psychological Symptoms of Dementia in Community-Dwelling Dementia Patients: A Systematic Review.* Front Psychiatry, 2021. **12**: p. 741059.
31. House, A.P. *Care and management of younger and older Australians living with dementia and behavioural and psychiatric symptoms of dementia (BPSD)*. 2013 [cited 2025 05/04/2025]; Available from: https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/Dementia.
32. Cunningham, C., S. Macfarlane, and H. Brodaty, *Language paradigms when behaviour changes with dementia: #BanBPSD.* Int J Geriatr Psychiatry, 2019. **34**(8): p. 1109-1113.
33. Australian Institute of Health and Welfare. *Dementia in Australia*. 2024 [cited 2025 05/04/2025]; Available from: https://www.aihw.gov.au/reports/dementia/dementia-in-aus/contents/population-health-impacts-of-dementia/prevalence-of-dementia.
34. Cloak, N., C. Schoo, and Y. Al Khalili, *Behavioral and Psychological Symptoms in Dementia*. 2025: StatPearls Publishing, Treasure Island (FL).
35. Alves, G.S., et al., *Neuroimaging Findings Related to Behavioral Disturbances in Alzheimer's Disease: A Systematic Review.* Curr Alzheimer Res, 2017. **14**(1): p. 61-75.
36. Ismail, Z., et al., *A comparison of the E-BEHAVE-AD, NBRS, and NPI in quantifying clinical improvement in the treatment of agitation and psychosis associated with dementia.* Am J Geriatr Psychiatry, 2013. **21**(1): p. 78-87.
37. Reisberg, B., et al., *The BEHAVE-AD assessment system: a perspective, a commentary on new findings, and a historical review.* Dement Geriatr Cogn Disord, 2014. **38**(1-2): p. 89-146.
38. Griffiths, A.W., et al., *Validation of the Cohen-Mansfield Agitation Inventory Observational (CMAI-O) tool - ERRATUM.* Int Psychogeriatr, 2020. **32**(2): p. 287.

39. Kim Burns, et al. *Behaviour Management - A Guide to Good Practice Managing Behavioural and Psychological Symptoms of Dementia (BPSD)*. 2012 [cited 2025 05/04/2025]; Available from: https://www.dementiaresearch.org.au/wp-content/uploads/2020/07/DCRC_BPSD_Guide_2012.pdf.
40. Livingston, G., et al., *Dementia prevention, intervention, and care: 2020 report of the Lancet Commission.* Lancet, 2020. **396**(10248): p. 413-446.
41. Na, R., et al., *A Systematic Review and Meta-Analysis of Nonpharmacological Interventions for Moderate to Severe Dementia.* Psychiatry Investig, 2019. **16**(5): p. 325-335.
42. Dagnino, A.P.A. and M.M. Campos, *Chronic Pain in the Elderly: Mechanisms and Perspectives.* Front Hum Neurosci, 2022. **16**: p. 736688.
43. Gress, K., et al., *A comprehensive review of partial opioid agonists for the treatment of chronic pain.* Best Practice & Research Clinical Anaesthesiology, 2020. **34**(3): p. 449-461.
44. Whalen, K.L., *Lippincott® Illustrated Reviews: Pharmacology, 8e*, ed. S.M. Lerchenfeldt and C.R. Giordano. 2023: Lippincott Williams & Wilkins, a Wolters Kluwer business.
45. Sen, A., et al., *Epilepsy in older people.* The Lancet, 2020. **395**(10225): p. 735-748.
46. Hanaya, R. and K. Arita, *The New Antiepileptic Drugs: Their Neuropharmacology and Clinical Indications.* Neurol Med Chir (Tokyo), 2016. **56**(5): p. 205-20.
47. Stahl, S.M. and G. Djokic, *Comparing the pharmacology and pharmacokinetics of antipsychotics: Choosing an antipsychotic and dosing a long-acting injectable.* European Neuropsychopharmacology, 2023. **73**: p. 108-118.
48. Srifuengfung, M., B.R.T. Pennington, and E.J. Lenze, *Optimizing treatment for older adults with depression.* Ther Adv Psychopharmacol, 2023. **13**: p. 20451253231212327.
49. Kaur, U., et al., *Antiepileptic drug therapy in the elderly: a clinical pharmacological review.* Acta Neurologica Belgica, 2019. **119**(2): p. 163-173.
50. Neft, M.W., et al., *Benzodiazepine and antipsychotic medication use in older adults.* Nurs Open, 2020. **7**(1): p. 4-6.
51. Nicholson, K., et al., *Prevalence of multimorbidity and polypharmacy among adults and older adults: a systematic review.* The Lancet Healthy Longevity, 2024. **5**(4): p. e287-e296.
52. Wojt, I.R., et al., *The Prevalence and Characteristics of Psychotropic-Related Hospitalizations in Older People: A Systematic Review and Meta-Analysis.* J Am Med Dir Assoc, 2021. **22**(6): p. 1206-1214.e5.
53. Corvaisier, M., et al., *Preventable or potentially inappropriate psychotropics and adverse health outcomes in older adults: systematic review and meta-analysis.* The Journal of nutrition, health and aging, 2024. **28**(4): p. 100187.
54. Johnell, K., et al., *Psychotropic drugs and the risk of fall injuries, hospitalisations and mortality among older adults.* Int J Geriatr Psychiatry, 2017. **32**(4): p. 414-420.
55. Donegan, K., et al., *Trends in diagnosis and treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective cohort study.* Lancet Public Health, 2017. **2**(3): p. e149-e156.
56. Jester, D.J., et al., *Prevalence of psychotropic polypharmacy in nursing home residents with dementia: a meta-analysis.* Int Psychogeriatr, 2021. **33**(10): p. 1083-1098.
57. Nørgaard, A., et al., *Psychotropic Polypharmacy in Patients with Dementia: Prevalence and Predictors.* J Alzheimers Dis, 2017. **56**(2): p. 707-716.
58. Orsel, K., et al., *Psychotropic drugs use and psychotropic polypharmacy among persons with Alzheimer's disease.* Eur Neuropsychopharmacol, 2018. **28**(11): p. 1260-1269.
59. Langballe, E.M., et al., *Short- and long-term mortality risk associated with the use of antipsychotics among 26,940 dementia outpatients: a population-based study.* Am J Geriatr Psychiatry, 2014. **22**(4): p. 321-31.
60. Rogowska, M., et al., *Implications of Adverse Outcomes Associated with Antipsychotics in Older Patients with Dementia: A 2011-2022 Update.* Drugs Aging, 2023. **40**(1): p. 21-32.

61. Mühlbauer, V., et al., *Antipsychotics for agitation and psychosis in people with Alzheimer's disease and vascular dementia.* Cochrane Database Syst Rev, 2021. **12**(12): p. Cd013304.
62. Mok, P.L.H., et al., *Multiple adverse outcomes associated with antipsychotic use in people with dementia: population based matched cohort study.* BMJ, 2024. **385**: p. e076268.
63. Rubino, A., et al., *Association of the US Food and Drug Administration Antipsychotic Drug Boxed Warning With Medication Use and Health Outcomes in Elderly Patients With Dementia.* JAMA Network Open, 2020. **3**(4): p. e203630-e203630.
64. Yunusa, I. and M.L. El Helou, *The Use of Risperidone in Behavioral and Psychological Symptoms of Dementia: A Review of Pharmacology, Clinical Evidence, Regulatory Approvals, and Off-Label Use.* Front Pharmacol, 2020. **11**: p. 596.
65. Australian Government Department of Health TGA. *Risperidone and Risk of Cerebrovascular Adverse Events in Dementia Patients*. 2015; Available from: https://www.tga.gov.au/sites/default/files/medicines-safety-update-volume-6-number-4-august-2015.pdf.
66. Australian Commission on Safety and Quality in Health Care (the Commission). *Reducing inappropriate use of psychotropic medicines*. 2022 [cited 2025 06/04/2025]; Available from: https://www.safetyandquality.gov.au/sites/default/files/2022-03/joint_statement_on_the_inappropriate_use_of_psychotropic_medicines_to_manage_the_behaviours_of_people_with_disability_and_older_people.pdf.
67. Bajracharya, R. and D.M. Qato, *Patterns of Psychoactive Medication Use in Community-Dwelling Older Adults in the US in 2016: A Descriptive Cross-Sectional Study.* J Aging Health, 2021. **33**(1-2): p. 86-100.
68. Grill, P., et al., *The burden of psychotropic and anticholinergic medicines use in care homes: population-based analysis in 147 care homes.* Age Ageing, 2021. **50**(1): p. 183-189.
69. Norris, P., et al., *Medicalisation or under-treatment? Psychotropic medication use by elderly people in New Zealand.* Health Sociology Review, 2011. **20**(2): p. 202-218.
70. Bezabhe, W.M., et al., *Ten-Year Trends in Psychotropic Prescribing and Polypharmacy in Australian General Practice Patients with and without Dementia.* J Clin Med, 2023. **12**(10).
71. Harrison, S.L., et al., *The dispensing of psychotropic medicines to older people before and after they enter residential aged care.* Med J Aust, 2020. **212**(7): p. 309-313.
72. Australian Commission on Safety and Quality in Health Care (the Commission). *Australian Atlas of Healthcare Variation Series*. 2021 [cited 2025 06/04/2025]; Available from: https://www.safetyandquality.gov.au/our-work/healthcare-variation/australian-atlas-healthcare-variation-series.
73. Mueller, C., et al., *Antipsychotic use in dementia: the relationship between neuropsychiatric symptom profiles and adverse outcomes.* Eur J Epidemiol, 2021. **36**(1): p. 89-101.
74. Yunusa, I., et al., *Assessment of Reported Comparative Effectiveness and Safety of Atypical Antipsychotics in the Treatment of Behavioral and Psychological Symptoms of Dementia: A Network Meta-analysis.* JAMA Network Open, 2019. **2**(3): p. e190828-e190828.
75. Nagata, T., et al., *Baseline Predictors of Antipsychotic Treatment Continuation and Response at Week 8 in Patients with Alzheimer's Disease with Psychosis or Aggressive Symptoms: An Analysis of the CATIE-AD Study.* J Alzheimers Dis, 2017. **60**(1): p. 263-272.
76. Nagata, T., et al., *Early Improvements of Individual Symptoms With Antipsychotics Predict Subsequent Treatment Response of Neuropsychiatric Symptoms in Alzheimer's Disease: A Re-Analysis of the CATIE-AD Study.* J Clin Psychiatry, 2020. **81**(2).
77. Belias, M., et al., *Statistical approaches to identify subgroups in meta-analysis of individual participant data: a simulation study.* BMC Medical Research Methodology, 2019. **19**(1): p. 183.

78. Veroniki, A.A., et al., *An Introduction to Individual Participant Data Meta-analysis.* Neurology, 2023. **100**(23): p. 1102-1110.
79. Howard, R., et al., *Baseline characteristics and treatment-emergent risk factors associated with cerebrovascular event and death with risperidone in dementia patients.* Br J Psychiatry, 2016. **209**(5): p. 378-384.

CHAPTER 2. Prevalence and risk factors of psychotropic medication use in Australian older adults

2.1. Chapter overview

This chapter investigates the prevalence and associated factors of psychotropic medication use among older adults in Australia. This study used two national data sources, the Pharmaceutical Benefits Scheme (PBS) and the 2021 Census. PBS is a national program that subsidises the cost of prescription medicines for Australians, particularly older adults who often receive concession benefits. The Repatriation PBS (RPBS) extends similar support to eligible veterans and their dependents, covering some medicines not listed on the general PBS. The 2021 Census is the national survey conducted on 10th August 2021 to estimate the overall population and provide information on the social, economic, and cultural characteristics of Australians. Using linked data from the 2021 Census and PBS, this study examined the use of six key psychotropic classes—antidepressants, antipsychotics, benzodiazepines and Z-drugs, antiepileptics, and opioids—as well as overall psychotropic use and psychotropic polypharmacy among adults aged 65 years and older (N = 3,850,281), stratified by 5-year age groups.

This chapter indicates that approximately one in three older Australians were prescribed at least one psychotropic medication, with antidepressants, opioids, and benzodiazepines being the most commonly used. Psychotropic polypharmacy was identified in 8.4% of the population. Several sociodemographic and clinical characteristics were significantly associated with psychotropic use. Individuals living in remote areas were less likely to receive psychotropics, whereas those residing in non-private dwellings or requiring assistance with core daily activities had substantially higher odds of use. Chronic conditions—including mental health disorders, respiratory diseases, cardiovascular conditions, cancer, arthritis, and kidney disease—were associated with increased psychotropic use.

Although antipsychotics are generally not recommended and require cautious use, people with dementia were found to be nearly three times more likely to receive these medications. Differences were also observed across population subgroups: Aboriginal and Torres Islander people and those born overseas had higher rates of benzodiazepine/Z-drug and opioid use. These findings underscore the need to further evaluate the quality use of psychotropics in high-risk subpopulations and highlight the importance of personalised care strategies in older adults.

This chapter addresses the first research aim outlined in **Chapter 1**, exploring the patterns and associated factors of psychotropic medication use among Australian older adults.

Chapter 2 is presented as a research manuscript publised in the journal **Drugs & Aging**.

2.2. Manuscript details

Le, H.T., Lau, E.C.Y., Chen, W. et al. Prevalence and Risk Factors for Psychotropic Medication Use in Older Adults in Australia: A Nationwide Data Linkage Study. Drugs Aging 42, 755–769 (2025). https://doi.org/10.1007/s40266-025-01220-6

Prevalence and risk factors for psychotropic medication use in older adults in Australia: a nationwide, data linkage study

Hieu T. Le[a], Edward C.Y. Lau[a], Weisi Chen[a], Christine Y. Lu[a, b, c], Tuan A. Nguyen[d,e,f],Lee-Fay Low[g], Sarah N Hilmer[b], Yun-Hee Jeon[h] and Edwin C.K. Tan[a,b]*

[a]The University of Sydney School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia

[b]Kolling Institute, Faculty of Medicine and Health, The University of Sydney and the Northern Local Health District, Sydney, New South Wales, Australia

[c]Department of Pharmacy, Royal North Shore Hospital, St Leonards, New South Wales, Australia

[d]Division of Social Gerontology, National Ageing Research Institute, Parkville, Victoria, Australia.

[e]School of Health Sciences, Swinburne University of Technology, Hawthorn, Victoria, Australia

[f]UniSA Clinical & Health Sciences, University of South Australia, Adelaide, South Australia, Australia

[g]The University of Sydney School of Health Sciences, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia

[h]Susan Wakil School of Nursing and Midwifery, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia

***Corresponding author:**

Dr Edwin C.K. Tan

Post: The University of Sydney School of Pharmacy, Faculty of Medicine and Health, Pharmacy and Bank Building A15, The University of Sydney, NSW, Australia, 2006

Email: edwin.tan@sydney.edu.au

***Running title**:* Use of psychotropic medication in Australian older adults

Abstract

Background and objectives: Psychotropic medications are associated with an increased risk of adverse drug events in older adults, yet national data on their use in Australia remain limited. This study aims to estimate the prevalence of psychotropic medication use among older Australians and to examine the sociodemographic factors associated with their use.

Methods: A retrospective cross-sectional study was conducted using national linked data from the 2021 Census and the Pharmaceutical Benefits Scheme (PBS). The study included all individuals aged 65+ who responded to the 2021 Census and received at least one PBS medication between 1st August and 31st October 2021. Prevalence of psychotropic medication use was calculated across 5-year age groups, and sociodemographic factors associated with each psychotropic subclass were assessed by logistic regression model.

Results: Among the 3,850,281 older adults, 31.1% received at least one psychotropic medication. Prevalence increased with age across all subclasses except antiepileptics. Antidepressants were the most commonly used psychotropics (19.9%). Those needing assistance with core activities (OR 2.05, 95% CI 2.03–2.06) and living in non-private dwellings (OR 2.02, 95% CI 1.99–2.05) were more likely to receive psychotropics. Conversely, higher educational level, socioeconomic status and non-English speaker were associated with a lower use of all psychotropic subclasses. Aboriginal and Torres Strait Islander people were linked to increased use of benzodiazepines (OR, 1.15; 95% CI, 1.10–1.20) and opioids (OR, 1.20; 95% CI, 1.16–1.23). Dementia was strongly associated with antipsychotic (OR, 2.59; 95% CI, 2.52–2.66) and antidepressant (OR, 1.42; 95% CI, 1.40–1.44) use. Arthritis significantly increased the likelihood of opioid use (OR, 2.03; 95% CI, 2.02–2.05).

Conclusion: Almost one third of the study population used psychotropic medications between August and October 2021. Aboriginal and Torres Strait Islander people, individuals with dementia, and those with arthritis had an increased likelihood of using certain psychotropic medications. Future research should evaluate the clinical appropriateness of psychotropics in these populations, with immediate implementation of strategies to ensure their use is limited to evidence-based indications.

Keywords:

Older adults, Aged, Psychotropic Drugs, Prescribing pattern

Key points

- Approximately one-third of older adults in Australia use psychotropic medications, with 8% experiencing psychotropic polypharmacy.
- Needing assistance with activities and living in non-private dwellings increased the likelihood of psychotropic use, while higher education and socioeconomic status were linked to lower use.
- Dementia was strongly associated with the use of antipsychotics and antidepressants, while arthritis significantly increased the likelihood of opioid use.

INTRODUCTION

Mental health conditions contribute significantly to the disease burden of older adults worldwide [1]. In Australia, it is estimated that the number of older people aged 65 and over will increase from 4.2 million in 2020 to 10.2 million by 2066 [2], and about 17.3% of people aged 60 to 85 are affected by at least one mental health condition [3], with depression and anxiety being the most common [1, 3].

Psychotropic medications are a broad term for medicines that affect cognition, emotions, and behaviours, and are commonly prescribed to treat mental health conditions in older adults. While psychotropics are commonly used for the management of mental health conditions, they can also be used for other conditions such as pain and insomnia. However, psychotropics are not without risks with previous studies showing that psychotropic medications increase the risk of falls [4, 5], strokes [6], hospitalisation [7] and even mortality in older adults [4].

Prior studies in Australia have utilised Pharmaceutical Benefits Scheme (PBS) dispensing data to investigate the prevalence of psychotropic use in older adults, but were limited to specific populations, such as people with dementia and residents of aged care homes [8-10]. Population-based studies on the prevalence of psychotropic use in community-dwelling older adults in Australia are limited to specific psychotropics classes (e.g., antipsychotics, opioids) by region in the Australian Atlas of Healthcare Variation, without deeper investigation of sociodemographic or clinical associations [11]. Similarly, while there are some studies on the prevalence of psychotropic medication use in the general older adult population conducted internationally [12-14], few have looked at the socioeconomic, sociodemographic, and cultural factors associated with their use. This is important to ensure judicious use of these potentially high-risk medications and identify subgroups at a higher risk. This study is the first to use nationwide data from 2021 Census and PBS dispensing records to investigate the prescribing practices of psychotropic medications across the entire population of Australians aged 65 years and over. The aims of this study are to (1) estimate the national prevalence of psychotropic medication use among older Australians and (2) determine risk factors associated with the use of different psychotropic classes in this population.

METHODS

Study design

We conducted a cross-sectional study using national data from the Person Level Integrated Data Asset (PLIDA) at the Australian Bureau of Statistics (ABS) [15]. This study used linked data from the 2021 Census and the PBS [15]. Participants aged 65 and over who received medications in the PBS from 1st August to 31st October 2021 were linked with respondents of Census 2021 through the same scrambled identifier. The study flow chart is presented in **Supplementary Figure 1** (see figure S1).

Data sources

The PBS offers subsidised access to prescribed medications for Australians. When a PBS medication is dispensed at an approved pharmacy, data such as patient demographics, prescriber information, and the supplying pharmacy are recorded [16]. Each PBS item code, which details the active ingredient, dosage, and dosage form, was mapped to the corresponding code in the Anatomical Therapeutic Chemical (ATC)

Classification system [17]. Combination products were classified according to the ATC codes of their individual active ingredients.

Census 2021 data was conducted on 10th August 2021 to estimate the overall population and provide information on the social, economic, and cultural characteristics of Australians [18]. The variables used in this study included registered marital status, aboriginality, country of birth, language spoken at home, selected long-term health conditions, highest educational attainment, remoteness, need for assistance with core activities, living status, living conditions, and socioeconomic status. Selected self-reported health conditions in this study comprised arthritis, cancer, diabetes, dementia, heart disease, stroke, kidney disease, lung conditions, asthma, and mental health conditions. Details of variables included are listed in **Supplementary Table 1** (see table S1).

Medication use

Medication use was defined as having at least one dispensing of a specific active ingredient during the three-month period (1st August - 31st October 2021). Vaccines (ATC J07), blood substitutes and perfusion solutions (ATC B05), and other miscellaneous items coded as Z and D were excluded from our study. Psychotropic medications were categorized as antidepressants (N06A), antipsychotics (N05A), benzodiazepines (N05BA, N05CD), Z-drugs (N05CF), antiepileptics (N03), opioids (N02A), and psychostimulants (N06B). Prochlorperazine (ATC N05AB04) was excluded as its main use is an antiemetic agent. Polypharmacy was defined as the dispensing of five or more medications during the study period, while hyper-polypharmacy was defined as the dispensing of ten or more medications [19]. Psychotropic polypharmacy was defined as the dispensing of at least two different classes of psychotropic medications during the study period [19].

Statistical analysis

The characteristics and prevalence of medication use among individuals 65 years and older were reported descriptively as proportions or as medians with corresponding interquartile ranges (IQRs). Prevalence of psychotropic use in the study period (August – October 2021) was reported across 5-year age strata. Additionally, annual prevalence (January – December 2021) for each psychotropic class was calculated as a sensitivity analysis. Separate multivariate logistic regression models were utilised to examine factors associated with the use of psychotropics and specific psychotropic subclasses. Missing data were managed using listwise deletion in the logistic regression model. Age, sex, registered marital status, aboriginality, country of birth, language spoken at home, various self-reported medical conditions (explored as dichotomous factors individually), education level, remoteness, needing assistance with core activities, living condition and socioeconomic level were initially included in the model based on the research team's clinical and research expertise and supporting evidence from previous literature [12]. Backward elimination was applied for variable selection, including covariates in the final model if their association with the outcome was significant ($p \leq 0.05$). Age, gender, education level, and self-reported mental health conditions were considered potential confounders based on clinical reasoning and were included in all models regardless of p-value. The final multivariable logistic regression model for each psychotropic class included the following factors: socioeconomic status, remoteness, living condition, needing assistance with core activities, selected self-reported health conditions, aboriginality, country of birth, and language

spoken at home. The variance inflation factor (VIF) for each included variable was checked to ensure the absence of multicollinearity (VIF<5) [20]. All statistical analyses were conducted using R version 4.3.0.

RESULTS

Baseline characteristics of cohort

A total of 3,850,281 participants were eligible for this study. The median age was 74 years (IQR: 69-80), with half being female (54%). The majority of participants were born in Australia (62%) and spoke English at home (81%). The median number of comorbidities was 1 (IQR: 0-2) with around one third of participants having two or more selected conditions. Almost half of the cohort were exposed to polypharmacy (49%) and 13% were exposed to hyper-polypharmacy. The proportion of individuals needing assistance with core activities, having long-term medical conditions (e.g., kidney disease, cancer and dementia), and residing in non-private dwellings increased with age. Arthritis was the most frequently reported condition, with 1,223,204 individuals (33%). Further cohort characteristics can be found in **Table 1.**

Prevalence of psychotropic use

The prevalence of psychotropic medication use among older people in Australia is presented in **Table 2**. Overall, 31.1% of the study cohort used at least one psychotropic medication, with 8.4% having psychotropic polypharmacy. Among psychotropic subclasses, antidepressants (83%) and opioids (65%) contributed the majority to psychotropic polypharmacy **(Supplementary Table 3)**. The prevalence of psychotropics, psychotropic polypharmacy and its subclasses generally increased with age. The distribution of psychotropic medication use by age group and sex is further presented in **Supplementary Figure 2**. Antidepressants were the most prevalent subclass, used by 19.9% of the cohort. Serotonin selective reuptake inhibitors (SSRIs) were the most common subclass of antidepressants across all age groups. Combined antidepressant therapy was used by 1.6% of the cohort. Opioids were the second most common psychotropic medication in this demographic (11.1%), followed by benzodiazepines and Z-drugs (6.2%). Antipsychotic use was most prevalent in people over 95 years old (4.2%), with second-generation antipsychotics being the most common (3.3% of the overall cohort). Sensitivity analysis showed that the 12-month prevalence in the 2021 calendar year had a similar pattern as the three-month prevalence with higher prevalence of benzodiazepine (12%) and opioid (22%) use (see table S2).

Factors associated with psychotropic use

Factors associated with psychotropic use are presented in **in Table 3, 4 and 5.** After adjusting for all variables, age no longer predicted psychotropic use in a linear fashion, with likelihood of psychotropic use increasing until age 80-84 and then decreasing from 85 onwards. Factors such as female gender, living alone, living in a non-private dwelling, needing assistance with core activities, and various health conditions were associated with greater likelihood of psychotropic use. Among these, self-reported mental health conditions had the highest odds ratio (OR: 8.65; 95% CI: 8.57-8.74; p<0.001). Conversely, those with higher socioeconomic status, living outside metropolitan areas, higher education levels, being born overseas, and speaking a language other than English at home had lower odds of psychotropic use. The predictors for psychotropic polypharmacy were similar.

Older age and female gender were associated with increased use of benzodiazepines and z-drugs, and lower use of antiepileptics. In addition, females had 72% higher odds of using antidepressants compared to males. Higher education level, socioeconomic status and speaking a language other than English were associated with a lower likelihood of use across all psychotropic classes. Conversely, individuals needing assistance with core activities and those living alone or in non-private dwellings had a higher risk of using all psychotropic classes compared to their counterparts. Aboriginal and Torres Strait Islander people was associated with higher use of benzodiazepines and opioids. Older individuals with self-reported dementia were more likely to receive antipsychotics (OR: 2.59; 95% CI: 2.52-2.66; p<0.001), antidepressants (OR: 1.42; 95% CI: 1.40-1.44; p<0.001), and antiepileptics (OR: 1.25; 95% CI: 1.21-1.29; p<0.001). Self-reported asthma or lung conditions were associated with higher likelihood of using opioids (OR: 1.34; 95% CI: 1.33–1.35; p<0.001), benzodiazepine and Z drugs (OR: 1.29; 95% CI: 1.28–1.31; p<0.001), and antidepressants (OR: 1.22; 95% CI: 1.21–1.23; p<0.001). Self-reported heart disease or stroke, cancer, and arthritis increased the odds of using all psychotropics, but lowered the odds of using antipsychotics. Kidney disease was associated with 20% higher odds of using opioids (OR: 1.20; 95% CI: 1.18–1.22; p<0.001). Having mental health conditions was significantly associated with the use of antipsychotics (OR: 9.96; 95% CI: 9.78-10.16; p<0.001) and antidepressants (OR: 10.19; 95% CI: 10.10-10.28; p<0.001).

DISCUSSION

To our knowledge, this study is the first to use linked national data from 2021 Census and PBS dispensing records to investigate the prescribing practices of psychotropic medications in older Australians. Overall, 31.1% of older adults used psychotropics, with the most common being antidepressants (19.9%), opioids (11.1%) and benzodiazepines (6.2%). Certain factors, such as medical conditions, living conditions, sociodemographic and socioeconomic status, were found to influence the use of psychotropics.

The present study found that almost a third of older adults aged 65 or above were using at least one psychotropic medication during the 3-month study period, which aligns with a previous study of a similar cohort in the United States [12]. In both studies, antidepressants were the most used psychotropic subclass [12]. The frequent use of antidepressants can be due to a high prevalence of depression in older adults, affecting more than one-third of this population [21]. The second most commonly used psychotropic medications in our study were opioids, used by over one in ten individuals, which aligns with previous research on community-dwelling older adults in the United States [22]. However, the 12-month prevalence of benzodiazepines and Z-drugs in our study was lower than what Luta reported among a Swiss cohort of older adults [23]. This difference might be attributed to variations in the time period or data sources, or, encouragingly, it may reflect efforts to avoid these medications in older adults due to their associated risks, including cognitive impairment, delirium, and falls [24]. The prevalence of antipsychotics in our study is similar to a previous national dispensing report in Australia [11]. 8.4% of the study participants experienced psychotropic polypharmacy, a rate similar to a study in Finland, where 7% of people exhibited psychotropic polypharmacy prior to an Alzheimer's disease diagnosis [25].

The prevalence of antidepressant, antipsychotic, and benzodiazepine use increased significantly with age. However, after adjusting for other variables, older age was associated with a higher likelihood of benzodiazepine use but a lower likelihood of using antipsychotics and antidepressants. Older adults with

higher socioeconomic status and higher education levels were less likely to use psychotropics across all subclasses, which is potentially explained by the increased likelihood of having better health literacy [26], enabling them to access and understand drug related information and potentially discuss with physicians the use of non-pharmacological management strategies. Furthermore, higher socioeconomic status and education are associated with improved quality of life [27] and better access to non-pharmacological mental health management strategies, which may also contribute to the lower use of psychotropics observed in this group. People living in remote areas also had a lower likelihood of using psychotropics, which may be linked to reduced access to healthcare services. In contrast, those living in non-private dwellings and those needing assistance with core activities had a higher odds of using psychotropics, possibly due to having more comorbidities and more severe disease states requiring pharmacological management. This may explain why the prevalence of psychotropic use in our study is lower than that reported in previous Australian studies focusing on individuals residing in residential aged care facilities [8, 9]. Our study included all Australians from the Census 2021, with the majority living in the community and only a small proportion residing in non-private dwellings such as aged care homes (4.5%). Although the rates of anxiety and mood disorders are higher among Aboriginal and Torres Strait Islander people compared to the general Australian population [29] likely due to the impact of historical trauma, social disadvantage, and systemic discrimination, we observed that this population is associated with lower use of antidepressants. This might be attributed to reduced access to care, cultural factors that may discourage seeking help from physicians, or the impact of new culturally sensitive guidelines promoting cautious prescribing [30], with a preference for non-pharmacological approaches in practice. Culturally and linguistically diverse (CALD) populations were less likely to use psychotropics, possibly due to the lower rate of mental health conditions [31] or language barriers, which discourage patients from seeking help [32]. However, those born overseas had a higher likelihood of using opioids and benzodiazepines. Prescribing opioids for pain management and benzodiazepines for insomnia often involves simpler, categorical assessments, such as rating pain on a scale or indicating the severity of insomnia. CALD populations may have lower health literacy [32], which can make it difficult to effectively communicate their symptoms to prescribers or lead to a preference for treatments with immediate effects, potentially resulting in increased use of short-acting agents like opioids and benzodiazepines. Future research should focus on understanding these differences in prescribing patterns and developing strategies to improve acceptance and health literacy within CALD populations to ensure more appropriate and effective treatment options.

The current study found that dementia status was associated with a higher use of antidepressants, antipsychotics, and antiepileptics, likely due to their role in managing behaviours and psychological symptoms of dementia (BPSD) [33, 34]. Although opioids, benzodiazepines, and Z-drugs may be prescribed for pain and insomnia in dementia [34, 35], our findings indicate that individuals with dementia had lower odds of using these medications after adjusting for other factors. This aligns with a declining trend in prescribing of these medications for people with dementia in Australia over the past decade [8] due to the findings of previous studies suggesting that benzodiazepines and Z-drugs could increase the risk of dementia [36] or worsen cognitive function. Additionally, opioids are not generally recommended for pain management in dementia due to limited evidence supporting their effectiveness and the significant risk of adverse effects and drug interactions [37], which may further explain the lower odds

observed. However, the prevalence of opioids, benzodiazepines, and Z-drugs, reported in studies on dementia cohorts [8, 10, 38] is higher than our findings. This difference may be because opioids, benzodiazepines, and Z-drugs are often prescribed to people with dementia for conditions beyond BPSD, as these individuals are more likely to have multiple medical conditions, be older, and reside in aged care homes. Individuals with heart disease or stroke were 32% less likely to use antipsychotics which is potentially attributed to prescriber reluctancy due to the risk of myocardial infarction and stroke following antipsychotic use [6]. Our study also revealed that older people with cancer and arthritis were more likely to use opioids. Current pain management guidelines for arthritis [39] do not recommend opioids as first-line treatment and caution their routine use [39] due to their modest benefits, with risks often outweighing benefits [40]. Therefore, future research should investigate the appropriateness of opioid prescribing in this population [41]. It is not surprising that individuals with mental health conditions had higher use of all subclasses of psychotropic medications, with the highest odds observed for antidepressants and antipsychotics. While these medications can be used in the management of mental health conditions in older adults, the risk of adverse drug events, particularly in older age, remains significant [42].

Strengths and limitations

This is the first study to utilise PBS and Census data to estimate the prevalence and risk factors of psychotropic use in older Australians. With a large, population-based cohort, our study is representative of the current demographic profile of older Australians. Furthermore, some factors identified, such as living status, language spoken at home, Indigenous status, and the need for assistance with core activities, have been under-researched in previous studies. This contributes to a deeper understanding of the factors associated with psychotropic prescribing in older adults and may inform future practice and policy interventions.

However, our study has some limitations. First, prevalent use of psychotropic drugs was defined as having at least one recorded dispensing of a psychotropic medication. Duration of use was not considered due to the lack of days of supply information in the PBS dataset. Second, as a cross-sectional design, it cannot establish a causal relationship between factors identified and psychotropic use. Third, due to the self-report nature of the Census, there is potential for respondent bias in reporting of demographics and factors. Forth, the 2021 Census may have been impacted by COVID-19, particularly in the data collection process for non-private dwellings [43]. Furthermore, the dataset did not capture privately dispensed medications or certain psychotropics, such as Z-drugs, which are reimbursed only through repatriation care and not to the general public. As a result, the prevalence of psychotropic medication use may be underestimated. Finally, PBS data only reflects dispensing records, not actual medication taking or the clinical appropriateness of prescriptions.

CONCLUSION

Almost one-third of older adults in Australia are dispensed psychotropic medications, with nearly one in ten experiencing psychotropic polypharmacy. The increased use of certain psychotropic medications among Aboriginal and Torres Strait Islander people, individuals with dementia, and those with arthritis highlights potential discrepancies in prescribing quality for these populations. While future research

should evaluate the clinical appropriateness of these high-risk medications, immediate action is needed to reduce their use and promote more judicious prescribing.

ACKNOWLEDGEMENTS

None

DECLARATIONS

Funding

ECKT is supported by a Dementia Australia Research Foundation Mid-Career Research Fellowship.

Conflicts of Interest

The authors have no competing interests to declare that are relevant to the content of this article.

Availability of data and material

Due to the ethical and legal aspects of the research, supporting data is not available.

Ethics approval

This study was conducted in accordance with the Declaration of Helsinki and was deemed negligible risk, receiving exemption from ethical approval by the University of Sydney Human Research Ethics Committee.

Author contributions

All authors meet the International Committee for Medical Journal Editors (ICMJE) authorship criteria. Conceptualisation: Christine Y. Lu, Tuan A. Nguyen, Edwin C.K. Tan. Methodology: Weisi Chen, Lee-Fay Low, Sarah N. Hilmer, Yun-Hee Jeon. Formal analysis and investigation: Hieu T. Le, Edward C.Y. Lau, Weisi Chen. Writing - original draft preparation: Hieu T. Le. Writing - review and editing: Edward C.Y. Lau, Christine Y. Lu, Tuan A. Nguyen, Lee-Fay Low, Sarah N. Hilmer, Yun-Hee Jeon, Edwin C.K. Tan. Supervision: Christine Y. Lu, Tuan A. Nguyen, Lee-Fay Low, Sarah N. Hilmer, Yun-Hee Jeon, Edwin C.K. Tan. All authors read and approved the final version.

Table 1. Baseline characteristics of study participants (aged 65 years and over by the end of 2021) who have linked Census 2021 and PBS data.

Characteristic	Total population[a]	Age group						
		65-69[a]	70-74[a]	75-79[a]	80-84[a]	85-89[a]	90-94[a]	95+[a]
	N =3,850,281	N =1,077,222	N =1,003,699	N = 764,622	N =508,549	N =302,227	N =147,827	N =46,135
Age	74 (69, 80)	67 (66, 68)	72 (71, 73)	77 (76, 78)	82 (81, 83)	87 (85, 88)	91 (90, 93)	96 (95, 98)
Sex								
Male	1,781,317 (46%)	510,339 (47%)	480,173 (48%)	363,373 (48%)	232,435 (46%)	127,429 (42%)	54,418 (37%)	13,150 (29%)
Female	2,068,964 (54%)	566,883 (53%)	523,526 (52%)	401,249 (52%)	276,114 (54%)	174,798 (58%)	93,409 (63%)	32,985 (71%)
Polypharmacy[#]	1,872,781 (49%)	371,143 (34%)	442,671 (44%)	411,147 (54%)	314,643 (62%)	202,205 (67%)	100,342 (68%)	30,630 (66%)
Hyper-polypharmacy[##]	515,985 (13%)	80,641 (7.5%)	109,997 (11%)	116,152 (15%)	97,996 (19%)	67,228 (22%)	33,775 (23%)	10,196 (22%)
Remoteness [b, f]								
Major cities	2,560,569 (67%)	708,021 (66%)	656,258 (65%)	505,608 (66%)	343,379 (68%)	209,589 (69%)	104,362 (71%)	33,352 (72%)
Inner regional	883,969 (23%)	246,941 (23%)	237,476 (24%)	179,434 (23%)	114,544 (23%)	65,171 (22%)	31,132 (21%)	9,271 (20%)
Outer regional	356,336 (9.3%)	105,133 (9.8%)	96,479 (9.6%)	70,408 (9.2%)	45,243 (8.9%)	24,749 (8.2%)	11,142 (7.5%)	3,182 (6.9%)
Remote/very remote or Unknown	49,407 (12.8%)	17127 (15.9%)	13486 (13.4%)	9172 (1.2%)	5383 (1.1%)	2718 (0.9%)	1191 (0.8%)	330 (0.7%)
Living status [c]								
Occupied private dwelling	3,660,644 (95%)	1,060,988 (98%)	983,919 (98%)	740,587 (97%)	477,038 (94%)	262,452 (87%)	109,491 (74%)	26,169 (57%)
Non-private dwelling	189,637 (4.9%)	16,234 (1.5%)	19,780 (2.0%)	24,035 (3.1%)	31,511 (6.2%)	39,775 (13%)	38,336 (26%)	19,966 (43%)

Living condition								
Living alone in a private dwelling	923,057 (24%)	206,670 (19%)	213,099 (21%)	185,932 (24%)	148,200 (29%)	102,919 (34%)	52,532 (36%)	13,705 (30%)
Living with other people in a private dwelling	2,663,999 (69%)	827,450 (77%)	746,660 (74%)	540,862 (71%)	323,092 (64%)	157,427 (52%)	56,198 (38%)	12,310 (27%)
Living in a non-private dwelling	189,637 (4.9%)	16,234 (1.5%)	19,780 (2.0%)	24,035 (3.1%)	31,511 (6.2%)	39,775 (13%)	38,336 (26%)	19,966 (43%)
Other	73,588 (1.9%)	26,868 (2.5%)	24,160 (2.4%)	13,793 (1.8%)	5,746 (1.1%)	2,106 (0.7%)	761 (0.5%)	154 (0.3%)
Registered marital status								
Married	2,249,109 (58%)	685,806 (64%)	643,171 (64%)	470,499 (62%)	275,799 (54%)	127,215 (42%)	40,404 (27%)	6,215 (13%)
Never married	209,548 (5.4%)	86,941 (8.1%)	55,770 (5.6%)	32,593 (4.3%)	18,290 (3.6%)	9,664 (3.2%)	4,761 (3.2%)	1,529 (3.3%)
Divorced	525,099 (14%)	185,510 (17%)	157,799 (16%)	100,932 (13%)	50,163 (9.9%)	21,508 (7.1%)	7,518 (5.1%)	1,669 (3.6%)
Separated	116,480 (3.0%)	45,723 (4.2%)	35,311 (3.5%)	20,548 (2.7%)	9,700 (1.9%)	3,836 (1.3%)	1,149 (0.8%)	213 (0.5%)
Widowed or Unknown[d]	750,046 (19.5%)	73,242 (6.8%)	111648 (11.1%)	140,050 (18.3%)	154597 (30.4%)	140,004 (46.3%)	93,995 (63.6%)	36,509 (79.1%)
Aboriginality								
Non-Indigenous	3,770,787 (98%)	1,054,097 (98%)	984,276 (98%)	750,174 (98%)	497,669 (98%)	295,369 (98%)	144,263 (98%)	44,939 (97%)
Aboriginal and/or Torres Strait Islander people	40,615 (1.1%)	16,944 (1.6%)	11,658 (1.2%)	6,484 (0.8%)	3,375 (0.7%)	1,542 (0.5%)	511 (0.3%)	101 (0.2%)
Unknown	38,879 (1.0%)	6,181 (0.6%)	7,765 (0.8%)	7,964 (1.0%)	7,505 (1.5%)	5,316 (1.8%)	3,053 (2.1%)	1,095 (2.4%)
Country of birth								

Australia	2,388,090 (62%)	704,695 (65%)	623,284 (62%)	468,181 (61%)	297,203 (58%)	174,552 (58%)	91,335 (62%)	28,840 (63%)
Overseas	1,364,092 (35%)	355,327 (33%)	359,714 (36%)	275,409 (36%)	193,203 (38%)	115,192 (38%)	49,971 (34%)	15,276 (33%)
Unknown	98,099 (2.5%)	17,200 (1.6%)	20,701 (2.1%)	21,032 (2.8%)	18,143 (3.6%)	12,483 (4.1%)	6,521 (4.4%)	2,019 (4.4%)
Language spoken at home								
English	3,133,230 (81%)	885,936 (82%)	834,986 (83%)	634,298 (83%)	400,399 (79%)	229,205 (76%)	113,123 (77%)	35,283 (76%)
Other	640,048 (17%)	180,606 (17%)	155,602 (16%)	115,669 (15%)	93,555 (18%)	60,715 (20%)	26,420 (18%)	7,481 (16%)
Unknown	77,003 (2.0%)	10,680 (1.0%)	13,111 (1.3%)	14,655 (1.9%)	14,595 (2.9%)	12,307 (4.1%)	8,284 (5.6%)	3,371 (7.3%)
Level of highest educational attainment								
Year 9 and below	741,251 (19%)	122,881 (11%)	164,053 (16%)	158,974 (21%)	132,985 (26%)	94,846 (31%)	50,532 (34%)	16,980 (37%)
Year 10 and above	1,203,236 (31%)	352,388 (33%)	327,533 (33%)	242,619 (32%)	148,559 (29%)	83,285 (28%)	38,016 (26%)	10,836 (23%)
Certificate I-IV and Diploma	855,869 (22%)	289,677 (27%)	237,756 (24%)	161,285 (21%)	95,766 (19%)	47,411 (16%)	19,306 (13%)	4,668 (10%)
Bachelor and above	616,419 (16%)	228,964 (21%)	178,307 (18%)	111,408 (15%)	58,302 (11%)	26,244 (8.7%)	10,492 (7.1%)	2,702 (5.9%)
Unknown	433,506 (11%)	83,312 (7.7%)	96,050 (9.6%)	90,336 (12%)	72,937 (14%)	50,441 (17%)	29,481 (20%)	10,949 (24%)
Area-level disadvantage quintiles								
Q1 (Most disadvantaged)	863,542 (22%)	225,938 (21%)	218,760 (22%)	173,359 (23%)	122,653 (24%)	74,781 (25%)	36,859 (25%)	11,192 (24%)

Q2	835,313 (22%)	231,478 (21%)	217,051 (22%)	167,099 (22%)	111,762 (22%)	66,254 (22%)	31,788 (22%)	9,881 (21%)
Q3	744,160 (19%)	214,781 (20%)	197,755 (20%)	146,911 (19%)	94,706 (19%)	55,365 (18%)	26,535 (18%)	8,107 (18%)
Q4	705,698 (18%)	204,350 (19%)	186,710 (19%)	138,333 (18%)	90,034 (18%)	52,699 (17%)	25,500 (17%)	8,072 (17%)
Q5 (Most advantaged)	682,418 (18%)	197,335 (18%)	180,142 (18%)	135,611 (18%)	86,011 (17%)	50,131 (17%)	25,167 (17%)	8,021 (17%)
Unknown	19,150 (0.5%)	3,340 (0.3%)	3,281 (0.3%)	3,309 (0.4%)	3,383 (0.7%)	2,997 (1.0%)	1,978 (1.3%)	862 (1.9%)
Count of comorbidities	1.00 (0.00, 2.00)	1.00 (0.00, 1.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)
Unknown	136942	33182	31763	26413	20449	14138	8085	2912
Count of comorbidities (in categories) [e]								
None of the selected condition	1,263,010 (33%)	443,359 (41%)	356,815 (36%)	231,364 (30%)	129,841 (26%)	64,702 (21%)	28,446 (19%)	8,483 (18%)
One condition	1,274,739 (33%)	350,573 (33%)	337,708 (34%)	258,437 (34%)	169,953 (33%)	98,032 (32%)	46,209 (31%)	13,827 (30%)
Two conditions	684,981 (18%)	157,355 (15%)	169,004 (17%)	144,290 (19%)	104,242 (20%)	66,142 (22%)	33,255 (22%)	10,693 (23%)
Three or more conditions	490,609 (13%)	92,753 (8.6%)	108,409 (11%)	104,118 (14%)	84,064 (17%)	59,213 (20%)	31,832 (22%)	10,220 (22%)
Unknown	136,942 (3.6%)	33,182 (3.1%)	31,763 (3.2%)	26,413 (3.5%)	20,449 (4.0%)	14,138 (4.7%)	8,085 (5.5%)	2,912 (6.3%)
Whether need assistance with core activities								
Yes	739,687 (19%)	96,427 (9.0%)	117,214 (12%)	129,648 (17%)	141,687 (28%)	130,759 (43%)	89,124 (60%)	34,828 (75%)

No	3,039,176 (79%)	968,787 (90%)	873,161 (87%)	621,418 (81%)	354,135 (70%)	161,209 (53%)	51,837 (35%)	8,629 (19%)
Unknown	71,418 (1.9%)	12,008 (1.1%)	13,324 (1.3%)	13,556 (1.8%)	12,727 (2.5%)	10,259 (3.4%)	6,866 (4.6%)	2,678 (5.8%)
Self-reported having asthma or lung condition	562,867 (15%)	149,172 (14%)	145,737 (15%)	118,099 (16%)	78,438 (16%)	45,324 (16%)	20,488 (15%)	5,609 (13%)
Unknown	136942	33182	31763	26413	20449	14138	8085	2912
Self-reported having diabetes	612,299 (16%)	157,891 (15%)	163,612 (17%)	131,202 (18%)	87,876 (18%)	48,346 (17%)	19,059 (14%)	4,313 (10.0%)
Unknown	136942	33182	31763	26413	20449	14138	8085	2912
Self-reported having heart disease or stroke	772,177 (21%)	144,745 (14%)	174,018 (18%)	165,774 (22%)	133,215 (27%)	91,681 (32%)	47,948 (34%)	14,796 (34%)
Unknown	136942	33182	31763	26413	20449	14138	8085	2912
Self-reported having kidney disease	137,875 (3.7%)	23,133 (2.2%)	28,134 (2.9%)	29,196 (4.0%)	25,632 (5.3%)	18,828 (6.5%)	9,925 (7.1%)	3,027 (7.0%)
Unknown	136942	33182	31763	26413	20449	14138	8085	2912
Self-reported having cancer	427,817 (12%)	94,280 (9.0%)	110,436 (11%)	96,437 (13%)	66,385 (14%)	38,152 (13%)	17,300 (12%)	4,827 (11%)
Unknown	136942	33182	31763	26413	20449	14138	8085	2912
Self-reported having arthritis	1,223,204 (33%)	274,995 (26%)	301,827 (31%)	260,221 (35%)	188,507 (39%)	119,024 (41%)	59,616 (43%)	19,014 (44%)
Unknown	136942	33182	31763	26413	20449	14138	8085	2912
Self-reported having mental health condition (including depression or anxiety)	343,528 (9.3%)	109,509 (10%)	85,402 (8.8%)	59,203 (8.0%)	38,425 (7.9%)	27,339 (9.5%)	16,873 (12%)	6,777 (16%)
Unknown	136942	33182	31763	26413	20449	14138	8085	2912
Self-reported having dementia	160,037 (4.3%)	7,445 (0.7%)	14,779 (1.5%)	25,414 (3.4%)	35,926 (7.4%)	37,876 (13%)	27,531 (20%)	11,066 (26%)

Unknown	136942	33182	31763	26413	20449	14138	8085	2912

[a]Median (IQR); N (%)

[b]Remoteness is based on the Accessibility/Remoteness Index of Australia Plus (ARIA+) provided by the ABS.

[c]ABS has noted that mix occupancy could occur with living status.

[d]Unknown values accounted for <0.1% in each age group.

[e]The selected long-term health conditions include arthritis, asthma, cancer (including remission), diabetes (excluding gestational diabetes), dementia, heart disease (including heart attack or angina), kidney disease, lung condition (including COPD or emphysema), mental health condition (including depression or anxiety), and stroke.

[f]Unknown values accounted for <0.3% in each age group.

[#]Polypharmacy was defined as the dispensing of five or more medications

[##]Hyper-polypharmacy was defined as the dispensing of ten or more medications

Table 2. Prevalence of psychotropic use (at least one dispensing) between the 1st of August and 31st of October 2021

Characteristic	Total population*	Age groups*						
		65-69	70-74	75-79	80-84	85-89	90-94	Age 95+
	N = 3,850,281	N = 1,077,222	N = 1,003,699	N = 764,622	N = 508,549	N = 302,227	N = 147,827	N = 46,135
Any psychotropics	1,196,545 (31.1%)	293,638 (27.3%)	287,003 (28.3%)	239,446 (31.3%)	175,283 (34.5%)	116,851 (38.7%)	62,911 (42.6%)	21,413 (46.4%)
Psychotropic polypharmacy**	323,586 (8.4%)	72,742 (6.8%)	73,373 (7.3%)	63,929 (8.4%)	49,779 (9.8%)	35,458 (11.7%)	20,878 (14.1%)	7,427 (16.1%)
Any antipsychotics#	76,232 (2.0%)	18,678 (1.7%)	16,569 (1.7%)	13,593 (1.8%)	11,194 (2.2%)	8,755 (2.9%)	5,515 (3.7%)	1,928 (4.2%)
First-generation antipsychotics	9,531 (0.2%)	2,107 (0.2%)	1,906 (0.2%)	1,566 (0.2%)	1,407 (0.3%)	1,205 (0.4%)	912 (0.6%)	428 (0.9%)
Second-generation antipsychotics	68,200 (1.8%)	17,066 (1.6%)	15,014 (1.5%)	12,229 (1.6%)	9,972 (2.0%)	7,673 (2.5%)	4,704 (3.2%)	1,542 (3.3%)
Combined antipsychotic medication use	1,499 (<0.1%)	495 (<0.1%)	351 (<0.1%)	202 (<0.1%)	185 (<0.1%)	123 (<0.1%)	101 (<0.1%)	42 (<0.1%)
Any antidepressants	764,307 (19.9%)	197,798 (18.4%)	189,371 (18.9%)	153,337 (20.1%)	107,448 (21.1%)	69,670 (23.1%)	35,700 (24.1%)	10,983 (23.8%)
TCA	175,467 (4.6%)	43,871 (4.1%)	44,855 (4.5%)	37,317 (4.9%)	26,106 (5.1%)	14,995 (5.0%)	6,493 (4.4%)	1,830 (4.0%)
SSRI	362,437 (9.4%)	97,471 (9.0%)	92,261 (9.2%)	72,458 (9.5%)	48,601 (9.6%)	31,070 (10.3%)	15,753 (10.7%)	4,823 (10.5%)
SNRI	153,587 (4.0%)	48,901 (4.5%)	41,602 (4.1%)	30,187 (3.9%)	17,785 (3.5%)	9,853 (3.3%)	4,234 (2.9%)	1,025 (2.2%)
Other antidepressants	137,589 (3.6%)	24,429 (2.3%)	26,819 (2.7%)	26,625 (3.5%)	24,112 (4.7%)	19,471 (6.4%)	12,064 (8.2%)	4,047 (8.8%)
Combined antidepressant medication use	62,915 (1.6%)	16,326 (1.5%)	15,679 (1.6%)	12,883 (1.7%)	8,919 (1.8%)	5,588 (1.8%)	2,787 (1.9%)	733 (1.6%)

Any benzodiazepines and z-drugs	240,609 (6.2%)	48,496 (4.5%)	53,887 (5.4%)	50,190 (6.6%)	39,665 (7.8%)	27,379 (9.1%)	15,467 (10.5%)	5,525 (12.0%)
Long-acting benzodiazepines[##]	82,180 (2.1%)	22,347 (2.1%)	21,188 (2.1%)	17,203 (2.2%)	11,105 (2.2%)	6,551 (2.2%)	2,923 (2.0%)	863 (1.9%)
Short-very short acting benzodiazepines	166,101 (4.3%)	28,264 (2.6%)	34,453 (3.4%)	34,503 (4.5%)	29,648 (5.8%)	21,591 (7.1%)	12,886 (8.7%)	4,756 (10.3%)
Combined benzodiazepine and z-drug medication use	8,882 (0.2%)	2,266 (0.2%)	2,254 (0.2%)	1,858 (0.2%)	1,179 (0.2%)	809 (0.3%)	387 (0.3%)	129 (0.3%)
Any opioids	428,406 (11.1%)	96,175 (8.9%)	96,290 (9.6%)	83,518 (10.9%)	65,826 (12.9%)	47,129 (15.6%)	28,378 (19.2%)	11,090 (24.0%)
Any antiepileptics	86,375 (2.2%)	22,291 (2.1%)	21,142 (2.1%)	17,324 (2.3%)	12,443 (2.4%)	7,873 (2.6%)	4,080 (2.8%)	1,222 (2.6%)

SNRI: Serotonin-noradrenaline reuptake inhibitor; SSRI: Serotonin-selective reuptake inhibitor; TCA: Tricyclic antidepressants

[*] **Median (IQR); N (%)**

[**] **Psychotropic polypharmacy was defined as at least two different psychotropic drug classes dispensed between 1st August and 31st Oct 2021.**

[#] **Any antipsychotic medication use was defined as the use of any first- and second-generation antipsychotics**

[##] **The medium length of action benzodiazepine bromazepam was included in the long-acting benzodiazepines.**

Table 3. Multivariable logistic regression analysis results of risk factors for any psychotropic use and psychotropic polypharmacy between 1st August and 31st October 2021 among all people in the study population.

Factors	**Any psychotropic drug classes***			**Psychotropic polypharmacy**		
	Odds Ratios	***CI***	***p***	***Odds Ratios***	***CI***	***p***
Age (Reference: 65-<70)						
70-<75	1.04	1.03 – 1.05	**<0.001**	1.03	1.02 – 1.04	**<0.001**
75-<80	1.11	1.11 – 1.12	**<0.001**	1.06	1.05 – 1.08	**<0.001**
80-<85	1.14	1.13 – 1.15	**<0.001**	1.02	1.00 – 1.03	**0.028**
85-<90	1.1	1.08 – 1.11	**<0.001**	0.9	0.88 – 0.92	**<0.001**
90-<95	0.96	0.94 – 0.97	**<0.001**	0.76	0.75 – 0.78	**<0.001**
>=95	0.81	0.79 – 0.83	**<0.001**	0.62	0.59 – 0.64	**<0.001**
Sex (Reference: Male)						
Female	1.46	1.45 – 1.47	**<0.001**	1.39	1.37 – 1.40	**<0.001**
Area-level disadvantage quintiles (Reference: Q1 - Most disadvantage)						
Q2	0.94	0.93 – 0.95	**<0.001**	0.92	0.91 – 0.93	**<0.001**
Q3	0.89	0.89 – 0.90	**<0.001**	0.86	0.85 – 0.87	**<0.001**
Q4	0.84	0.84 – 0.85	**<0.001**	0.8	0.79 – 0.81	**<0.001**
Q5 (Most advantaged)	0.79	0.78 – 0.79	**<0.001**	0.72	0.71 – 0.73	**<0.001**
Remoteness (Reference: Metropolitan)						
Inner regional	0.98	0.97 – 0.99	**<0.001**	0.94	0.93 – 0.95	**<0.001**
Outer regional	0.96	0.95 – 0.97	**<0.001**	0.91	0.89 – 0.92	**<0.001**
Remote/Very remote	0.84	0.82 – 0.87	**<0.001**	0.75	0.72 – 0.79	**<0.001**
Level of highest educational attainment (Reference: Year 9 or below)						
Year 10 and above	0.93	0.92 – 0.94	**<0.001**	0.94	0.93 – 0.95	**<0.001**

Certificate I-IV and Diploma	0.82	0.82 – 0.83	**<0.001**	0.82	0.80 – 0.83	**<0.001**
Bachelor and above	0.72	0.71 – 0.72	**<0.001**	0.72	0.71 – 0.74	**<0.001**
Living status (Reference: Living with someone in private dwelling)						
Living alone in a private dwelling	1.07	1.06 – 1.07	**<0.001**	1.11	1.10 – 1.12	**<0.001**
Living in a non-private dwelling	2.02	1.99 – 2.05	**<0.001**	2.57	2.53 – 2.61	**<0.001**
Assistance with core activities (Reference: Do not require assistance with core activities)						
Need assistance for core activities	2.05	2.03 – 2.06	**<0.001**	2.75	2.72 – 2.78	**<0.001**
Self-reported health conditions (Reference: Without self-reported health condition)						
Dementia	1.23	1.21 – 1.25	**<0.001**	-	-	-
Asthma or lung conditions	1.26	1.25 – 1.27	**<0.001**	1.34	1.32 – 1.35	**<0.001**
Diabetes	1.1	1.09 – 1.10	**<0.001**	1.09	1.07 – 1.10	**<0.001**
Heart disease or stroke	1.07	1.06 – 1.08	**<0.001**	1.04	1.03 – 1.05	**<0.001**
Cancer	1.22	1.21 – 1.23	**<0.001**	1.25	1.23 – 1.26	**<0.001**
Arthritis	1.39	1.38 – 1.40	**<0.001**	1.45	1.44 – 1.47	**<0.001**
Mental health condition(s)	8.65	8.57 – 8.74	**<0.001**	4.38	4.33 – 4.43	**<0.001**
Kidney disease	1.08	1.07 – 1.10	**<0.001**	1.1	1.08 – 1.12	**<0.001**
Country of birth (Reference: Australia)						

Born overseas	0.95	0.94 – 0.96	**<0.001**	0.97	0.96 – 0.98	**<0.001**
Language used at home (Reference: English)						
Use other language than English at home	0.66	0.65 – 0.66	**<0.001**	0.62	0.61 – 0.63	**<0.001**
Aboriginality (Reference: Non-Indigenous)						
Aboriginal and/or Torres Strait Islander people	-	-	-	1.07	1.03 – 1.11	**<0.001**
Intercept	0.25	0.25 – 0.25	<0.001	0.04	0.04 – 0.04	**<0.001**
Observations		3157262			3140808	
*Aboriginality was excluded due to small number of observations						

Table 4. Multivariable logistic regression analysis results of risk factors for any antipsychotic, antidepressant and benzodiazepine/Z-drug use between 1st August and 31st October 2021 among all people in the study population.

Factors	Any antipsychotics*			Any antidepressants			Any benzodiazepines and Z-drugs		
	Odds Ratios	*CI*	*p*	*Odds Ratios*	*CI*	*p*	*Odds Ratios*	*CI*	*p*
Age (Reference: 65-<70)									
70-<75	0.9	0.88 – 0.93	**<0.001**	1.04	1.04 – 1.05	**<0.001**	1.18	1.16 – 1.20	**<0.001**
75-<80	0.8	0.78 – 0.82	**<0.001**	1.09	1.08 – 1.10	**<0.001**	1.39	1.37 – 1.41	**<0.001**
80-<85	0.68	0.66 – 0.71	**<0.001**	1.05	1.04 – 1.06	**<0.001**	1.55	1.52 – 1.57	**<0.001**
85-<90	0.56	0.54 – 0.58	**<0.001**	0.97	0.95 – 0.98	**<0.001**	1.6	1.56 – 1.63	**<0.001**
90-<95	0.45	0.43 – 0.47	**<0.001**	0.78	0.77 – 0.79	**<0.001**	1.61	1.57 – 1.65	**<0.001**
>=95	0.34	0.32 – 0.37	**<0.001**	0.57	0.55 – 0.58	**<0.001**	1.57	1.51 – 1.63	**<0.001**
Sex (Reference: Male)									
Female	0.98	0.96 – 1.00	**0.029**	1.72	1.71 – 1.73	**<0.001**	1.48	1.47 – 1.50	**<0.001**
Area-level disadvantage quintiles (Reference: Q1 - Most disadvantage)									
Q2	0.91	0.89 – 0.93	**<0.001**	0.98	0.97 – 0.99	**<0.001**	0.95	0.94 – 0.96	**<0.001**
Q3	0.88	0.86 – 0.91	**<0.001**	0.93	0.93 – 0.94	**<0.001**	0.93	0.92 – 0.95	**<0.001**
Q4	0.88	0.86 – 0.91	**<0.001**	0.89	0.88 – 0.90	**<0.001**	0.92	0.90 – 0.93	**<0.001**
Q5 (Most advantaged)	0.87	0.84 – 0.90	**<0.001**	0.84	0.83 – 0.85	**<0.001**	0.9	0.89 – 0.92	**<0.001**
Remoteness (Reference: Metropolitan)									
Inner regional	0.86	0.84 – 0.88	**<0.001**	1.04	1.03 – 1.05	**<0.001**	0.82	0.81 – 0.83	**<0.001**
Outer regional	0.81	0.79 – 0.84	**<0.001**	1	0.98 – 1.01	0.465	0.76	0.74 – 0.77	**<0.001**

Remote/Very remote	0.71	0.65 – 0.78	**<0.001**	0.91	0.88 – 0.93	**<0.001**	0.58	0.55 – 0.62	**<0.001**
Level of highest educational attainment (Reference: Year 9 or below)									
Year 10 and above	0.86	0.84 – 0.88	**<0.001**	0.93	0.93 – 0.94	**<0.001**	1.03	1.01 – 1.04	**<0.001**
Certificate I-IV and Diploma	0.71	0.69 – 0.73	**<0.001**	0.83	0.82 – 0.84	**<0.001**	0.9	0.88 – 0.91	**<0.001**
Bachelor and above	0.7	0.68 – 0.72	**<0.001**	0.72	0.71 – 0.72	**<0.001**	0.92	0.91 – 0.94	**<0.001**
Living status (Reference: Living with someone in private dwelling)									
Living alone in a private dwelling	1.42	1.39 – 1.45	**<0.001**	1.05	1.04 – 1.06	**<0.001**	1.15	1.14 – 1.16	**<0.001**
Living in a non-private dwelling	3.05	2.97 – 3.14	**<0.001**	1.36	1.34 – 1.38	**<0.001**	1.55	1.52 – 1.58	**<0.001**
Assistance with core activities (Reference: Do not require assistance with core activities)									
Need assistance for core activities	2.89	2.83 – 2.96	**<0.001**	1.68	1.66 – 1.69	**<0.001**	1.54	1.52 – 1.56	**<0.001**
Self-reported health conditions (Reference: Without self-reported health condition)									
Dementia	2.59	2.52 – 2.66	**<0.001**	1.42	1.40 – 1.44	**<0.001**	0.65	0.64 – 0.67	**<0.001**
Asthma or lung conditions	0.93	0.91 – 0.95	**<0.001**	1.22	1.21 – 1.23	**<0.001**	1.29	1.28 – 1.31	**<0.001**
Diabetes	1.09	1.06 – 1.11	**<0.001**	1.13	1.13 – 1.14	**<0.001**	0.93	0.92 – 0.94	**<0.001**
Heart disease or stroke	0.68	0.66 – 0.70	**<0.001**	1.03	1.02 – 1.04	**<0.001**	1.08	1.07 – 1.10	**<0.001**
Cancer	0.97	0.94 – 0.99	**0.011**	1.03	1.02 – 1.04	**<0.001**	1.21	1.19 – 1.22	**<0.001**
Arthritis	0.57	0.56 – 0.59	**<0.001**	1.19	1.18 – 1.20	**<0.001**	1.2	1.19 – 1.21	**<0.001**
Mental health condition(s)	9.96	9.78 – 10.16	**<0.001**	10.19	10.10 – 10.28	**<0.001**	2.26	2.23 – 2.29	**<0.001**

Kidney disease	-	-	-	0.96	0.94 – 0.97	**<0.001**	1.1	1.07 – 1.12	**<0.001**
Country of birth (Reference: Australia)									
Born overseas	-	-	-	0.9	0.89 – 0.91	**<0.001**	1.02	1.01 – 1.03	**<0.001**
Language used at home (Reference: English)									
Use other language than English at home	-	-	-	0.64	0.63 – 0.64	**<0.001**	0.83	0.81 – 0.84	**<0.001**
Aboriginality (Reference: Non-Indigenous)									
Aboriginal and/or Torres Strait Islander people	-	-	-	0.9	0.88 – 0.93	**<0.001**	1.15	1.10 – 1.20	**<0.001**
Intercept	0.01	0.01 – 0.01	**<0.001**	0.13	0.13 – 0.13	**<0.001**	0.03	0.03 – 0.03	**<0.001**
Observations	3228456			3140808			3140808		
*Self-reported kidney diseases, Country of birth, language used at home, and Aboriginality were excluded due to small number of observations									

Table 5. Multivariable logistic regression analysis results of risk factors for any opioid and antiepileptic use between 1st August and 31st October 2021 among all people in the study population.

Factors	Any opioids			Any antiepileptics*		
	Odds Ratios	*CI*	*p*	*Odds Ratios*	*CI*	*p*
Age (Reference: 65-<70)						
70-<75	0.97	0.96 – 0.98	**<0.001**	0.95	0.93 – 0.97	**<0.001**
75-<80	0.99	0.97 – 1.00	**0.01**	0.89	0.87 – 0.91	**<0.001**
80-<85	1	0.99 – 1.01	0.958	0.76	0.74 – 0.78	**<0.001**
85-<90	0.98	0.96 – 0.99	**0.007**	0.58	0.56 – 0.60	**<0.001**
90-<95	0.95	0.94 – 0.97	**<0.001**	0.44	0.42 – 0.46	**<0.001**
>=95	0.96	0.93 – 0.99	**0.005**	0.31	0.29 – 0.34	**<0.001**
Sex (Reference: Male)						
Female	1.06	1.05 – 1.07	**<0.001**	0.88	0.87 – 0.90	**<0.001**
Area-level disadvantage quintiles (Reference: Q1 - Most disadvantage)						
Q2	0.91	0.90 – 0.92	**<0.001**	0.94	0.92 – 0.97	**<0.001**
Q3	0.84	0.83 – 0.85	**<0.001**	0.92	0.90 – 0.94	**<0.001**
Q4	0.76	0.75 – 0.77	**<0.001**	0.92	0.90 – 0.95	**<0.001**
Q5 (Most advantaged)	0.65	0.64 – 0.66	**<0.001**	0.91	0.89 – 0.94	**<0.001**
Remoteness (Reference: Metropolitan)						
Inner regional	1.01	1.00 – 1.02	**0.022**	0.92	0.90 – 0.94	**<0.001**
Outer regional	1.05	1.03 – 1.06	**<0.001**	0.84	0.81 – 0.86	**<0.001**
Remote/Very remote	0.94	0.91 – 0.98	**0.002**	0.71	0.65 – 0.77	**<0.001**

Level of highest educational attainment (Reference: Year 9 or below)						
Year 10 and above	0.94	0.93 – 0.95	**<0.001**	0.93	0.91 – 0.95	**<0.001**
Certificate I-IV and Diploma	0.88	0.87 – 0.89	**<0.001**	0.86	0.84 – 0.88	**<0.001**
Bachelor and above	0.72	0.71 – 0.73	**<0.001**	0.85	0.83 – 0.87	**<0.001**
Living status (Reference: Living with someone in private dwelling)						
Living alone in a private dwelling	1.01	1.00 – 1.02	**0.019**	1.02	1.00 – 1.04	0.083
Living in a non-private dwelling	2.45	2.41 – 2.49	**<0.001**	2.13	2.07 – 2.20	**<0.001**
Assistance with core activities (Reference: Do not require assistance with core activities)						
Need assistance for core activities	2.46	2.43 – 2.48	**<0.001**	3.33	3.27 – 3.39	**<0.001**
Self-reported health conditions (Reference: Without self-reported health condition)						
Dementia	0.71	0.69 – 0.72	**<0.001**	1.25	1.21 – 1.29	**<0.001**
Asthma or lung conditions	1.34	1.33 – 1.35	**<0.001**			
Diabetes	1.13	1.12 – 1.15	**<0.001**	0.87	0.85 – 0.89	**<0.001**
Heart disease or stroke	1.07	1.06 – 1.08	**<0.001**	1.28	1.25 – 1.30	**<0.001**
Cancer	1.49	1.47 – 1.50	**<0.001**	1.07	1.05 – 1.10	**<0.001**
Arthritis	2.03	2.02 – 2.05	**<0.001**	0.86	0.85 – 0.88	**<0.001**
Mental health condition(s)	1.25	1.24 – 1.27	**<0.001**	2.36	2.31 – 2.40	**<0.001**
Kidney disease	1.2	1.18 – 1.22	**<0.001**	-	-	-

Country of birth (Reference: Australia)						
Born overseas	1.05	1.04 – 1.06	**<0.001**	0.85	0.83 – 0.87	**<0.001**
Language used at home (Reference: English)						
Use other language than English at home	0.65	0.65 – 0.66	**<0.001**	0.62	0.60 – 0.64	**<0.001**
Aboriginality (Reference: Non-Indigenous)						
Aboriginal and/or Torres Strait Islander people	1.2	1.16 – 1.23	**<0.001**	-	-	-
Intercept	0.08	0.08 – 0.08	**<0.001**	0.02	0.02 – 0.02	**<0.001**
Observations	3140808			3157262		
*Self-reported kidney diseases and Aboriginality were excluded due to small number of observations						

REFERENCES

1. Prince, M.J., et al., The burden of disease in older people and implications for health policy and practice. Lancet, 2015. 385(9967): p. 549-62;10.1016/s0140-6736(14)61347-7

2. Australian Institute of Health and Welfare. Older Australians. 2021 https://www.aihw.gov.au/getmedia/73a6a317-b508-4ecc-834a-cb0a54378b9d/older-australians.pdf?v=20240702075543&inline=true. Accessed 2024 12/08/2024

3. Australian Bureau of Statistics. National Study of Mental Health and Wellbeing. 2020-2022 https://www.abs.gov.au/statistics/health/mental-health/national-study-mental-health-and-wellbeing/latest-release. Accessed 2024 19/08/2024

4. Johnell, K., et al., Psychotropic drugs and the risk of fall injuries, hospitalisations and mortality among older adults. Int J Geriatr Psychiatry, 2017. 32(4): p. 414-420;10.1002/gps.4483

5. Seppala, L.J., et al., Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: II. Psychotropics. J Am Med Dir Assoc, 2018. 19(4): p. 371.e11-371.e17;10.1016/j.jamda.2017.12.098

6. Zivkovic, S., et al., Antipsychotic drug use and risk of stroke and myocardial infarction: a systematic review and meta-analysis. BMC Psychiatry, 2019. 19(1): p. 189;10.1186/s12888-019-2177-5

7. Wojt, I.R., et al., The Prevalence and Characteristics of Psychotropic-Related Hospitalizations in Older People: A Systematic Review and Meta-Analysis. J Am Med Dir Assoc, 2021. 22(6): p. 1206-1214.e5;10.1016/j.jamda.2020.12.035

8. Bezabhe, W.M., et al., Ten-Year Trends in Psychotropic Prescribing and Polypharmacy in Australian General Practice Patients with and without Dementia. J Clin Med, 2023. 12(10);10.3390/jcm12103389

9. Harrison, S.L., et al., The dispensing of psychotropic medicines to older people before and after they enter residential aged care. Med J Aust, 2020. 212(7): p. 309-313;10.5694/mja2.50501

10. Lau, E.C.Y., et al., Antidementia and Psychotropic Drug Use in Older People With Dementia in Australia: A National Data Linkage Study. Journal of the American Medical Directors Association, 2024;10.1016/j.jamda.2024.105237

11. Australian Commission on Safety and Quality in Health Care. Australian Atlas of Healthcare Variation Series. 2021 https://www.safetyandquality.gov.au/our-work/healthcare-variation/australian-atlas-healthcare-variation-series. Accessed 2024 03/09/2024

12. Bajracharya, R. and D.M. Qato, Patterns of Psychoactive Medication Use in Community-Dwelling Older Adults in the US in 2016: A Descriptive Cross-Sectional Study. J Aging Health, 2021. 33(1-2): p. 86-100;10.1177/0898264320959293

13. Norris, P., et al., Medicalisation or under-treatment? Psychotropic medication use by elderly people in New Zealand. Health Sociology Review, 2011. 20(2): p. 202-218;10.5172/hesr.2011.20.2.202

14. Grill, P., et al., The burden of psychotropic and anticholinergic medicines use in care homes: population-based analysis in 147 care homes. Age Ageing, 2021. 50(1): p. 183-189;10.1093/ageing/afaa122

15. Australian Bureau of Statistics. Person Level Integrated Data Asset (PLIDA). 2023 https://www.abs.gov.au/about/data-services/data-integration/integrated-data/person-level-integrated-data-asset-plida. Accessed 2024 02/08/2024

16. Mellish, L., et al., The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. BMC Res Notes, 2015. 8: p. 634;10.1186/s13104-015-1616-8

17. WHO Collaborating Centre for Drug Statistics Methodology. International language for drug utilization research. 2024 https://atcddd.fhi.no. Accessed 2024 06/09/2024

18. Australian Bureau of Statistics. Census methodology. 2021 https://www.abs.gov.au/census/guide-census-data/census-methodology/2021. . Accessed 2024 02/08/2024

19. National Association of State Mental Health Program Directors (NASMHPD). TECHNICAL REPORT ON PSYCHIATRIC POLYPHARMACY. 2001 https://www.nasmhpd.org/sites/default/files/Polypharmacy.pdf. Accessed 2024 27/11/2024

20. Kim, J.H., Multicollinearity and misleading statistical results. Korean J Anesthesiol, 2019. 72(6): p. 558-569;10.4097/kja.19087

21. Cai, H., et al., Global prevalence of depression in older adults: A systematic review and meta-analysis of epidemiological surveys. Asian Journal of Psychiatry, 2023. 80: p. 103417;https://doi.org/10.1016/j.ajp.2022.103417

22. Bromley, M.I., et al., Burden of Chronic and Heavy Opioid Use Among Elderly Community Dwellers in the U.S. AJPM Focus, 2024. 3(2): p. 100175;https://doi.org/10.1016/j.focus.2023.100175

23. Luta, X., et al., Patterns of benzodiazepine prescription among older adults in Switzerland: a cross-sectional analysis of claims data. BMJ Open, 2020. 10(1): p. e031156;10.1136/bmjopen-2019-031156

24. American Geriatrics Society American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc, 2023. 71(7): p. 2052-2081;10.1111/jgs.18372

25. Orsel, K., et al., Psychotropic drugs use and psychotropic polypharmacy among persons with Alzheimer's disease. European Neuropsychopharmacology, 2018. 28(11): p. 1260-1269;https://doi.org/10.1016/j.euroneuro.2018.04.005

26. van der Heide, I., et al., The relationship between health, education, and health literacy: results from the Dutch Adult Literacy and Life Skills Survey. J Health Commun, 2013. 18 Suppl 1(Suppl 1): p. 172-84;10.1080/10810730.2013.825668

27. Wang, J. and L. Geng, Effects of Socioeconomic Status on Physical and Psychological Health: Lifestyle as a Mediator. Int J Environ Res Public Health, 2019. 16(2);10.3390/ijerph16020281

28. Freeman, A., et al., The role of socio-economic status in depression: results from the COURAGE (aging survey in Europe). BMC Public Health, 2016. 16(1): p. 1098;10.1186/s12889-016-3638-0

29. Page, I.S., et al., Estimating the difference in prevalence of common mental disorder diagnoses for Aboriginal and Torres Strait Islander peoples compared to the general Australian population. Epidemiol Psychiatr Sci, 2022. 31: p. e44;10.1017/s2045796022000233

30. Brown, A.D., et al., Depression in Aboriginal men in central Australia: adaptation of the Patient Health Questionnaire 9. BMC Psychiatry, 2013. 13: p. 271;10.1186/1471-244x-13-271

31. The Australian Institute of Health and Welfare. Chronic health conditions among culturally and linguistically diverse Australians, 2021. 2023 https://www.aihw.gov.au/getmedia/02b5dcaa-4a41-4984-85e3-cdc8edc35c95/chronic-health-conditions-among-culturally-and-linguistically-diverse-australians-2021.pdf?v=20230119101621&inline=true. Accessed 2024 27/11/2024

32. Khatri, R.B. and Y. Assefa, Access to health services among culturally and linguistically diverse populations in the Australian universal health care system: issues and challenges. BMC Public Health, 2022. 22(1): p. 880;10.1186/s12889-022-13256-z

33. Australian Institute of Health and Welfare. Dementia in Australia. 2021 https://www.aihw.gov.au/getmedia/60d5d0da-fd52-4962-ae7d-d1692c3a7433/dementia-in-australia.pdf?v=20240814172349&inline=true. Accessed 2024 15/08/2024

34. Magierski, R., et al., Pharmacotherapy of Behavioral and Psychological Symptoms of Dementia: State of the Art and Future Progress. Front Pharmacol, 2020. 11: p. 1168;10.3389/fphar.2020.01168

35. Bessey, L.J. and A. Walaszek, Management of Behavioral and Psychological Symptoms of Dementia. Curr Psychiatry Rep, 2019. 21(8): p. 66;10.1007/s11920-019-1049-5

36. Wu, C.C., et al., Benzodiazepine Use and the Risk of Dementia in the Elderly Population: An Umbrella Review of Meta-Analyses. J Pers Med, 2023. 13(10);10.3390/jpm13101485

37. Achterberg, W.P., et al., Are Chronic Pain Patients with Dementia Being Undermedicated? J Pain Res, 2021. 14: p. 431-439;10.2147/jpr.S239321

38. Maust, D.T., et al., Prevalence of Psychotropic and Opioid Prescription Fills Among Community-Dwelling Older Adults With Dementia in the US. Jama, 2020. 324(7): p. 706-708;10.1001/jama.2020.8519

39. Glennon, V., An Australian living guideline for the pharmacological management of inflammatory arthritis. Australia & New Zealand musculoskeletal clinical trials network, 2023

40. Abdel Shaheed, C., et al., Efficacy, safety, and dose-dependence of the analgesic effects of opioid therapy for people with osteoarthritis: systematic review and meta-analysis. Med J Aust, 2022. 216(6): p. 305-311;10.5694/mja2.51392

41. Langford, A.V., et al., Clinical practice guideline for deprescribing opioid analgesics: summary of recommendations. Medical Journal of Australia, 2023. 219(2): p. 80-89

42. O'Mahony, D., et al., STOPP/START criteria for potentially inappropriate prescribing in older people: version 3. Eur Geriatr Med, 2023. 14(4): p. 625-632;10.1007/s41999-023-00777-y

43. Harding, S., et al. Report on the quality of 2021 Census data. 2022 https://www.abs.gov.au/system/files/documents/0df3c55493211cbb3d71ba17520f28de/SIAP%20report%20on%20the%20quality%20of%202021%20Census%20data.pdf. Accessed 2024 21/08/2024

2.3. Supplementary materials

Supplementary Table 1: Characteristics of variables used.

Variable	Source	Type	Value/Units
Age	PBS	Numeric	Year
Sex	PBS	Categorical	Female/Male
Medications	PBS	Nominal	Medication ATC codes
Registered marital status	2021 Census	Categorical	Married/Never married/Divorced/ Separated/Widowed or Unknown
Aboriginality	2021 Census	Categorical	Non-Indigenous/Aboriginal and/or Torres Strait Islander people/Unknown
Country of birth	2021 Census	Nominal	Australia/Overseas/Unknown
Language spoken at home	2021 Census	Nominal	English/Other/Unknown
Self-reported health condition*	2021 Census	Categorical	Yes/No/Unknown for each health conditions included in 2021 Census.
Level of highest educational attainment	2021 Census	Categorical	Years 9 and below/Years 10 and above/ Certificate I-IV and Diploma/Bachelor and above/Unknown
Remoteness[#]	2021 Census	Categorical	Major cities/Inner regional/Outer regional/Remote/very remote/Unknown
Needs assistance with core activities	2021 Census	Categorical	No/Yes/Unknown
Living condition	2021 Census	Categorical	Living alone in a private dwelling/Living with other people in a private dwelling/ Living in a non-private dwelling[^]/Other
Living status	2021 Census	Categorical	Occupied private dwelling/ Non-private dwelling
Area-level disadvantage quintiles[^^]	2021 Census	Continuous	Index scores, scores were then further categorized into 5 levels and analyzed as a categorical variable in the present study: Q1 (Most disadvantaged) to Q5 (Most advantaged)
*Selected health conditions include arthritis, asthma, cancer (including remission), diabetes (excluding gestational diabetes), dementia, heart disease (including heart attack or angina), kidney disease, lung condition (including COPD or emphysema), mental health condition (including depression or anxiety), and stroke.			
#Remoteness is based on the Accessibility/Remoteness Index of Australia Plus - ARIA+ provided by ABS.			
^non-private dwellings are dwellings that provide communal accommodation, which includes a range of different categories, such as nursing home, public and private hospital, hotel, motel, bed and breakfast, prison, and immigration detention center.			
^^Socioeconomic is measured by the Index of Relative Socio-economic Advantage and Disadvantage, represented as area-level disadvantage quintiles.			

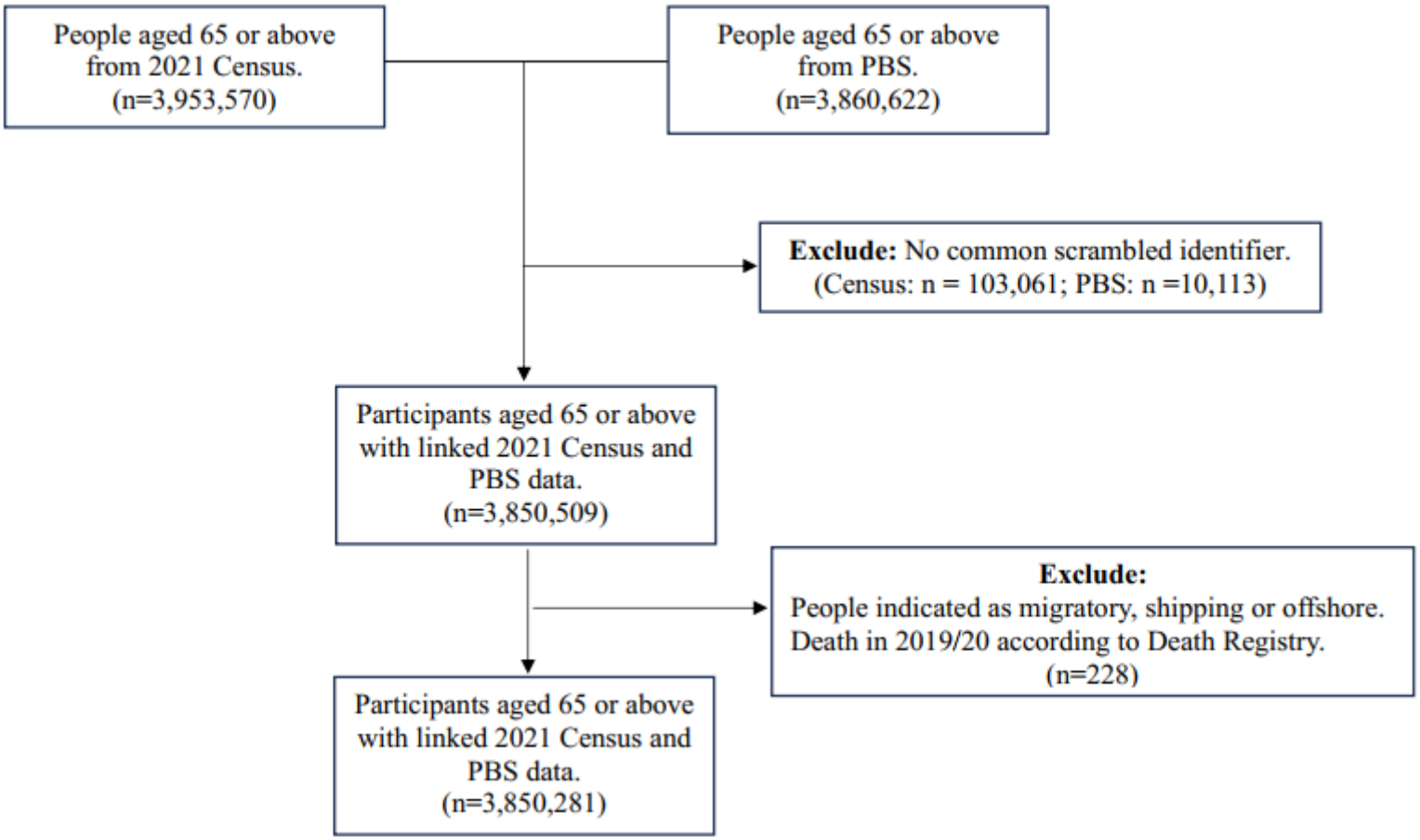
Supplementary table 2: **Prevalence of medication use in 2021 calendar year (aged 65 years and over by the end of 2021)**

Characteristics	Total population	Age groups						
		65-69	70-74	75-79	80-84	85-89	90-94	95+
	N = 3,850,281[1]	N = 1,077,222[1]	N = 1,003,699[1]	N = 764,622[1]	N = 508,549[1]	N = 302,227[1]	N = 147,827[1]	N = 46,135[1]
Any psychotropic use	1,654,896 (43%)	420,276 (39%)	405,213 (40%)	332,021 (43%)	237,464 (47%)	153,169 (51%)	79,919 (54%)	26,834 (58%)
Any antipsychotic use	102,150 (2.7%)	23,114 (2.1%)	20,891 (2.1%)	18,045 (2.4%)	15,774 (3.1%)	12,839 (4.2%)	8,358 (5.7%)	3,129 (6.8%)
Any antidepressant use	904,150 (23%)	235,373 (22%)	223,431 (22%)	181,050 (24%)	127,421 (25%)	82,213 (27%)	41,740 (28%)	12,922 (28%)
Any benzodiazepine use	460,160 (12%)	102,144 (9.5%)	109,086 (11%)	96,284 (13%)	71,990 (14%)	46,989 (16%)	25,120 (17%)	8,547 (19%)
Any opioid use	831,830 (22%)	206,257 (19%)	199,340 (20%)	164,896 (22%)	120,473 (24%)	80,108 (27%)	44,330 (30%)	16,426 (36%)
Any antiepileptic use	114,434 (3.0%)	28,829 (2.7%)	27,648 (2.8%)	22,967 (3.0%)	16,747 (3.3%)	10,719 (3.5%)	5,669 (3.8%)	1,855 (4.0%)

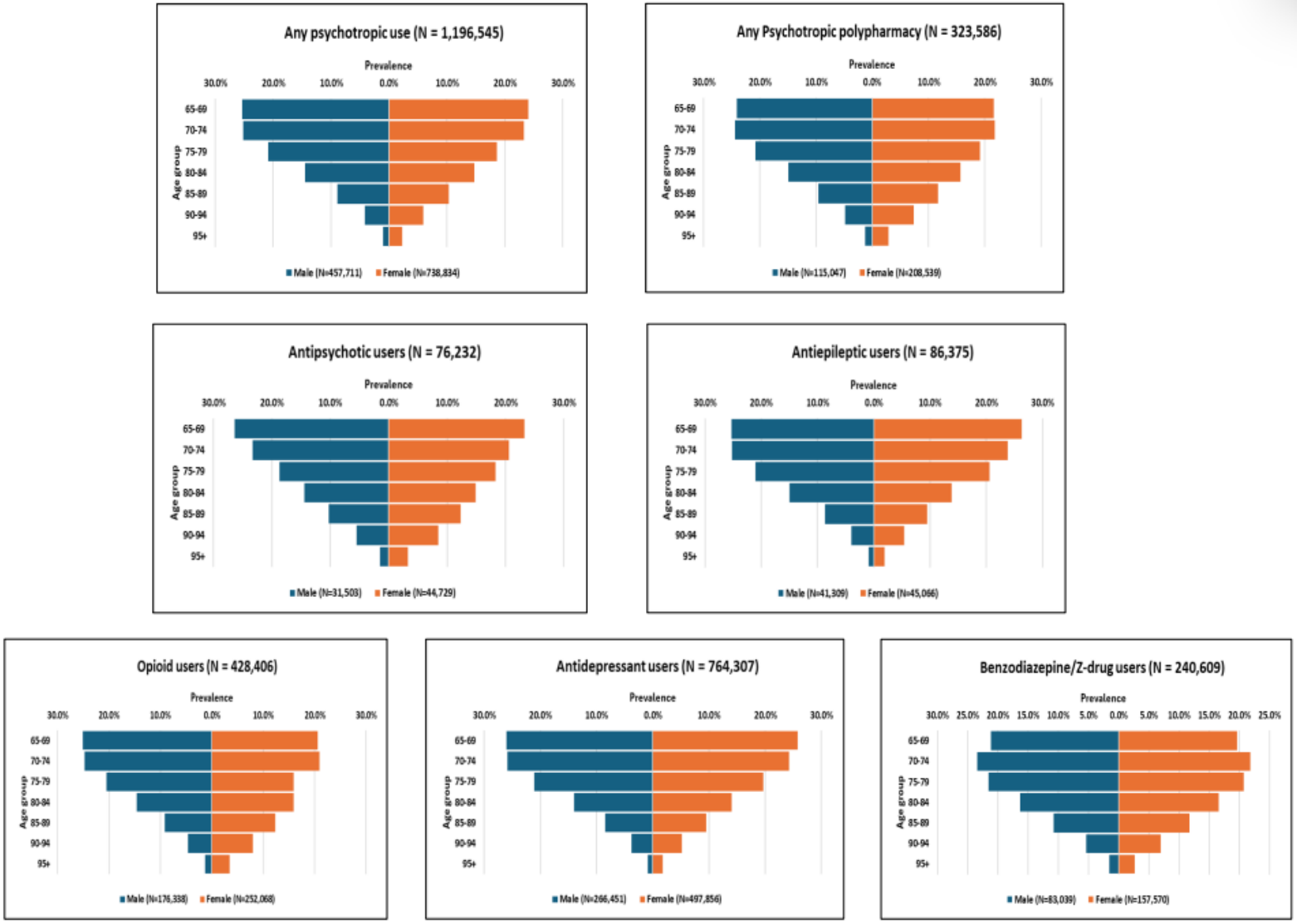
[1] n (%)

Supplementary Table 3. Prevalence of each drug class in people with psychotropic polypharmacy.

People with psychotropic polypharmacy	Total population*	Age groups*						
		65-69	70-74	75-79	80-84	85-89	90-94	Age 95+
	N = 323,586	N = 72,742	N = 73,373	N = 63,929	N = 49,779	N = 35,458	N = 20,878	N = 7,427
Antidepressants	267,996 (83%)	61,552 (85%)	61,781 (84%)	53,222 (83%)	40,698 (82%)	28,754 (81%)	16,404 (79%)	5,585 (75%)
Opioids	209,729 (65%)	45,423 (62%)	46,303 (63%)	40,942 (64%)	32,817 (66%)	23,992 (68%)	14,709 (70%)	5,543 (75%)
Benzodiazepines and Z-drugs	139,005 (43%)	29,307 (40%)	31,345 (43%)	28,325 (44%)	21,983 (44%)	15,461 (44%)	9,217 (44%)	3,367 (45%)
Antipsychotics	57,847 (18%)	13,849 (19%)	12,499 (17%)	10,384 (16%)	8,610 (17%)	6,735 (19%)	4,266 (20%)	1,504 (20%)
Antiepileptics	49,455 (15%)	12,920 (18%)	11,992 (16%)	9,738 (15%)	7,024 (14%)	4,498 (13%)	2,517 (12%)	766 (10%)



Supplementary Figure 1: Study flow chart



Supplementary Figure 2: Prevalence of psychotropic medication use by age group and sex

2.4. Research presentation

Preliminary results were presented in an oral presentation at the ASCEPT, APFP & APSA Joint Congress, Melbourne, 2024 as:

Hieu T. Le, Edward C.Y. Lau, Weisi Chen, Christine Y. Lu, Tuan A. Nguyen, Lee-Fay Low, Sarah N Hilmer, Yun-Hee Jeon and Edwin C.K. Tan. Prevalence and risk factors for psychotropic medication use in older adults in Australia: a nationwide, data linkage study.

2.5. Ethic approval

The study in this chapter was conducted in accordance with the Declaration of Helsinki and was deemed negligible risk, receiving exemption from ethical approval by the University of Sydney Human Research Ethics Committee **(Appendix B)**.

CHAPTER 3. Treatment modifiers and predictors of risperidone response in people with dementia: an individual participant meta-analysis of six clinical trials

3.1. Chapter overview

As highlighted in **Chapter 1**, antipsychotics are among the highest-risk medications used in people with dementia. Findings from **Chapter 2** further demonstrate that, as of 2021, older Australians living with dementia are more likely to be prescribed antipsychotics. Given that risperidone is the only antipsychotic approved in Australia for the treatment of behaviours and psychological symptoms of dementia (BPSD), this chapter aims to introduce a foundational step to promote the personalised use of antipsychotics in people with dementia. More specifically, it focuses on identifying which BPSD symptoms are most responsive to risperidone, as well as the treatment modifiers and predictors of therapeutic response.

To address these aims, this study employed an individual participant data meta-analysis (IPD-MA) of six clinical trials involving risperidone, including those submitted for regulatory approval of its BPSD indication in Australia. The findings contribute to growing evidence that risperidone is primarily effective in treating psychosis, aggression, and anxiety/phobias, but not other BPSD. Additionally, several factors related to risperidone's pharmacokinetics and pharmacodynamics were found to influence treatment outcomes. Notably, early response at week 2 strongly predicted subsequent response at weeks 4 and 8.

These results highlight the challenges of antipsychotic prescribing and therefore support the individualised treatment approaches for BPSD, although further research is warranted to fully evaluate the benefit–risk balance across different patient subgroups. This chapter addresses the second research objective outlined in **Chapter 1**.

Chapter 3 is presented as a research manuscript accepted for publication in the journal Alzheimer's & Dementia.

3.2. Manuscript details

Hieu T. Le, BPharm (Hons), Edward C.Y. Lau (Hons), Christine Y. Lu, Sarah N Hilmer, Yun-Hee Jeon, Lee-Fay Low, Tuan A. Nguyen, and Edwin C.K. Tan (2025). Treatment Modifiers and Predictors of Risperidone Response in Dementia: An Individual Participant Meta-Analysis of Six Randomised Controlled Trials. Alzheimer's and Dementia. (Accepted for publication)

Treatment Modifiers and Predictors of Risperidone Response in Dementia: An Individual Participant Meta-Analysis of Six Randomised Controlled Trials

Hieu T. Le, BPharm (Hons)[a], Edward C.Y. Lau, BPharmMgmt (Hons)[a], Christine Y. Lu, PhD[a,b,c], Sarah N Hilmer, PhD[b], Yun-Hee Jeon, PhD[d] , Lee-Fay Low, PhD[e], Tuan A. Nguyen, PhD[f,g,h], and Edwin C.K. Tan, PhD[a,b*]

[a]*The University of Sydney School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia*

[b]*Kolling Institute, Faculty of Medicine and Health, The University of Sydney and the Northern Local Health District, Sydney, New South Wales, Australia*

[c]*Department of Pharmacy, Royal North Shore Hospital, St Leonards, New South Wales, Australia*

[d]*Susan Wakil School of Nursing and Midwifery, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia*

[e]*The University of Sydney School of Health Sciences, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia*

[f]*School of Health Sciences, Swinburne University of Technology, Hawthorn, Victoria, Australia*

[g]*Division of Aged Care and Social Gerontology, National Ageing Research Institute, Parkville, Victoria, Australia.*

[h]*UniSA Clinical & Health Sciences, University of South Australia, Adelaide, South Australia, Australia*

The authors declare no conflicts of interest.

***Corresponding author:**

Dr Edwin C.K. Tan

Post: The University of Sydney School of Pharmacy, Faculty of Medicine and Health, Pharmacy and Bank Building A15, The University of Sydney, NSW, Australia, 2006

Email: edwin.tan@sydney.edu.au

RESEARCH IN CONTEXT

Systematic review: We conducted a literature review using the Web of Science and PubMed databases. Existing research on antipsychotic use in dementia primarily consists of aggregate-data meta-analyses or single-trial studies, with only one individual participant data meta-analysis (IPD-MA) addressing factors related to adverse events. No IPD-MA has been conducted to explore potential treatment modifiers or predictors of antipsychotic response to specific behaviours and psychological symptoms of dementia.

Interpretation: Risperidone modestly improved specific symptoms, including aggression, psychosis, and anxiety/phobia. Subgroup analyses indicated that pharmacokinetic- and pharmacodynamic-related factors may affect efficacy, and early response could predict later symptom improvement.

Future directions: Future studies should explore the potential treatment modifiers identified in this study and focus on strategies to balance the risks and benefits of risperidone use, ultimately fostering more personalised treatment decisions.

HIGHLIGHTS

- Risperidone modestly reduces symptoms of psychosis, aggression, and anxiety/phobias.
- Risperidone shows no effect on activity, affective, or sleep disturbances.
- Patient factors (body mass index, endocrine disease, ethnicity) may affect response.
- Positive response by week 2 predicts significant improvement later.

ABSTRACT

INTRODUCTION

Risperidone is approved in Australia for the treatment of behaviours and psychological symptoms of dementia (BPSD), despite modest efficacy and known risks, including stroke and mortality. Identifying responsive symptoms, treatment modifiers and predictors is crucial for personalised treatment.

METHOD

A one-stage individual participant data meta-analysis of six randomised controlled trials (Risperidone: N=1009; Placebo: N=711) was conducted. Mixed-effects models assessed treatment effects, modifiers, and predictors, with BPSD measured via the BEHAVE-AD scale.

RESULTS

Risperidone showed modest benefits after 8 weeks for aggression (standardised mean difference [SMD]: -0.22; p<0.001), psychosis (SMD: -0.23; p=0.001), and anxiety/phobias (SMD: -0.19; p=0.014), but not for activity, affective, or sleep disturbances. Pharmacokinetic/pharmacodynamic-related factors (e.g., body mass index, endocrine disease, ethnicity) potentially modified treatment effects. Early response at week 2 predicted improvement at week 8 (OR: 4.46; p<0.001).

DISCUSSION

Risperidone offered symptom-specific benefits for aggression, psychosis and anxiety/phobias. Early response at week 2 predicted treatment outcomes, while certain patient characteristics (e.g., BMI, ethnicity, endocrine disease) may modify the treatment response. Further research is needed to optimise the benefit–risk balance and individualise therapy.

***Keywords*:** Dementia, Antipsychotics, Risperidone, Behaviours and Psychological Symptoms associated with Dementia, BPSD, Neuropsychiatric Symptoms, Risperidone, IPD-MA

1. INTRODUCTION

There are around 57 million people living with dementia globally (1), and this number is projected to increase to nearly 158 million cases in 2050 (2). Throughout the course of dementia, people often exhibit changed behaviours associated with cognitive decline, commonly referred to as behaviours and psychological symptoms of dementia (BPSD) or sometimes described as neuropsychiatric symptoms or responsive behaviours (3, 4). These include manifestations such as psychosis, aggression, agitation, anxiety, depression, changes in sleep or appetite, and apathy (3). BPSD are prevalent among people with dementia, with estimates reaching 32% in community-dwelling populations (5) and up to 90% in hospitalised patients and nursing home residents (6, 7).

Antipsychotics are often used to manage BPSD in people living with dementia, with the prevalence reaching up to 37.5% (8, 9). These symptoms vary widely between individuals, and current evidence suggests that antipsychotics offer only modest benefits in treating psychosis and agitation in this population (10-12). Meanwhile, these medications can increase the risk of adverse events including cardiovascular disease, stroke, and mortality in older people (10, 11, 13). In light of these risks, antipsychotics should only be initiated for severe symptoms or cases where non-pharmacological approaches prove ineffective (8, 10, 13). Therefore, identifying treatment modifiers, which are the patient-specific characteristics that define subgroups likely to experience greater benefit or higher risk from medication, can facilitate more targeted and effective treatment strategies (14, 15). Additionally, exploring predictors indicating the likelihood of therapeutic success can help clinicians personalise treatment decisions, whether to continue the current therapy or consider alternative approaches.

Individual participant data meta-analysis (IPD-MA) currently offers the most robust evidence for detecting subgroup effects because it can standardise data across studies and prevent ecological bias common in aggregate analyses (16, 17). Furthermore, IPD-MA can clarify whether observed effects apply uniformly or are modified by specific patient characteristics, thereby providing high-quality evidence on treatment modifiers and predictors of an outcome (17-19). Current research on antipsychotic use in dementia has mainly relied on aggregate-data meta-analyses (3, 11), or single-trial studies (20, 21), with only one IPD-MA exploring factors associated with adverse events (3, 22). To date, no IPD-MA has been performed to investigate potential treatment modifiers or predictors of antipsychotic response across both overall and specific symptom domains of BPSD. Given that risperidone remains the only antipsychotic approved for managing BPSD in some countries, including Australia, Canada, the United Kingdom, and New Zealand (3, 13), our study aims to use IPD-MA to identify treatment modifiers and predictors of risperidone response in individuals with dementia experiencing different types of BPSD.

2. METHODS

2.1 Data sources and access

Data were obtained from the Yale Open Data Access (YODA) Project, an independent platform that enables secure, transparent sharing of clinical trial data. YODA was selected due to its rigorous scientific review process and access to harmonised datasets suitable for secondary analysis (23, 24). We searched this repository for studies involving individuals with dementia and Alzheimer's disease. After identifying relevant trials, we reviewed the associated documentation to select datasets that met the following eligibility criteria: (1) adult participants diagnosed with dementia and exhibiting BPSD,

(2) participants involved in double-blind placebo-controlled trials receiving risperidone treatment, and (3) IPD were available for the primary outcome. Once the potentially eligible studies were identified, we requested access to the participant-level datasets through the standard procedure outlined on the website (24).

2.2 Trial characteristics

A total of 7 trials involving risperidone for the treatment of BPSD in individuals with dementia were identified. One trial was excluded because it was not placebo-controlled, leaving 6 eligible trials for inclusion in the study. Among these, four trials—USA-63 (ClinicalTrials.gov registration NCT00253123) (25), INT-24 (NCT00249145) (26), AUS-5 (NCT00249158) (27) and USA-232 (NCT00034762) (28) – have had their primary results published. This IPD-MA also includes two unpublished trials: BEL-14 (n = 39), and INT-83 (n = 18). We included all individuals receiving either placebo or risperidone in this analysis. Trial durations varied: 12 weeks for USA-63, INT-24, and AUS-5; 8 weeks for USA-232 and INT-83; and 4 weeks for BEL-14. Most trials involved men and women aged 55 or older diagnosed with Alzheimer's disease, vascular dementia, or mixed type dementia based on DSM-IV criteria (29), while BEL-14 using Berg criteria for diagnosis of senile dementia of the Alzheimer's type (30). All trials, except for BEL-14, included participants with a Mini-Mental State Examination (MMSE) score 23 or lower. USA-63 and INT-24 required participants to have a Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD) total score of 8 or higher, along with a global rating of 1 or more on the same scale. For USA-232 and INT-83, an inclusion criterion was a score of at least 2 on any item of the BEHAVE-AD psychosis subscale. Only AUS-5 used Cohen-Mansfield Agitation Inventory (CMAI) frequency score to include participants (31). All trials excluded participants with a diagnosis of other psychiatric conditions. The USA-63 studies employed three fixed-dose risperidone regimens (0.5 mg, 1 mg, or 2 mg daily), while the other studies used flexible dosing. Dosing ranges included 0.5–4 mg daily in INT-24, 0.5–2 mg in AUS-5, 1–4 mg in BEL-14, and 1–1.5 mg in USA-232 and INT-83. All trials used BEHAVE-AD score as the efficacy parameter, while AUS-5, INT-24 and USA-63 also included CMAI score as an additional parameter. Supplementary Table S1 provides a summary of the trial details.

2.3 Risk of bias assessment

Six trials AUS-5, BEL-14, INT-24, INT-83, USA-63 and USA-232 were assessed for risk of bias (RoB) using "RoB 2 tool" proposed by the Cochrane group (32). Two authors independently graded these trials as "low risk of bias," "high risk of bias," or "some concerns" in the following five domains: risk of bias arising from the randomisation process, risk of bias due to deviations from the intended interventions, missing outcome data, risk of bias in measurement of the outcome, and risk of bias in selection of the reported result. Supplementary Figure S1 provides the RoB of these trials.

2.4 Outcome variables: The BEHAVE-AD rating score

BPSD were assessed by the BEHAVE-AD total scale and subscales at week 4 and week 8 (33). The BEHAVE-AD is a 25-item scale consisting of 7 subscales: A. Paranoid and Delusional Ideation (7 items); B. Hallucinations (5 items); C. Activity Disturbances (3 items); D. Aggressiveness (3 items); E. Diurnal Rhythm Disturbances (1 item); F. Affective Disturbances (2 items); and G. Anxieties and Phobias (4 items). Each item of the BEHAVE-AD scale was initially rated as absent (0) or present; if present, the severity was further classified into one of three categories, where 1 = present, 2 = present with emotional component, and 3 = present with both emotional and physical components (34).

Additionally, a global rating assessed the overall impact of symptoms on patients and caregivers, scored from 0 (not at all) to 3 (severely) (35). In this study, we defined psychosis as the combination of items in both subscale A and subscale B, consistent with the definition used in the original trial (25, 27). BEHAVE-AD scores were captured at baseline, as well as at week 2, 4, and 8. We analysed BEHAVE-AD scores as both dichotomous and continuous outcomes. A clinically significant therapeutic response was defined dichotomously as a ≥30% reduction in the BEHAVE-AD total score from baseline (25-28). For continuous outcomes, we retained raw scores for the total scale, each individual subscale, and the global rating scale. An early response was defined as meeting the therapeutic response threshold at week 2, while any reduction in score from baseline at week 2 was classified as early improvement. Further details of the BEHAVE-AD rating scale are provided in Appendix 1.

2.5 Covariate extraction

Covariates were gathered at baseline and during the 4- and 8-week periods, including demographic information at baseline (age, sex, body mass index [BMI], ethnicity), clinical conditions at baseline (MMSE score, dementia diagnosis, comorbidities, BEHAVE-AD score, presence of BPSD), laboratory results at baseline (creatinine levels), mean risperidone dose and the use of concomitant psychotropic medications during 4 and 8 weeks. Psychotropic medications, with their corresponding Anatomical Therapeutic Chemical (ATC) code (36), were defined as: anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A) and anti-dementia medications (N06D) (9). The presence of BPSD at baseline was classified as follows: Psychosis (score ≥2 on any items in subscales A and B), Activity disturbances (score ≥1 on any items in subscale C), Aggression (score ≥1 on any items in subscale D), Sleep disturbances (score ≥1 on any items in subscale E), Affective disturbance (score ≥1 on any items in subscale F), and Anxieties/Phobias (score ≥1 on any items in subscale G) (27).

Trial BEL-14 did not provide participant-level data on comorbidities, ethnicity, or dementia diagnosis; INT-24 lacked participant-level data on comorbidities; and INT-83 did not collect baseline creatinine measurements. Additionally, trial AUS-5 did not capture BEHAVE-AD scores at week 2. To maintain consistency when integrating data across six trials, we constructed two master datasets. Dataset A included data from all available trials but had fewer variables: age, sex, body mass index (BMI), The Mini Mental State Examination (MMSE) scores, baseline BEHAVE-AD total scores and each subcomponent score, presence of BPSD at baseline, risperidone mean dose, and concomitant psychotropic medications. Dataset B contained data from three trials only (AUS-5, USA-63, and USA-232) but included all variables from Dataset A along with additional variable including ethnicity, comorbidities, eGFR and dementia diagnosis. A detailed summary of variables in each dataset is provided in Supplementary Table S2.

2.6 Statistical analysis

Descriptive analyses

The baseline characteristics of participants were reported descriptively as proportions or as means/medians with corresponding standard deviations (SDs)/interquartile ranges (IQRs). We conducted a one-stage IPD-MA using a multivariable mixed-effects regression with random intercepts (17). This approach accounts for heterogeneity between studies in baseline risks (intercepts), while assuming uniform predictor effects across all studies (19). Outcomes were reported at week 4 and 8, as odds ratios (ORs) for dichotomous outcomes and standard mean differences (SMDs) for continuous

outcomes, with 95% confidence intervals (CIs). SMD values of 0.2, 0.5, and 0.8 correspond to small, medium, and large effects, respectively (37).

Estimating risperidone effects in total population and subpopulation

We evaluated the effectiveness of risperidone compared to placebo in the overall study population and in subpopulations, which were defined as the presence of specific BPSD at baseline. Outcomes assessed in the total population were the BEHAVE-AD total score and the global rating scale. In subpopulations defined by symptoms, the corresponding BEHAVE-AD subscale scores were used as the assessment.

Exploring modifiers of risperidone treatment

Treatment modifiers are patient characteristics that may influence how a treatment response differs in the subgroup of individuals who possess those characteristics. To explore potential treatment modifiers for the BEHAVE-AD total score and its subscales, we tested interaction terms between baseline covariates and the treatment group (38). We applied random-intercept models combined with an S-learner strategy to ensure the robustness of IPD-MA (19). All treatment-factor interactions were adjusted for other confounding variables using Dataset A. If the variable was exclusively present in Dataset B (e.g., comorbidities, dementia diagnosis), adjustments were made using Dataset B. After identifying interaction terms that were statistically significant, we performed subgroup analyses to further ensure the robustness of our findings (38, 39).

Identifying predictors of treatment response

Predictors are baseline characteristics or treatment-emergent factors that may help estimate the likelihood of a future outcome. For the analysis of predictors of therapeutic response, we restricted the sample to participants receiving risperidone only. Both logistic and linear mixed-effects regression models were applied to examine treatment response at week 4 and 8. Variables included in the final models were based on clinical reasoning and previous literature (20-22), including age, sex, ethnicity, BMI, MMSE score, dementia diagnosis, presence of BPSD symptoms at baseline, total and subscale BEHAVE-AD score, psychotropic medication use at baseline, concomitant psychotropic medications during the trials, risperidone dose, and early response to treatment. We developed two type of models: one that included only baseline variables and another that incorporated both baseline and treatment-emergent variables.

The variance inflation factor (VIF) for each included variable was checked to ensure the absence of multicollinearity (VIF<5) (40). A p-value <0.05 was considered statistically significant. As for the multivariable regression analysis for the predictors of treatment response, (8 outcomes at each endpoint), a Bonferroni corrected p value (<0.05/44 = 0.00113) was considered statistically significant in either Dataset A or B (41). Logistic and linear mixed effects models were fitted using the glmer and lmer function in package lme4 (42). Incomplete covariate data were accommodated under a Missing-at-Random (MAR) assumption through the full-information maximum-likelihood estimation inherent in these mixed-effects models (43). Statistical analyses were performed using R version 4.3.0.

3. RESULTS

3.1 Baseline patient characteristics

The analysis included 1,009 patients receiving risperidone and 711 patients receiving placebo. Both groups had a mean age [SD] of 83 (risperidone: 83 [8]; placebo: 83 [7]) years, with males comprising 30% of the total cohort. Participants were predominantly Caucasian (88% in both groups), with median (IQR) MMSE scores of 8 (12) for risperidone and 9 (12) for placebo. The most common BPSD in both groups were aggression, followed by activity disturbances and psychosis. Mean (SD) baseline BEHAVE-AD total scores were similar between groups [risperidone: 16 (8); placebo: 17 (9)]. Cardiovascular conditions were the predominant comorbidities (69% risperidone; 67% placebo). Hypnotics and sedatives were the most frequently used psychotropic medications at baseline (risperidone: 9.8%; placebo: 12%). Additional details of the cohort characteristics are presented in Table 1.

3.2 Treatment effects of risperidone in total population and subpopulation

In the overall population, risperidone use was not statistically associated with achieving a therapeutic response at both week 4 (OR: 1.23; 95% CI: 0.97–1.56), and at week 8 (OR: 1.30; 95% CI: 1.01–1.67) after the Bonferroni correction (Supplementary Table S3). Meanwhile, mean reductions in BEHAVE-AD total scores and global rating scales from baseline were statistically significant at both time points (Figure 1). Beneficial effects of risperidone were seen for the aggression (Week 4 SMD: -0.17; 95% CI: -0.28 to -0.06; Week 8 SMD: -0.22; 95% CI: -0.34 to -0.10) and anxieties and phobias (Week 4 SMD: -0.16; 95% CI: -0.30 to -0.02; Week 8 SMD: -0.19; 95% CI: -0.35 to -0.04) subpopulations. By week 8, psychosis subgroups (SMD: -0.23; 95% CI: -0.37 to -0.09) showed lower BEHAVE-AD psychosis score. Interestingly, people without sleep disturbance at baseline showed a statistically higher score for sleep disturbance at week 4 (SMD: 0.10; 95% CI: 0.01 to 0.20).

3.3 Treatment modifiers of risperidone effect

We identified statistically significant interactions between baseline characteristics and treatment effect for several outcomes at weeks 4 and 8. These characteristics included BMI, sex, ethnicity, MMSE score, and the presence of active cardiovascular, endocrine, and neurological diseases. Only statistically significant interactions are reported in Supplementary Table S4. Subgroup analysis of risperidone response to different outcomes is shown in Figure 2. Risperidone statistically significantly improved the BEHAVE-AD total score at week 8 among participants with a normal BMI (Week 4 SMD: –0.22; 95% CI: –0.35 to –0.09; Week 8 SMD: –0.23; 95% CI: –0.38 to –0.09) and those with currently active neurological conditions (SMD: –0.36; 95% CI: –0.57 to –0.15). For the BEHAVE-AD global rating scale, males receiving risperidone showed greater improvement compared to placebo at week 4 (SMD: –0.34; 95% CI: –0.54 to –0.15). Additionally, participants without endocrine diseases at baseline who used risperidone had lower BEHAVE-AD aggression score at week 8 (SMD: –0.32; 95% CI: –0.46 to –0.17). Reduction in this score was also seen among those with anxieties/phobias (Week 8 SMD: -0.31; 95%CI: -0.45 to -0.17) and sleep disturbances (Week 8 SMD: -0.38; 95%CI: -0.56 to -0.20) at baseline. Among Caucasian participants, risperidone users had a statistically significant reduction in the BEHAVE-AD anxieties and phobias subscale at week 8 compared to non-users (SMD: –0.20; 95% CI: –0.32 to –0.07). Modest or no statistically significant treatment effects were observed in the remaining BEHAVE-AD subscales across all subgroups.

3.4 Predictors of therapeutic response

Table 2 presents the results of the multivariate mixed-effects logistic regression examining predictors of therapeutic response. No statistically significant factor was found in models including only baseline

variables. Models with treatment-emergent variables showed that early response at week 2 was strongly associated with achieving therapeutic response at both week 4 (OR: 9.04; 95% CI: 6.10–13.39) and week 8 (OR: 4.46; 95% CI: 3.01–6.61). A sensitivity analysis using Dataset B, which included additional adjustment for comorbidities, shared consistent results (Supplementary Table S5). No other predictors were found to be significantly associated with therapeutic response.

3.5 Predictors of symptom improvement

Table 3 presents the statistically significant results of the linear mixed-effects regression models, including treatment-emergent factors, for the BEHAVE-AD total score and its subscales at week 8. Across all models, early score reduction at week 2 was consistently associated with lower symptom scores after 8 weeks. A unit increase in the baseline MMSE score was modestly associated with greater reductions in the BEHAVE-AD total score, aggression, and activity disturbances, but associated with increased psychosis and anxieties/phobias scores. In the BEHAVE-AD total score model, concomitant use of anxiolytics was associated with higher scores (SMD: 0.23; 95% CI: 0.05 to 0.41). Baseline use of antidementia medications was linked to a reduction in aggression scores (SMD: –0.31; 95% CI: –0.50 to –0.13). Results for full models of Dataset A at both weeks are provided in Supplementary Table S6. A sensitivity analysis using Dataset B showed similar findings (Supplementary Table S7). Models that included only baseline variables indicated that MMSE was statistically significant in relation to some of the subscales (Supplementary Tables S8 and S9).

4. DISCUSSION

4.1. Summary of main findings

To the best of our knowledge, this is the first study to apply an IPD-MA approach to evaluate treatment response, treatment modifiers and predictors of risperidone in people with dementia. Our findings show that risperidone provided a modest benefit in achieving a therapeutic response at week 8. Symptom-specific analyses revealed that individuals with baseline psychosis experienced a reduction in psychosis scores by week 8, while those with aggression and anxiety showed improvement at week 4. No significant benefit was observed for other BEHAVE-AD components. We also identified several demographic and clinical factors that modified risperidone's effect on the BEHAVE-AD total score and its subcomponents. Notably, achieving an early therapeutic response at week 2 was a strong predictor of continued response at both week 4 and week 8.

4.2. Discussion of main results

Our study demonstrated that risperidone did not produce a clinically significant reduction in the BEHAVE-AD total score but showed modest effect in alleviating aggression, and anxieties/phobias symptoms after 4 weeks, and psychosis symptoms after 8 weeks in people with dementia. These findings align with those of a Cochrane review (11) and a systematic review by Guanghua et. al. (44), despite the use of mixed outcome measures including BEHAVE-AD and the Neuropsychiatric Inventory (NPI). However, while the Cochrane review reported non-significant effects of risperidone for psychosis, both our analysis and the Guanghua et. al's review observed statistically significant benefits. This discrepancy may be attributed to our use of IPD from six trials and Guanghua et al.'s inclusion of a larger number of studies, compared to the smaller, aggregate-level evidence used in the Cochrane review. The improvement in aggression, anxieties and phobias might be explained by risperidone's sedative and antidepressant effects by blocking serotonin 5-HT2A, α1 and α2 adrenergic and H1

histaminergic receptors (13). No statistically significant effects of risperidone on other neuropsychiatric symptoms were seen, supporting current clinical guidelines that recommend its use only for severe cases of psychosis or aggression when non-pharmacological interventions have failed (12, 13, 45). Interestingly, risperidone appeared to worsen sleep disturbances in individuals without such symptoms at baseline, consistent with findings from a previous open-label trial (46). Antipsychotics may exert both sedative and insomnia-inducing effects, depending on their receptor activity and individual patient factors (47). Although the underlying mechanism remains unclear, this observation reinforces the recommendation that risperidone be reserved for short-term use, as treatment beyond 12 weeks is associated with an increased risk of adverse events (12). A previous analysis using a similar trial cohort reported higher rates of cerebrovascular adverse events and mortality associated with risperidone use (22), reinforcing the need to reserve pharmacological intervention as a last resort in this population.

In subgroup analyses, we observed that patients with normal BMI, those without active endocrine diseases at baseline, being male and Caucasian may appear to benefit more from risperidone treatment, demonstrating statistically significant interactions with treatment effects, although the effect size is small. These findings suggest that certain patient characteristics, possibly reflecting underlying pharmacokinetic and pharmacodynamic factors, might influence how effectively risperidone can reduce psychosis, aggression and anxiety/phobias. Risperidone primarily acts via dopamine D2 and serotonin 5-HT2A receptor antagonism, with moderate affinity for α1-adrenergic and H1 receptors. It is primarily metabolised by the hepatic enzyme cytochrome (CYP) 2D6 into its active metabolite, 9-hydroxy-risperidone, which shares similar pharmacological properties with risperidone itself (48). Both compounds are predominantly eliminated through renal excretion (48). The identified treatment modifiers—sex (49-52), BMI (53-55), endocrine status (56, 57), and ethnicity (58-60)—are consistent with previous evidence suggesting these factors may influence pharmacokinetics [e.g. altered drug distribution (54, 56, 57), CYP activity (48, 50, 59, 61) or plasma protein biding (53, 54), P-glycoprotein function (48, 54)] or pharmacodynamics [e.g. variations in receptor D2 and 5-HT2A genes (55, 60, 62), different receptor affinity (51, 52)] of risperidone. However, they only partially explain the observed variability as the precise relationship between risperidone plasma concentration and clinical outcomes remains uncertain (61) and may not follow a simple linear pattern (63). Additionally, risperidone-induced weight gain (64) may alter its metabolism and excretion, potentially influencing clinical outcomes. However, it is important to interpret these subgroup findings cautiously, as they were not prespecified (39). Thus, these findings should be viewed as hypothesis-generating, requiring validation in future studies to confirm clinical implications (38).

Among risperidone users, we found that achieving early therapeutic response or improvement at week 2 significantly predicted subsequent response at weeks 4 and 8 in both total and individual symptom scores. This finding aligns with a previous study on Alzheimer's disease patients treated with antipsychotics, which reported that symptom improvements observed at week 2 were associated with treatment outcomes at week 8 (21). Clinically, evaluating response at week 2 could inform decisions about continuing antipsychotic treatment, helping to minimise associated risks (14). However, BPSD may also be influenced by non-pharmacological factors, such as addressing unmet needs or environmental triggers (65), which were not mentioned in the trial protocol. Higher baseline cognitive function (higher MMSE scores) was modestly linked to improvements in most BEHAVE-AD subscales but were paradoxically associated with slightly worse outcomes in psychosis and anxiety/phobia

symptoms. These mixed findings reflect the complex and sometimes contradictory relationship between cognitive impairment and BPSD. While some studies have reported psychosis was associated with worsening cognitive function (66, 67), others have shown minimal or even slight improvement (44). Given the modest associations observed, further research is needed to clarify whether baseline cognition can inform treatment decisions and optimise benefit–risk balance. The concomitant use of anxiolytics during the trials predicted higher overall symptom scores, possibly due to greater baseline symptom severity. However, this combination should be cautiously avoided due to an increased risk of adverse events, including stroke and mortality (12). Finally, higher symptom severity at baseline consistently predicted higher severity score compared to those without those conditions, suggesting the modest benefits observed with risperidone.

4.3 Strengths and limitations

This study analysed data from multiple clinical trials conducted across different regions, enhancing the generalisability of the findings. The one-stage (centred) IPD-MA approach we employed can minimise the presence of ecological bias across studies (16). Additionally, using a random-intercept, S-learner strategy aligns with current recommendations for estimating individualised treatment effects in IPD-MA analyses, which can provide a better performance (19). However, several limitations should be acknowledged. First, not all existing risperidone trials were included in the analysis, as only those available through the YODA database were accessible. While this may introduce selection bias and limit the exploration of broader subgroups, our findings are consistent with those of a prior pooled meta-analysis of 18 studies, supporting the robustness of our results (44). Second, certain covariates, such as genetic factors influencing drug metabolism (e.g., CYP2D6 (48)) were unavailable, as they were not collected in the dataset. Third, as the study population was predominantly Caucasian, the findings may not generalise to Asian, African, and other ethnic groups, where CYP2D6 pharmacogenetic variability can alter risperidone pharmacokinetics and response. Forth, detailed information about concomitant medications and specific comorbidities was not collected by the trials, potentially complicating the interpretation of our results. Additionally, reliance on the MAR assumption may bias pooled estimates. Finally, due to the limitations of the dataset, symptom assessment was restricted to the BEHAVE-AD scale. The Neuropsychiatric Inventory (NPI), which is now more commonly used in both clinical and research settings, was not available in these trials (68).

4.4 Future research and implications

This study adds to existing evidence supporting the effectiveness of risperidone in managing psychosis, aggression, and possibly anxiety in people with dementia. Nonetheless, developing a data-driven prediction model to identify patients most likely to benefit or experience harm could substantially improve clinical decision-making, support personalised BPSD management, and ultimately enhance patient outcomes. Previous research has demonstrated that well-designed prediction models of antipsychotic use in people with schizophrenia, can assist clinicians in personalising treatment, optimising therapeutic effectiveness, and reducing the likelihood of adverse effects (69). In addition, subgroups that may influence treatment response—possibly due to risperidone's pharmacokinetics and pharmacodynamics—were identified, and these hypotheses should be tested to enable clinically meaningful interpretation. Finally, early response at week 2 was strongly associated with achieving response at weeks 4 and 8, suggesting that early treatment evaluation could help guide more informed clinical decisions (14).

5. CONCLUSION

Risperidone demonstrates modest effectiveness for treating psychosis, aggression, and anxiety in people with dementia, while showing limited impact on other symptoms. Treatment response may vary depending on individual pharmacodynamic/pharmacokinetic-related factors. Early improvement by week 2 appears to be a strong indicator of continued response at weeks 4 and 8. Future research should focus on developing tools to better balance the risks and benefits of antipsychotic use, ultimately supporting more personalised and effective treatment decisions.

ACKNOWLEDGEMENT

This study, carried out under YODA Project 2024-0492, used data obtained from the Yale University Open Data Access Project, which has an agreement with JANSSEN RESEARCH & DEVELOPMENT, L.L.C. The interpretation and reporting of research using this data are solely the responsibility of the authors and does not necessarily represent the official views of the Yale University Open Data Access Project or JANSSEN RESEARCH & DEVELOPMENT, L.L.C.

DECLARATION OF INTEREST

None

REFERENCES

[1] Organization WH. Dementia 2025 [Available from: https://www.who.int/news-room/fact-sheets/detail/dementia.
[2] Nichols E, Steinmetz JD, Vollset SE, Fukutaki K, Chalek J, Abd-Allah F, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. The Lancet Public Health. 2022;7(2):e105-e25.
[3] Yunusa I, Alsumali A, Garba AE, Regestein QR, Eguale T. Assessment of Reported Comparative Effectiveness and Safety of Atypical Antipsychotics in the Treatment of Behavioral and Psychological Symptoms of Dementia: A Network Meta-analysis. JAMA Netw Open. 2019;2(3):e190828.
[4] Burley CV, Chenoweth L, Casey ANS, Brodaty H. Changed behaviours associated with cognitive decline: Views of people living with dementia, families and healthcare professionals. Alzheimer's & Dementia. 2021;17:e051963.
[5] Anantapong K, Jiraphan A, Aunjitsakul W, Sathaporn K, Werachattawan N, Teetharatkul T, et al. Behavioural and psychological symptoms of people with dementia in acute hospital settings: a systematic review and meta-analysis. Age and Ageing. 2025;54(1).
[6] Kwon CY, Lee B. Prevalence of Behavioral and Psychological Symptoms of Dementia in Community-Dwelling Dementia Patients: A Systematic Review. Front Psychiatry. 2021;12:741059.
[7] Roe J, Coulson S, Ockerby C, Hutchinson AM. Staff perceptions of caring for people exhibiting behavioural and psychological symptoms of dementia in residential aged care: A cross-sectional survey. Australas J Ageing. 2020;39(3):237-43.
[8] Kirkham J, Sherman C, Velkers C, Maxwell C, Gill S, Rochon P, et al. Antipsychotic Use in Dementia. Can J Psychiatry. 2017;62(3):170-81.
[9] Lau ECY, Chen W, Lu CY, Hilmer SN, Jeon YH, Tan ECK. Antidementia and Psychotropic Drug Use in Older People with Dementia in Australia: A National Data Linkage Study. J Am Med Dir Assoc. 2024;25(11):105237.
[10] Tampi RR, Tampi DJ, Balachandran S, Srinivasan S. Antipsychotic use in dementia: a systematic review of benefits and risks from meta-analyses. Ther Adv Chronic Dis. 2016;7(5):229-45.
[11] Mühlbauer V, Möhler R, Dichter MN, Zuidema SU, Köpke S, Luijendijk HJ. Antipsychotics for agitation and psychosis in people with Alzheimer's disease and vascular dementia. Cochrane Database Syst Rev. 2021;12(12):Cd013304.
[12] Simon Bell, Ravi Bhat, Sue Brennan, Malcolm Clark, Megan Corlis, Christopher EthertonBeer, et al. Clinical Practice Guidelines for the Appropriate Use of Psychotropic Medications in People Living with Dementia and in Residential Aged Care: Summary of Recommendations and Good Practice Statements: Monash University, Parkville, Australia; 2022 [Available from: https://www.monash.edu/__data/assets/pdf_file/0005/3458417/Clinical-Practice-Guideline-for-the-Appropriate-Use-of-Psychotropic-Medications-in-People-Living-with-dementia-and-in-Residential-Aged-Care.pdf.
[13] Yunusa I, El Helou ML. The Use of Risperidone in Behavioral and Psychological Symptoms of Dementia: A Review of Pharmacology, Clinical Evidence, Regulatory Approvals, and Off-Label Use. Front Pharmacol. 2020;11:596.
[14] Devanand DP. Prediction of Response to Antipsychotics in Patients with Dementia Remains a Conundrum. Am J Geriatr Psychiatry. 2017;25(7):717-8.
[15] Tan TJD, Lau ECY, Le TH, Lu CY, Hilmer SN, Jeon Y-H, et al. Predictors and Moderators of Hospitalisation and Mortality in People with Dementia Using Antipsychotics: Systematic Review. Drugs & Aging. 2025.
[16] Belias M, Rovers MM, Reitsma JB, Debray TPA, IntHout J. Statistical approaches to identify subgroups in meta-analysis of individual participant data: a simulation study. BMC Medical Research Methodology. 2019;19(1):183.
[17] Veroniki AA, Seitidis G, Tsivgoulis G, Katsanos AH, Mavridis D. An Introduction to Individual Participant Data Meta-analysis. Neurology. 2023;100(23):1102-10.

[18] Debray TP, Riley RD, Rovers MM, Reitsma JB, Moons KG. Individual participant data (IPD) meta-analyses of diagnostic and prognostic modeling studies: guidance on their use. PLoS Med. 2015;12(10):e1001886.
[19] Bouvier F, Chaimani A, Peyrot E, Gueyffier F, Grenet G, Porcher R. Estimating individualized treatment effects using an individual participant data meta-analysis. BMC Med Res Methodol. 2024;24(1):74.
[20] Nagata T, Nakajima S, Shinagawa S, Plitman E, Nakayama K, Graff-Guerrero A, et al. Baseline Predictors of Antipsychotic Treatment Continuation and Response at Week 8 in Patients with Alzheimer's Disease with Psychosis or Aggressive Symptoms: An Analysis of the CATIE-AD Study. J Alzheimers Dis. 2017;60(1):263-72.
[21] Nagata T, Shinagawa S, Yoshida K, Noda Y, Shigeta M, Mimura M, et al. Early Improvements of Individual Symptoms With Antipsychotics Predict Subsequent Treatment Response of Neuropsychiatric Symptoms in Alzheimer's Disease: A Re-Analysis of the CATIE-AD Study. J Clin Psychiatry. 2020;81(2).
[22] Howard R, Costafreda SG, Karcher K, Coppola D, Berlin JA, Hough D. Baseline characteristics and treatment-emergent risk factors associated with cerebrovascular event and death with risperidone in dementia patients. Br J Psychiatry. 2016;209(5):378-84.
[23] Krumholz HM, Waldstreicher J. The Yale Open Data Access (YODA) Project--A Mechanism for Data Sharing. N Engl J Med. 2016;375(5):403-5.
[24] Project TY. The YODA Project [Available from: https://yoda.yale.edu/.
[25] Katz IR, Jeste DV, Mintzer JE, Clyde C, Napolitano J, Brecher M. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group. J Clin Psychiatry. 1999;60(2):107-15.
[26] De Deyn PP, Rabheru K, Rasmussen A, Bocksberger JP, Dautzenberg PL, Eriksson S, et al. A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology. 1999;53(5):946-55.
[27] Brodaty H, Ames D, Snowdon J, Woodward M, Kirwan J, Clarnette R, et al. A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. J Clin Psychiatry. 2003;64(2):134-43.
[28] Mintzer J, Greenspan A, Caers I, Van Hove I, Kushner S, Weiner M, et al. Risperidone in the treatment of psychosis of Alzheimer disease: results from a prospective clinical trial. Am J Geriatr Psychiatry. 2006;14(3):280-91.
[29] Cooper J. Diagnostic and statistical manual of mental disorders (4th edn, text revision)(DSM–IV–TR) Washington, DC: American Psychiatric Association 2000. 943 pp.£ 39.99 (hb). ISBN 0 89042 025 4. The British Journal of Psychiatry. 2001;179(1):85-.
[30] Berg L, Hughes CP, Coben LA, Danziger WL, Martin RL, Knesevich J. Mild senile dementia of Alzheimer type: research diagnostic criteria, recruitment, and description of a study population. J Neurol Neurosurg Psychiatry. 1982;45(11):962-8.
[31] Cohen-Mansfield J. Instruction manual for the Cohen-Mansfield agitation inventory (CMAI). Research Institute of the Hebrew Home of Greater Washington. 1991;1991.
[32] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj. 2019;366:l4898.
[33] Reisberg B, Borenstein J, Salob SP, Ferris SH, Franssen E, Georgotas A. Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. J Clin Psychiatry. 1987;48 Suppl:9-15.
[34] Reisberg B, Auer SR, Monteiro IM. Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) Rating Scale. International Psychogeriatrics. 1997;8:301-8.
[35] Reisberg B, Monteiro I, Torossian C, Auer S, Shulman MB, Ghimire S, et al. The BEHAVE-AD assessment system: a perspective, a commentary on new findings, and a historical review. Dement Geriatr Cogn Disord. 2014;38(1-2):89-146.
[36] World Health Organization. Anatomical Therapeutic Chemical (ATC) Classification [Available from: https://atcddd.fhi.no/atc_ddd_index/.

[37] Andrade C. Mean Difference, Standardized Mean Difference (SMD), and Their Use in Meta-Analysis: As Simple as It Gets. J Clin Psychiatry. 2020;81(5).
[38] Wang X, Piantadosi S, Le-Rademacher J, Mandrekar SJ. Statistical Considerations for Subgroup Analyses. J Thorac Oncol. 2021;16(3):375-80.
[39] Barraclough H, Govindan R. Biostatistics Primer: What a Clinician Ought to Know: Subgroup Analyses. Journal of Thoracic Oncology. 2010;5(5):741-6.
[40] Kim JH. Multicollinearity and misleading statistical results. Korean J Anesthesiol. 2019;72(6):558-69.
[41] Abdi H. Bonferroni and Šidák corrections for multiple comparisons. Encyclopedia of measurement and statistics. 2007;3(01):2007.
[42] Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. Journal of Statistical Software. 2015;67(1):1 - 48.
[43] Gabrio A, Plumpton C, Banerjee S, Leurent B. Linear mixed models to handle missing at random data in trial-based economic evaluations. Health Econ. 2022;31(6):1276-87.
[44] Zhou G, Yin S, Zhang S, Hao F, Ma L. Risperidone for the Treatment of Dementia-Related Psychosis: A Systematic Review and Meta-Analysis. Dement Geriatr Cogn Disord. 2024:1-15.
[45] Guidelines NIfHaCE. Dementia: Assessment, management and support for people living with dementia and their carers. London: National Institute for Health and Care Excellence (NICE); 2018.
[46] Kurz A, Schwalen S, Schmitt A. Effects of risperidone on behavioral and psychological symptoms associated with dementia in clinical practice. International Psychogeriatrics. 2005;17(4):605-16.
[47] Valencia Carlo YE, Saracco-Alvarez RA, Valencia Carlo VA, Vázquez Vega D, Natera Rey G, Escamilla Orozco RI. Adverse effects of antipsychotics on sleep in patients with schizophrenia. Systematic review and meta-analysis. Front Psychiatry. 2023;14:1189768.
[48] Soria-Chacartegui P, Villapalos-García G, Zubiaur P, Abad-Santos F, Koller D. Genetic Polymorphisms Associated With the Pharmacokinetics, Pharmacodynamics and Adverse Effects of Olanzapine, Aripiprazole and Risperidone. Front Pharmacol. 2021;12:711940.
[49] Hoekstra S, Bartz-Johannessen C, Sinkeviciute I, Reitan SK, Kroken RA, Løberg E-M, et al. Sex differences in antipsychotic efficacy and side effects in schizophrenia spectrum disorder: results from the BeSt InTro study. npj Schizophrenia. 2021;7(1):39.
[50] Yoon S, Jeong S, Jung E, Kim KS, Jeon I, Lee Y, et al. Effect of CYP3A4 metabolism on sex differences in the pharmacokinetics and pharmacodynamics of zolpidem. Scientific Reports. 2021;11(1):19150.
[51] Williams OOF, Coppolino M, George SR, Perreault ML. Sex Differences in Dopamine Receptors and Relevance to Neuropsychiatric Disorders. Brain Sci. 2021;11(9).
[52] Soloff PH, Price JC, Mason NS, Becker C, Meltzer CC. Gender, personality, and serotonin-2A receptor binding in healthy subjects. Psychiatry Res. 2010;181(1):77-84.
[53] Sun X, He R, Xiao Y, Xiu M, Sun M, Wu F, et al. Interaction between baseline BMI and baseline disease severity predicts greater improvement in negative symptoms in first-episode schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2024;274(6):1327-32.
[54] Paulzen M, Haen E, Stegmann B, Hiemke C, Gründer G, Lammertz SE, et al. Body mass index (BMI) but not body weight is associated with changes in the metabolism of risperidone; A pharmacokinetics-based hypothesis. Psychoneuroendocrinology. 2016;73:9-15.
[55] Dang LC, Samanez-Larkin GR, Castrellon JJ, Perkins SF, Cowan RL, Zald DH. Associations between dopamine D2 receptor availability and BMI depend on age. Neuroimage. 2016;138:176-83.
[56] Dostalek M, Akhlaghi F, Puzanovova M. Effect of Diabetes Mellitus on Pharmacokinetic and Pharmacodynamic Properties of Drugs. Clinical Pharmacokinetics. 2012;51(8):481-99.
[57] Agahi S, Amouzegar A, Honarvar M, Azizi F, Mehran L. Interrelationship between thyroid hormones and reduced renal function, a review article. Thyroid Research. 2024;17(1):14.
[58] Olagunju AT, Wang J, Edet B, Onwuameze OE, Macaluso M. Racial and Ethnic Considerations for the Clinical Practice of Psychopharmacology and Research Methodology: A Narrative Review of the Growing Body of Literature. J Psychiatr Pract. 2025;31(2):56-64.

[59] Frederiksen T, Areberg J, Schmidt E, Stage TB, Brøsen K. Does ethnicity impact CYP2D6 genotype-phenotype relationships? Clin Transl Sci. 2023;16(6):1012-20.
[60] Wiers CE, Towb PC, Hodgkinson CA, Shen PH, Freeman C, Miller G, et al. Association of genetic ancestry with striatal dopamine D2/D3 receptor availability. Mol Psychiatry. 2018;23(8):1711-6.
[61] Wang X, Huang J, Lu J, Li X, Tang H, Shao P. Risperidone plasma level, and its correlation with CYP2D6 gene polymorphism, clinical response and side effects in chronic schizophrenia patients. BMC Psychiatry. 2024;24(1):41.
[62] Blasi G, Selvaggi P, Fazio L, Antonucci LA, Taurisano P, Masellis R, et al. Variation in Dopamine D2 and Serotonin 5-HT2A Receptor Genes is Associated with Working Memory Processing and Response to Treatment with Antipsychotics. Neuropsychopharmacology. 2015;40(7):1600-8.
[63] Chen Q, Min J, Yin H, Xia W, Shen Y, Shu M. Relationship between clinical efficacy and plasma concentration-dose ratio of risperidone in patients with schizophrenia. Int Clin Psychopharmacol. 2024;39(1):17-22.
[64] Tek C, Kucukgoncu S, Guloksuz S, Woods SW, Srihari VH, Annamalai A. Antipsychotic-induced weight gain in first-episode psychosis patients: a meta-analysis of differential effects of antipsychotic medications. Early Interv Psychiatry. 2016;10(3):193-202.
[65] Caspar S, Davis ED, Douziech A, Scott DR. Nonpharmacological Management of Behavioral and Psychological Symptoms of Dementia: What Works, in What Circumstances, and Why? Innov Aging. 2018;2(1):igy001.
[66] Nagata T, Nakajima S, Shinagawa S, Plitman E, Graff-Guerrero A, Mimura M, et al. Psychosocial or clinico-demographic factors related to neuropsychiatric symptoms in patients with Alzheimer's disease needing interventional treatment: analysis of the CATIE-AD study. Int J Geriatr Psychiatry. 2017;32(12):1264-71.
[67] Proitsi P, Hamilton G, Tsolaki M, Lupton M, Daniilidou M, Hollingworth P, et al. A Multiple Indicators Multiple Causes (MIMIC) model of Behavioural and Psychological Symptoms in Dementia (BPSD). Neurobiology of Aging. 2011;32(3):434-42.
[68] Saari T, Koivisto A, Hintsa T, Hänninen T, Hallikainen I. Psychometric Properties of the Neuropsychiatric Inventory: A Review. J Alzheimers Dis. 2022;86(4):1485-99.
[69] Kim EY, Kim J, Jeong JH, Jang J, Kang N, Seo J, et al. Machine learning prediction model of the treatment response in schizophrenia reveals the importance of metabolic and subjective characteristics. Schizophrenia Research. 2025; 275:146-55.

Table 1: Patient characteristics

Baseline characteristic	Characteristic of total population	
	PLACEBO, N = 711*	**RISPERIDONE, N = 1,009***
Trial (N, %)		
AUS-5	169 (23.8%)	167 (16.6%)
BEL-14	19 (2.7%)	20 (2.0%)
INT-24	114 (16.0%)	115 (11.4%)
INT-83	8 (1.1%)	10 (1.0%)
USA-063	163 (22.9%)	462 (45.8%)
USA-232	238 (33.5%)	235 (23.3%)
Age (Years; Mean, SD)	83 (8)	83 (7)
Sex (N, %)		
Female	497 (70%)	702 (70%)
Male	214 (30%)	307 (30%)
BMI	23.3 (4.7)	23.2 (4.6)
Unknown	52	81
MMSE score at baseline (Median, IQR)	9 (12)	8 (12)
Unknown	30	31
Psychotropic medication use at baseline (N, %)		
Any anxiolytic use at baseline	44 (6.2%)	53 (5.3%)
Any hypnotics and sedatives use at baseline	86 (12%)	99 (9.8%)
Any antidepressant use at baseline	33 (4.6%)	49 (4.9%)
Any anti-dementia drug use at baseline	85 (12%)	71 (7.0%)
BEHAVE-AD score at baseline (Mean, SD)		
Total BEHAVE-AD score at baseline	17 (9)	16 (8)
Unknown	23	29
BEHAVE-AD psychosis subscale score at baseline	5.7 (4.9)	5.4 (4.3)
Unknown	23	29
BEHAVE-AD activity disturbances subscale score at baseline	2.98 (2.27)	2.87 (2.16)
Unknown	0	3
BEHAVE-AD aggressiveness subscale score at baseline	4.63 (2.79)	4.55 (2.92)
Unknown	0	3
BEHAVE-AD sleep subscale score at baseline	0.74 (0.93)	0.70 (0.93)
Unknown	0	3
BEHAVE-AD affective disturbance subscale score at baseline	1.04 (1.40)	0.87 (1.26)
Unknown	2	9
BEHAVE-AD anxieties and phobias subscale score at baseline	1.92 (2.04)	1.79 (2.01)
Unknown	2	9
BEHAVE-AD global rating score at baseline	1.82 (0.78)	1.83 (0.75)

Unknown	1	3
Presence of BPSD at baseline (N, %)		
Presence of psychosis symptoms at baseline	498 (71%)	677 (68%)
Unknown	7	15
Presence of activity disturbances at baseline	622 (87%)	868 (86%)
Unknown	0	3
Presence of aggressiveness symptoms at baseline	655 (92%)	896 (89%)
Unknown	0	3
Presence of affective disturbance symptoms at baseline	338 (48%)	433 (43%)
Unknown	0	3
Presence of sleep disturbance symptoms at baseline	332 (47%)	438 (44%)
Unknown	0	3
Presence of anxieties and phobias symptoms at baseline	475 (67%)	650 (65%)
Unknown	0	3
Race (N, %) †		
Caucasian	502 (88%)	762 (88%)
Other	33 (5.8%)	37 (4.3%)
Black	35 (6.1%)	65 (7.5%)
Dementia type (N, %) †		
Alzheimer's	428 (76%)	629 (74%)
Mixed type dementia	41 (7.2%)	74 (8.7%)
Vascular dementia	97 (17%)	146 (17%)
Unknown	4	15
eGFR (ml/min; Mean, SD) †	62 (18)	62 (17)
Unknown	4	2
Any currently active cardiovascular disease (N, %) †	381 (67%)	595 (69%)
Unknown	0	2
Any currently active endocrine disease (N, %) †	173 (30%)	241 (28%)
Unknown	0	1
Any currently active neurological disease (N, %) †	162 (28%)	290 (34%)
Unknown	1	1
Number of participants at week 4	640	888
Number of participants at week 8	543	768

Abbreviation: *BPSD, Behaviours and psychological symptoms associated with dementia; MMSE, Mini-Mental State Examination; eGFR, estimated glomerular filtration rate*

*n (%); Mean (SD)
†Data obtained from 3 trials only (AUS-5, USA-063 and USA-232). Denominators are the number of placebo (N=570) and risperidone (N=864) in this dataset.

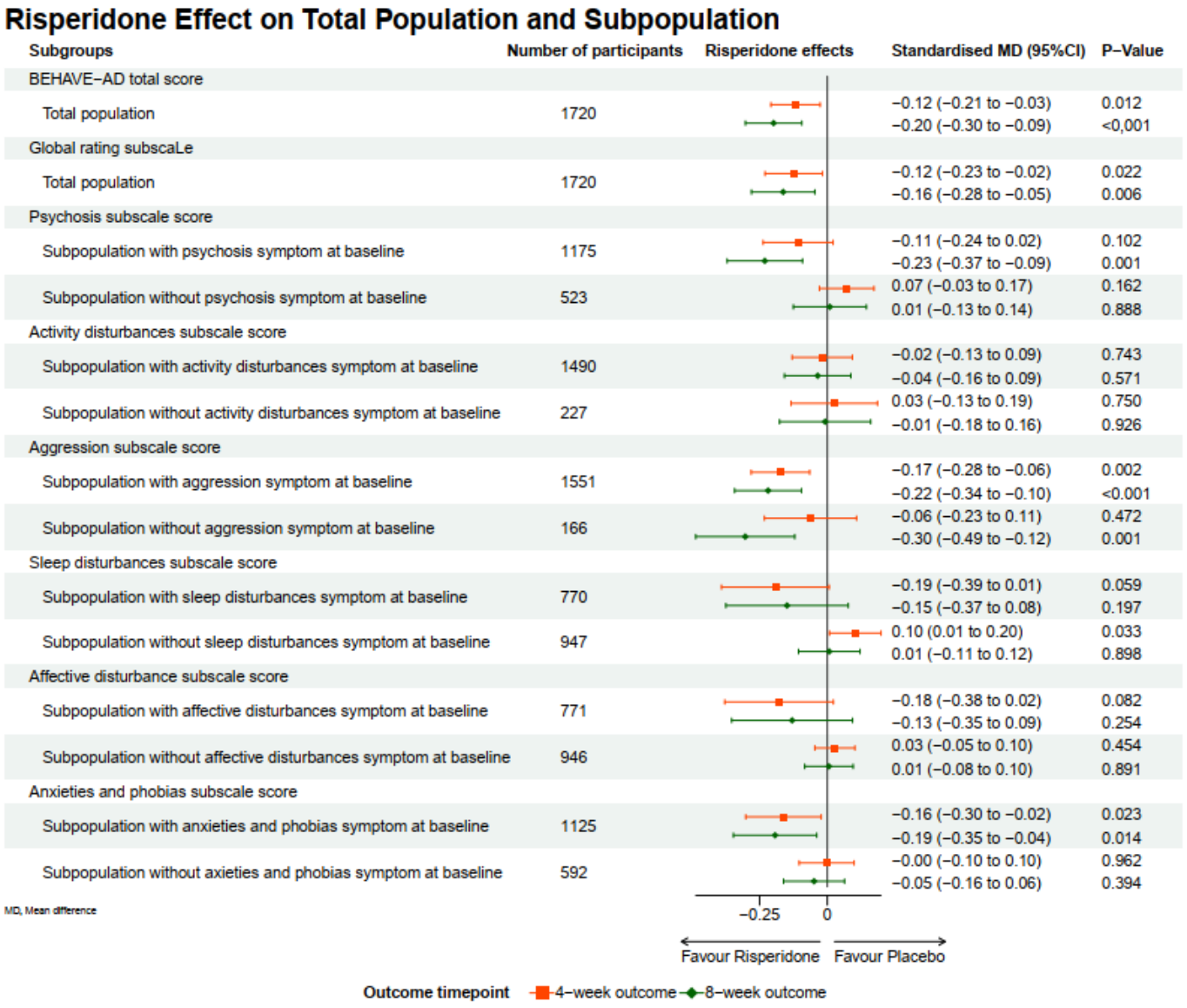


Figure 1: Risperidone effect on total population and subpopulation

Subgroup Analysis of Risperidone Response in different outcomes

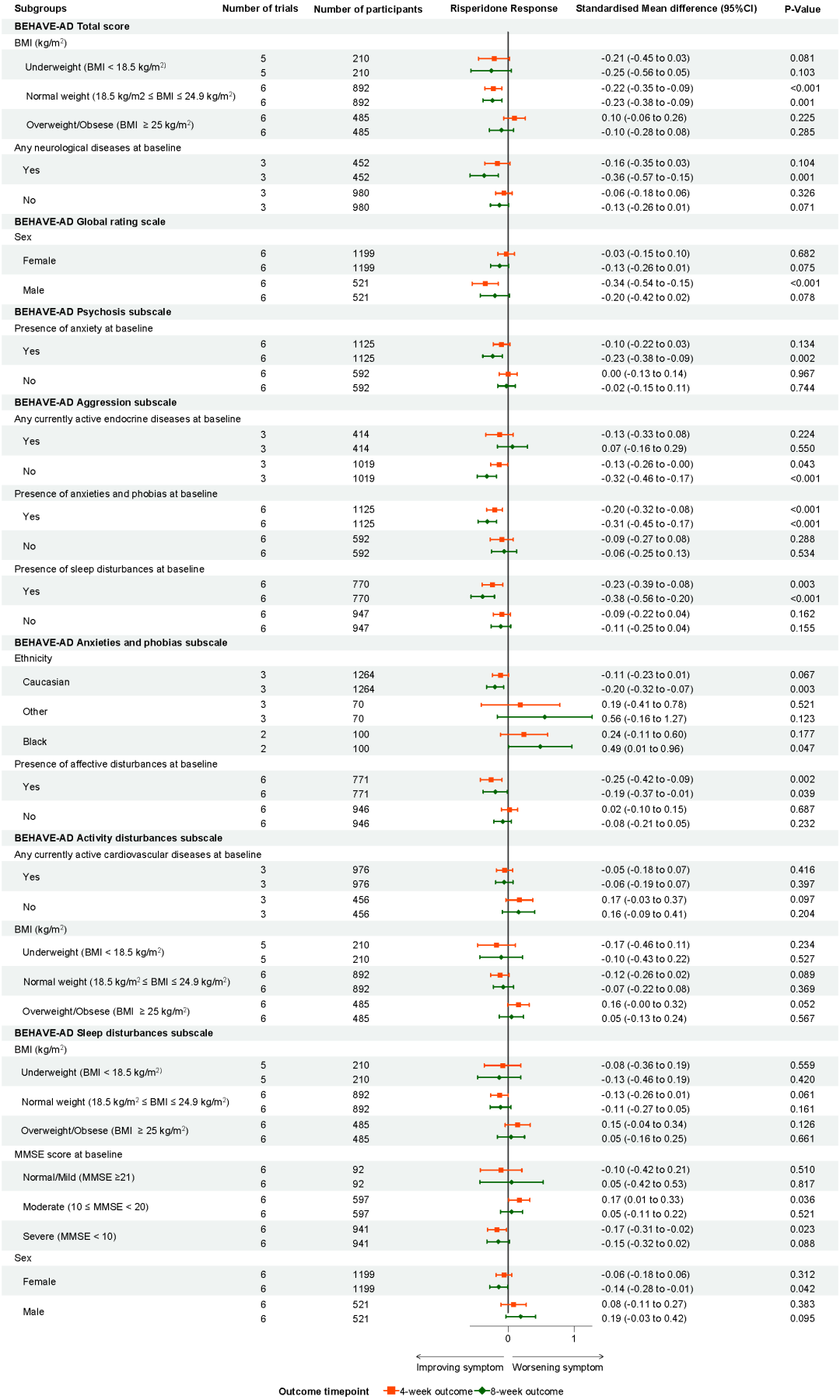


Figure 2: Subgroup analysis of risperidone effect in different outcomes

Table 2: Multivariable mixed-effect logistic regression model of therapeutic response among risperidone users at week 4 and 8

Predictors of therapeutic response		WEEK 4		WEEK 8	
		OR (95% CI)	p	OR (95% CI)	p
Model 1					
Age		1 (0,98; 1,02)	0,861	0,99 (0,96; 1,01)	0,285
Male (Reference: Female)		1,08 (0,76; 1,53)	0,668	0,93 (0,64; 1,37)	0,726
Body mass index (BMI)		0,96 (0,93; 1)	0,027	0,99 (0,96; 1,03)	0,739
MMSE score		1 (0,98; 1,03)	0,866	1 (0,97; 1,02)	0,745
Use of psychotropic medications at baseline					
	Anxiolytics	1,09 (0,55; 2,18)	0,799	1,02 (0,46; 2,25)	0,960
	Hypnotics and sedatives	0,96 (0,55; 1,68)	0,897	1,65 (0,91; 2,99)	0,101
	Antidepressants	1,32 (0,62; 2,8)	0,440	0,42 (0,17; 1,04)	0,060
	Anti-dementias	1,82 (0,95; 3,47)	0,069	1,15 (0,59; 2,27)	0,675
BEHAVE-AD total score at baseline		1,13 (0,9; 1,41)	0,303	0,75 (0,58; 0,96)	0,025
Presence of BPSD at baseline (Reference: No symptom)					
	Psychosis	1,3 (0,88; 1,92)	0,183	0,98 (0,65; 1,49)	0,929
	Activity disturbances	1,02 (0,65; 1,61)	0,922	1,17 (0,71; 1,94)	0,537
	Aggression	0,86 (0,51; 1,43)	0,553	1,11 (0,64; 1,94)	0,713

	Affective disturbance	0,96 (0,62; 1,19)	0,351	0,98 (0,73; 1,49)	0,827
	Sleep disturbances	1,14 (0,82; 1,58)	0,444	0,93 (0,65; 1,33)	0,700
	Anxieties and phobias	1,05 (0,75; 1,47)	0,779	0,96 (0,76; 1,56)	0,643
Number of observations		**741**		**646**	
Number of trials		**6**		**5**	
Model 2					
Early response (Reference: No response)		9.04 (6.1-13.39)	**<0.001[#]**	4.46 (3.01; 6.61)	**<0.001[#]**
Age		0.99 (0.97-1.02)	0,630	1.01 (0.98; 1.04)	0,484
Male (Reference: Female)		0.93 (0.6-1.46)	0,768	0.91 (0.58; 1.43)	0,680
Body mass index (BMI)		0.96 (0.92-1)	0,042	1.01 (0.97; 1.06)	0,538
MMSE score		1.01 (0.98-1.05)	0,508	1.01 (0.98; 1.04)	0,583
Use of psychotropic medications at baseline					
	Anxiolytics	0.79 (0.28-2.26)	0,665	2.34 (0.72; 7.58)	0,157
	Hypnotic and sedatives	2.17 (0.58-8.02)	0,248	0.5 (0.14; 1.73)	0,27
	Antidepressants	1.16 (0.45-2.99)	0,762	1.67 (0.62; 4.54)	0,31
	Anti-dementias	1.68 (0.79-3.57)	0,175	0.67 (0.33; 1.36)	0,267
BEHAVE-AD total score at baseline		1.00 (0.97-1.04)	0,870	1.01 (0.97; 1.05)	0,710
Concomitant use of psychotropic medications					

	Anxiolytics	0.88 (0.45-1.75)	0,719	0.58 (0.3; 1.11)	0,100
	Hypnotics and sedatives	0.7 (0.24-2.03)	0,508	1.42 (0.52; 3.85)	0,491
Mean dose of risperidone		0.91 (0.59-1.4)	0,668	1.4 (0.93; 2.11)	0,104
Presence of BPSD at baseline (Reference: No symptom)					
	Psychosis	1.41 (0.86-2.32)	0,171	1.02 (0.62; 1.67)	0,936
	Activity disturbances	0.79 (0.45-1.39)	0,407	0.81 (0.45; 1.46)	0,476
	Aggression	1.17 (0.63-2.15)	0,619	1.27 (0.68; 2.37)	0,456
	Affective disturbance	0.67 (0.45-1.01)	0,058	1.23 (0.81; 1.88)	0,328
	Sleep disturbances	1.11 (0.73-1.68)	0,619	1.18 (0.77; 1.81)	0,455
	Anxieties and phobias	1.19 (0.78-1.8)	0,427	1.26 (0.83; 1.92)	0,286
Number of observations		**620**		**536**	
Number of trials		**5**		**4**	

BPSD, Behaviours and psychological symptoms associated with dementia; MMSE, Mini-Mental State Examination; OR, odds ratio

Model 1 includes baseline variables only. Model 2 includes baseline variables and treatment-emergent variables. Model 2 does not include AUS-5 trial as the BEHAVE-AD total score was not captured at week 2.

[#]Values are significant results after Bonferroni correction (p value <0.05/44 = 0.00113)

Table 3. Mixed-effect linear regression model of predictors of all outcomes at week 8

Predictors of BEHAVE-AD total and sub-score at week 8	Total score	Psychosis	Activity disturbances	Aggressiveness	Sleep disturbances	Affective disturbances	Anxieties and phobias	Global rating
	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)	SMD (95% CI)
Early reduction in BEHAVE-AD rating score (Reference: No reduction)								
Total score	-0,08 (-0,09; -0,08)	-	-	-	-	-	-	-
Psychosis subscale score	-	-0,2 (-0,21; -0,19)	-	-	-	-	-	-
Activity disturbances subscale	-	-	-0,31 (-0,35; -0,28)	-	-	-	-	-
Aggression subscale score	-	-	-	-0,27 (-0,29; -0,25)	-	-	-	-
Sleep disturbance subscale	-	-	-	-	-0,99 (-1,07; -0,92)	-	-	-
Affective disturbance subscale	-	-	-	-	-	-0,6 (-0,65; -0,54)	-	-
Anxieties and phobias subscale	-	-	-	-	-	-	-0,34 (-0,37; -0,3)	-
Global rating subscale score	-	-	-	-	-	-	-	-0,77 (-0,83; -0,71)
Age	-	-	-		-	-	-	-
Male (Reference: Female)	-							
BMI	-							-
MMSE	-0,01 (-0,02; -0,01)	0,02 (0,01; 0,03)		-0,03 (-0,04; -0,02)	-	-	0,02 (0,01; 0,03)	
Use of psychotropic medications at baseline (Reference: Not using medication)								
Anxiolytics	-	-		-	-	-	-	-
Hypnotic and sedatives	-	-	-		-	-	-	-

Anti-dementias	-		-	-0,31 (-0,5; -0,13)	-	-	-	-
Concomitant use of psychotropic medications								
Anxiolytics		-	-	-	-	-		-
Hypnotics and sedatives	-	-	-		-	-	-	-
Presence of BPSD at baseline (Reference: No symptom)								
Psychosis	0,64 (0,51; 0,76)	0,49 (0,38; 0,6)	-0,25 (-0,4; -0,1)	-0,38 (-0,51; -0,25)	-		-	-
Activity disturbances	0,42 (0,26; 0,57)	-	0,91 (0,73; 1,09)	-0,49 (-0,65; -0,34)	-	-	-	-
Aggression	0,6 (0,44; 0,76)	-0,41 (-0,54; -0,27)	-	0,86 (0,7; 1,03)	-		-	-
Affective disturbance	0,36 (0,26; 0,47)	-	-0,3 (-0,43; -0,18)	-0,21 (-0,32; -0,1)	-	1,33 (1,2; 1,45)	-	
Sleep disturbances	0,35 (0,24; 0,46)		-	-0,25 (-0,36; -0,14)	1,72 (1,58; 1,85)	-	-	-
Anxieties and phobias	0,36 (0,25; 0,47)	-	-	-0,38 (-0,49; -0,27)	-	-	0,92 (0,79; 1,04)	-
BEHAVE-AD total score at baseline	-	0,81 (0,74; 0,88)	0,51 (0,41; 0,6)	0,73 (0,65; 0,81)		0,29 (0,21; 0,37)	0,37 (0,28; 0,46)	0,37 (0,28; 0,45)
Number of observations	541	541	541	541	541	541	541	541
Number of trials	4	4	4	4	4	4	4	4

BEHAVE-AD, Behavioural pathology in Alzheimer's disease; SMD, Standardised mean difference; BPSD, Behaviours and psychological symptoms of dementia

All p-values of variable included in this table are significant results after Bonferroni correction (p value <0.05/44 = 0.00113)

3.3. Supplementary materials

Refer to Appendix A: Chapter 3 Supplementary Materials.

Supplementary Figure S1. Risk of bias assessment

Supplementary Table S1. Trials characteristic

Supplementary Table S2. Details of variable in each dataset.

Supplementary Table S3. Mixed-effect logistic regression model of treatment effect in total populations in both datasets, measured by therapeutic response at week 4 and week 8.

Supplementary Table S4. Results of interaction terms between treatment effect and covariates. Table shows statistically significant interactions only.

Supplementary Table S5. Mixed-effect logistic regression model of therapeutic response among risperidone users in dataset B

Supplementary Table S6. Full mixed-effect linear regression models of Dataset A in all outcomes

Supplementary Table S7. Full mixed-effect linear regression models of Dataset B in all outcomes

Supplementary Table S8. Linear regression models for baseline variables in Dataset A (Full)

Supplementary Table S9. Linear regression models for baseline variables in Dataset B (Full)

Appendix 1. BEHAVIORAL PATHOLOGY IN ALZHEIMER'S DISEASE (BEHAVE-AD)

3.4. Research presentation

Preliminary results were presented as an oral presentation at Personalised and Precision Medicine section, International Pharmaceutical Federation (FIP) 83rd World Congress, Copenhagen, 2025.

3.5. Ethic approval

The study in this chapter was conducted in accordance with the Declaration of Helsinki and was deemed negligible risk, receiving exemption from ethical approval by the University of Sydney Human Research Ethics Committee (**Appendix B**).

CHAPTER 4. Discussion and conclusion

4.1. Chapter overview

This chapter provides an overarching summary and critical discussion of the key findings regarding patterns of psychotropic use among older adults in Australia, and foundational steps to optimising antipsychotic use in people with dementia, as explored in **Chapters 2 and 3**. These findings are evaluated in light of the objectives outlined in **Chapter 1**, offering a cohesive narrative of how the thesis contributes to addressing gaps in the current literature. The chapter also reflects on the broader implications of these findings for clinical practice and policy, outlines avenues for future research, and concludes with a discussion of the thesis's overall strengths and limitations.

4.2. Summary of key findings

This thesis investigated patterns and factors associated with psychotropic and antipsychotic use among Australian older adults, with a particular focus on individuals living with dementia. **Chapter 2**, using national linked data, revealed that approximately one in three older Australians were prescribed at least one psychotropic medication, most commonly antidepressants, opioids, and benzodiazepines. Psychotropic polypharmacy was observed in 8.4% of this population, raising concerns about the cumulative risks associated with multiple psychotropic exposures.

Importantly, **Chapter 2** identified a range of sociodemographic and clinical characteristics associated with increased psychotropic use. Individuals residing in non-private dwellings, requiring assistance with core activities of daily living, or living with chronic conditions such as cardiovascular disease, dementia, arthritis, or kidney disease were significantly more likely to receive psychotropic prescriptions. Differences in use patterns were also observed across subpopulations, with higher rates of benzodiazepine/Z-drug and opioid use among Indigenous Australians and people born overseas. People with dementia had nearly threefold higher odds of being prescribed antipsychotics—despite known safety concerns—highlighting the need for greater scrutiny and targeted deprescribing efforts in this vulnerable group.

Building on these findings, **Chapter 3** aimed to generate more specific evidence to support personalised antipsychotic prescribing in dementia. This study focused on risperidone, which remains the only antipsychotic approved for managing BPSD in some countries, including Australia. The study involved an individual participant data meta-analysis (IPD-MA) of six clinical trials evaluating risperidone for the treatment of behaviours and psychological symptoms of dementia (BPSD)—including trials submitted for regulatory approval of risperidone’s indication in Australia. The analysis confirmed that risperidone is primarily effective in alleviating psychosis, aggression, and anxiety/phobias, with little evidence of benefit for other BPSD domains such as sleep, activities and affective disturbances. This suggests that the use of risperidone for non-target symptoms should be avoided to minimise unnecessary exposure. Furthermore, several potential pharmacokinetic and pharmacodynamic factors—such as body mass index (BMI), endocrine diseases, race and sex—were found to influence treatment response. Notably, early symptom improvement at week 2 was a strong and consistent predictor of response at later timepoints (weeks 4 and 8), indicating a valuable window for early treatment evaluation and decision-making. Collectively,

these findings support a more targeted, symptom-specific, and time-sensitive approach to antipsychotic prescribing in dementia, aligning with principles of quality use of medicines and personalised care.

4.3. Significance of findings and future directions

4.3.1. Antipsychotic use in dementia: The need for personalised care

Antipsychotic prescribing in people living with dementia remains a critical and complex challenge. Despite longstanding efforts through clinical guidelines and government regulations to restrict their use, antipsychotics continue to be widely prescribed in this vulnerable population. As shown in **Chapter 2**, individuals with dementia are still significantly more likely to receive antipsychotic medications, highlighting a persistent disconnect between policy recommendations and real-world practice. Alarming findings from our recent analysis of 22,710 Australians with dementia further illustrate the severity of the issue: 86.2% of antipsychotic users met at least one high-risk criterion, raising serious concerns about the safety and appropriateness of current prescribing patterns [1]. Although risperidone remains the only antipsychotic approved in Australia for the short-term management of BPSD, off-label use of other antipsychotics is still common. This raises important questions around clinical oversight, therapeutic benefit, and unmonitored risks—particularly given the narrow evidence base supporting such use. These concerns are compounded by emerging evidence from **Chapter 3** that highlights how individual characteristics—including BMI, sex, race, and endocrine comorbidities—can influence a patient's response to risperidone. Additionally, comorbid conditions and concurrent medications common in people with dementia may further modify risperidone's pharmacokinetic and pharmacodynamic profiles. Therefore, even when prescribed within recommended indications, a 'one-size-fits-all' approach may fail to deliver safe or effective care. In addition, while antipsychotics may act on similar receptor targets, their pharmacokinetic properties—such as metabolism, bioavailability, half-life, and active metabolite production—differ markedly between agents. Taken together, these findings emphasise the urgent need for a more tailored, patient-specific approach to antipsychotic prescribing—one that considers both the clinical presentation and the underlying biological variability of each patient.

To begin addressing this complex issue, **Chapter 3** offers one practical solution by identifying early treatment response, particularly within the first two weeks, as a strong predictor of longer-term benefit. This insight offers clinicians a practical, evidence-based checkpoint to re-evaluate the appropriateness of continuing risperidone therapy. While current Australian guidelines recommend discontinuing risperidone after 12 weeks, they offer limited guidance on how and when to assess treatment progress along the way. Incorporating a formal two-week review into prescribing protocols could enhance clinical decision-making, minimise unnecessary exposure, and prompt earlier deprescribing when appropriate. However, while this strategy offers an important step toward more responsive care, it does not fully resolve the broader challenge of personalising antipsychotic use—particularly in the context of individual patient variability in treatment response, risk of adverse outcomes, and pharmacological complexity. While observational cohort studies of antipsychotic use in dementia have demonstrated an increased risk of cardiovascular complications—such as myocardial infarction, venous thromboembolism, and heart failure—as well as falls and death [2], the findings remain mixed. A recent network meta-analysis reported that risperidone may elevate the risk of cardiovascular disease and mortality, although the latter was not statistically

significant [3]. Therefore, beyond evaluating therapeutic outcomes, a comprehensive understanding of treatment risks is essential to guide safe prescribing. Future research should apply advanced methodologies to confirm treatment modifiers and explore pharmacokinetic and pharmacodynamic factors in specific high-risk subgroups. This would enable a more personalised, cautious, and evidence-informed approach to antipsychotic use in people living with dementia.

4.3.2. Laying the Groundwork for Data-Driven Personalised Antipsychotic Prescribing

Given the complexity and variability in antipsychotic treatment response among individuals with dementia as highlighted earlier, advancing toward more tailored prescribing is both necessary and challenging. While **Chapter 3** provides a crucial first step by identifying early treatment response as a useful clinical marker, it does not fully resolve the broader challenge of individualising care. Nevertheless, it lays a foundation for future efforts to support personalised prescribing from the outset. One promising strategy is the development of predictive tools that enable clinicians to assess the likely balance of benefits and risks before initiating therapy [4, 5]. These tools, driven by real-world data and robust analytic methods, can serve as clinical decision aids to guide more personalised and evidence-informed prescribing [5]. In recent years, predictive models have shown promise in psychiatric settings [6, 7], such as in schizophrenia and depressive disorders, where tools have been developed to estimate treatment response and risk of adverse outcomes [7, 8]. However, to date, no such models exist for guiding antipsychotic use in people with dementia. Extending this personalised, data-driven approach to dementia care—particularly for antipsychotics like risperidone—represents both a timely and necessary direction for future research and clinical application. Building on this thesis, a clear stepwise roadmap for future research and clinical application is proposed to strengthen the evidence base and support safer prescribing [9].

The first step is to conduct a comprehensive systematic review and individual participant data meta-analysis (IPD-MA) of all of risperidone's clinical trials for the treatment of BPSD. While the current thesis included six major trials, a broader IPD-MA would offer a more robust understanding of risperidone's therapeutic effects and allow for more detailed subgroup analyses to identify treatment modifiers. A recent systematic review identified 18 relevant studies, including 11 randomised controlled trials (RCTs) [10]. Ideally, obtaining individual-level data from these RCTs would allow for the assessment of both overall efficacy and differential responses across patient subgroups—thereby advancing precision prescribing in dementia care [9-11]. Furthermore, incorporating additional patient characteristics, biomarkers, and genetic data would further enhance the precision and utility of risperidone treatment recommendations. To date, only one study has conducted an IPD-MA examining a limited range of outcomes—specifically mortality and cerebrovascular adverse events—and included only a small number of trials [12]. Therefore, further efforts are needed to develop more comprehensive models that predict a broader spectrum of adverse outcomes associated with risperidone use, including sedation, extrapyramidal symptoms, metabolic disturbances, major adverse cardiovascular events, QT prolongation, pneumonia, and falls [2, 3]. Models built from this data would help characterise patients at heightened risk and guide risk-aware prescribing decisions.

The second step involves integrating both therapeutic response and adverse event prediction models into a unified decision-support tool. Recently, machine learning (ML) and artificial intelligence (AI) methods

have increasingly been applied in healthcare to develop clinical prediction models, demonstrating strong predictive performance and the ability to handle complex datasets [4, 13]. These advanced approaches are particularly suited to capturing interactions between numerous comorbidities and concomitant therapies, offering potential advantages over traditional statistical methods [4]. By leveraging ML and AI algorithms, the resulting prediction models can more accurately estimate individual-level risks and therapeutic responses. Such ML- and AI-based models would thus provide clinicians with powerful, evidence-based decision-making tools, enabling personalised and risk-aware prescribing of medications like risperidone in clinical practice.

Third, this tool should be externally validated using real-world data sources such as electronic medical records (EMRs), hospital datasets, or national claims data. This validation process is essential to ensure generalisability and practical relevance in diverse clinical settings. Finally, once validated, this tool can be incorporated into prescribing workflows to support more informed and personalised use of risperidone in dementia care. Building on this approach, future research could extend this modelling framework to other antipsychotics frequently prescribed off-label in older adults, allowing for comprehensive comparisons of therapeutic benefits and risk profiles across different agents. Moreover, this approach should not be limited to antipsychotics. Given the broad spectrum of psychotropic medications used in older adults—including antidepressants, benzodiazepines, antiepileptics, and opioids—predictive models tailored to each drug class could support more nuanced, patient-specific decision-making across the continuum of mental health care in ageing populations. These tools could also help prioritise patients for medication reviews, flag high-risk prescribing combinations, and inform shared decision-making between clinicians, patients, and families. In sum, by laying the groundwork for such a personalised approach, this thesis opens a pathway for future innovation in medication safety, effectiveness, and equity for older adults living with complex care needs.

4.3.3. Addressing Cultural Factors in Psychotropic Prescribing

While clinical efficacy and safety are essential considerations in psychotropic prescribing, this thesis suggests that these alone might not be sufficient. The results highlight the need for a broader, person-centred framework that accounts for cultural, linguistic, and social determinants of health—particularly when prescribing for diverse and vulnerable populations.

Chapter 3 demonstrated that risperidone's overall therapeutic response across behaviour symptoms of dementia is limited. This supports the importance of prioritising non-pharmacological interventions as the foundation of care. In fact, behaviour changes in dementia are not driven by symptoms alone—they are influenced by a wide range of contextual factors, including social environment, caregiver stress, unmet needs, and cultural background [14, 15]. Thus, effective management of BPSD requires a holistic, individualised approach that extends well beyond pharmacology.

Findings from **Chapter 2** reinforce this need by illustrating the pattern of psychotropic use that might vary among different cultural and groups. Aboriginal and Torres Strait Islander people exhibited markedly higher use of opioids and benzodiazepines/Z-drugs. While this may partly reflect a greater burden of pain-related conditions [16] and psychological distress [17], it cannot be disentangled from the broader historical and structural context in which these patterns emerge. In fact, national data show that First

Nations people had higher rates of opioid misuse [18] compared to the general population. Studies suggest that patterns of psychotropic use among Indigenous Australians are influenced not only by health needs but also by broader social and historical disadvantage [19]. Factors such as lower access to education, employment, and culturally safe healthcare—often shaped by intergenerational trauma and marginalisation—can contribute to both under- and over-prescribing, as well as non-medical use [19]. Addressing these patterns requires culturally informed prescribing strategies that consider these underlying determinants. Similarly, the lower rates of psychotropic prescribing among culturally and linguistically diverse (CALD) populations present a different set of concerns. This may suggest under-recognition or under-treatment of psychiatric disorders due to language barriers, stigma, or differing cultural perceptions of mental health. These disparities reflect a potential mismatch between patient needs and clinical decision-making, possibly leading to inequitable care. To bridge these gaps, prescribing models must evolve to incorporate culturally responsive practices. This includes developing validated assessment tools tailored to CALD populations, improving access to interpreter services, enhancing cultural competence training for clinicians, and embedding cultural safety into healthcare policy and program design.

In summary, this thesis suggests that psychotropic prescribing in older adults should be guided not only by pharmacological evidence but also by a deep understanding of patient context. Moving forward, healthcare systems must prioritise equity, cultural responsiveness, and community engagement to ensure that treatment is not only effective and safe, but also respectful, inclusive, and person-centred.

4.4. Strengths and limitations

4.4.1. Strengths

This thesis has several strengths. First, the population-level data used in **Chapter 2** are among the most comprehensive available. Drawing on linked national datasets that cover nearly 88% of the Australian older adult population—approximately 3.8 million individuals out of 4.2 million [20]—this chapter provides a highly representative snapshot of psychotropic medication use across diverse demographic and clinical subgroups in 2021. This large sample size enhances the external validity and generalisability of the findings and allows for robust subgroup analyses, including populations often underrepresented in clinical research, such as Indigenous Australians and people from culturally and linguistically diverse (CALD) backgrounds. Second, **Chapter 3** synthesises individual-level data from six pivotal clinical trials of risperidone, including those originally submitted to support the regulatory approval of risperidone for the treatment of behaviours and psychological symptoms of dementia (BPSD) in Australia [21]. This dataset includes one trial conducted specifically in Australia and New Zealand, adding to the clinical relevance of the findings for local practice [22].

Importantly, the use of individual participant data meta-analysis (IPD-MA)—specifically, a one-stage centred model—ensures consistency in data handling and reduces ecological bias that can arise in traditional meta-analyses. This approach is widely recognised as the gold standard for evaluating treatment effects across heterogeneous clinical trials [11, 23]. A key methodological strength of IPD-MA lies in its ability to standardise both covariates and outcome measures across trials. This is particularly important in the context of antipsychotic trials for BPSD, which often use a variety of behavioural rating

scales (e.g., Behavioral Pathology in Alzheimer's Disease Rating Scale [BEHAVE-AD], Neuropsychiatric Inventory score [NPI], Brief Psychiatric Rating Scale [BPSR], Cohen-Mansfield Agitation Inventory [CMAI]). While conventional meta-analyses may be restricted to trials that use similar outcomes, IPD-MA facilitates harmonisation of these outcomes, thus enabling the inclusion of more data and increasing statistical power [11]. Although this thesis was limited to trials reporting the BEHAVE-AD score due to data availability, the analytical framework and findings lay the groundwork for future IPD-MAs that integrate other trial datasets using different outcome measures. Furthermore, IPD-MA offers a unique advantage in enabling subgroup analyses, which are essential for investigating personalised treatment approaches. While observational studies have raised concerns about risperidone's association with adverse events such as falls, cardiovascular complications, hospitalisations, and mortality [2], the evidence remains inconclusive and varies between cohorts. A recent network meta-analysis of randomised control trials suggested that while risperidone may increase the risk of cardiovascular events and possibly mortality, it may also be associated with a reduced risk of falls compared to placebo [24]. However, these findings are often derived from studies with limited statistical power to explore subgroup effects. By pooling individual data across trials, IPD-MA enhances the ability to detect treatment modifiers and estimate risks within specific high-risk subgroups [11, 25]—such as individuals with diabetes, a history of stroke, or high frailty levels [26]—who may respond differently to treatment or be more susceptible to harm. Finally, the use of a random-intercept S-learner strategy to estimate individualised treatment effects further strengthens the analytical robustness of this thesis [23]. This approach reflects contemporary best practice in precision medicine and causal inference, allowing for more accurate and clinically meaningful identification of which patients are most likely to benefit—or be harmed—by risperidone therapy [23].

4.4.2. Limitations

While this thesis offers valuable contributions to understanding and optimising psychotropic medication use in older adults and people with dementia, several limitations should be acknowledged. Firstly, as discussed in earlier chapters, each study presented in this thesis carries inherent limitations that influence the scope and generalisability of the findings. In **Chapter 2**, the cross-sectional design using 2021 Census-linked data restricts the ability to infer causality between modifiable factors and psychotropic use. Additionally, reliance on self-reported variables (e.g. long-term health conditions) may introduce response bias, particularly among cognitively impaired individuals such as those with dementia. While the prevalence of dementia in Australia used in this thesis aligns with accepted national estimates, some inconsistency across data sources exists, which may influence generalisability [27]. Some medications, such as Z-drugs (e.g., zolpidem and zopiclone), were not captured in the PBS dataset because they are subsidised only under the Repatriation Pharmaceutical Benefits Scheme (RPBS). As a result, the prevalence of use for these medications may have been underestimated, and the extent of Z-drugs exposure in older adults could be higher than reported in this thesis. In **Chapter 3**, limitations stem largely from the nature of the dataset. Although six clinical trials were included, some important baseline variables—such as specific comorbidities, biomarkers, and genetic polymorphisms were either unavailable or inconsistently reported across studies. The absence of these potential treatment modifiers may reduce the accuracy and applicability of the model to real-world clinical populations. Moreover, the trials were selected from a single data repository (YODA), which may limit representativeness and external validity. As such, while

Chapter 3 contributes a foundational step toward personalised prescribing, the findings should be interpreted as hypothesis-generating and require further validation in broader, real-world cohorts.

Secondly, this thesis focuses on antipsychotic prescribing, with risperidone used as a case study to demonstrate the potential for personalised pharmacological strategies in dementia care. While this targeted approach allows for deeper analysis and provides valuable insights into a high-risk medication, it also limits the generalisability of the findings. Risperidone is just one of several psychotropic medications used in the management of BPSD, and even within this antipsychotic class, other agents—such as quetiapine, olanzapine, or aripiprazole—are often used off-label with varying risk profiles and pharmacological characteristics. More broadly, antipsychotics represent only one class within a wide array of psychotropic medications commonly used in older adults. **Chapter 2** of this thesis revealed that these other psychotropic classes are widely used among older Australians, often in combination, and disproportionately among certain high-risk subgroups. However, these patterns were not explored in depth, nor were personalisation strategies proposed. Future research should address this critical gap by applying similar analytical frameworks—such as predictive modelling and subgroup analyses—to other psychotropic classes. This would allow for a more comprehensive understanding of how to optimise psychotropic prescribing across the entire pharmacological landscape relevant to older people.

Furthermore, the focus of this thesis on pharmacological treatment alone overlooks several essential dimensions of dementia care. Non-pharmacological interventions, including behaviour therapy, caregiver support programs, environmental modifications, and occupational engagement, are widely recommended as first-line approaches for managing BPSD. These strategies not only offer safer alternatives to psychotropic medications but also address underlying unmet needs that often drive behaviour symptoms. Additionally, dementia care requires attention to broader care goals such as maintaining functional independence, preserving quality of life, supporting caregivers, and planning for end-of-life care. A truly patient-centred, evidence-informed model of dementia care must integrate pharmacological and non-pharmacological strategies within a unified, multidisciplinary framework. In sum, while this thesis offers an important foundation for personalising antipsychotic use, particularly risperidone, it represents only one piece of a much larger puzzle. Future research must extend beyond a single drug or drug class to include a wider range of psychotropic medications and encompass the non-drug dimensions of care that are critical to the well-being of people living with dementia.

4.5. Conclusion

There is a pressing need to re-evaluate how psychotropic medications are prescribed to older adults, particularly those living with dementia. This thesis has shown that psychotropic use—including polypharmacy—is substantially prevalent in this population, with notable disparities across vulnerable subgroups such as individuals with dementia, those from culturally and linguistically diverse (CALD) backgrounds, and Aboriginal and Torres Islander people. These patterns raise concerns about the appropriateness, safety, and equity of current prescribing practices.

While this thesis provides a foundational step toward optimising antipsychotic use—particularly risperidone, it also highlights that this is just one piece of a larger challenge. Real progress will require sustained, multi-level efforts involving clinical, regulatory, cultural, and systemic change. Future research

must continue to expand this work across other psychotropic classes and integrate both pharmacological and non-pharmacological strategies to ensure safer, more effective, and person-centred care for older people.

Reference

1. Le, H.T., et al., *Potentially high-risk antipsychotic use in people with dementia: a national data linkage study.* J Am Med Dir Assoc, in press.
2. Mok, P.L.H., et al., *Multiple adverse outcomes associated with antipsychotic use in people with dementia: population based matched cohort study.* BMJ, 2024. **385**: p. e076268.
3. Yunusa, I., et al., *Assessment of Reported Comparative Effectiveness and Safety of Atypical Antipsychotics in the Treatment of Behavioral and Psychological Symptoms of Dementia: A Network Meta-analysis.* JAMA Network Open, 2019. **2**(3): p. e190828-e190828.
4. Hassan, N., et al., *Road map for clinicians to develop and evaluate AI predictive models to inform clinical decision-making.* BMJ Health Care Inform, 2023. **30**(1).
5. Selby, J.V. and B.H. Fireman, *Building Predictive Models for Clinical Care-Where to Build and What to Predict?* JAMA Netw Open, 2021. **4**(1): p. e2032539.
6. Webb, C.A., et al., *Personalized prediction of antidepressant v. placebo response: evidence from the EMBARC study.* Psychol Med, 2019. **49**(7): p. 1118-1127.
7. Liu, S., et al., *Prediction of antipsychotic drug efficacy for schizophrenia treatment based on neural features of the resting-state functional connectome.* Translational Psychiatry, 2025. **15**(1): p. 137.
8. Guo, L.-K., et al., *Prediction of treatment response to antipsychotic drugs for precision medicine approach to schizophrenia: randomized trials and multiomics analysis.* Military Medical Research, 2023. **10**(1): p. 24.
9. Debray, T.P., et al., *A framework for developing, implementing, and evaluating clinical prediction models in an individual participant data meta-analysis.* Stat Med, 2013. **32**(18): p. 3158-80.
10. Zhou, G., et al., *Risperidone for the Treatment of Dementia-Related Psychosis: A Systematic Review and Meta-Analysis.* Dementia and Geriatric Cognitive Disorders, 2024. **54**(2): p. 120-134.
11. Veroniki, A.A., et al., *An Introduction to Individual Participant Data Meta-analysis.* Neurology, 2023. **100**(23): p. 1102-1110.
12. Howard, R., et al., *Baseline characteristics and treatment-emergent risk factors associated with cerebrovascular event and death with risperidone in dementia patients.* Br J Psychiatry, 2016. **209**(5): p. 378-384.
13. Del Fabro, L., et al., *Machine learning methods to predict outcomes of pharmacological treatment in psychosis.* Translational Psychiatry, 2023. **13**(1): p. 75.
14. Cloak, N., C. Schoo, and Y. Al Khalili, *Behavioral and Psychological Symptoms in Dementia*. 2025: StatPearls Publishing, Treasure Island (FL).
15. Na, R., et al., *A Systematic Review and Meta-Analysis of Nonpharmacological Interventions for Moderate to Severe Dementia.* Psychiatry Investig, 2019. **16**(5): p. 325-335.
16. Australian Institute of Health and Welfare & National Indigenous Australians Agency. *Measure 1.08 Cancer, Aboriginal and Torres Strait Islander Health Performance Framework website*. 2023 [cited 2025 14/04/2025]; Available from: https://www.indigenoushpf.gov.au/measures/1-08-cancer#:~:text=The%20rate%20of%20disease%20burden,per%201%2C000%20people%2C%20respectively).
17. Jorm, A.F., et al., *Mental health of Indigenous Australians: a review of findings from community surveys.* Med J Aust, 2012. **196**: p. 118-21.
18. Health, A.I.o. and Welfare, *First Nations people's use of alcohol, tobacco, e-cigarettes and other drugs*. 2024, AIHW: Canberra.
19. Michelle Catto and Neil Thomson. *Review of illicit drug use among Indigenous peoples*. 2008 [cited 2025 19/05/2025]; Available from: https://healthinfonet.ecu.edu.au/healthinfonet/getContent.php?linkid=590637&title=Review+of+illicit+

drug+use+among+Indigenous+peoples#:~:text=The%20greater%20level%20of%20substance,ill%2Dhealth%20%5B2%5D.
20. Australian Institute of Health and Welfare. *Older Australians*. 2024 [cited 2025 05/04/2025]; Available from: https://www.aihw.gov.au/reports/older-people/older-australians/contents/health/health-disability-status.
21. Australian Drug Information. *AusDI*. 2025; Available from: https://www.ausdi.com/.
22. Brodaty, H., et al., *A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia.* J Clin Psychiatry, 2003. **64**(2): p. 134-43.
23. Bouvier, F., et al., *Estimating individualized treatment effects using an individual participant data meta-analysis.* BMC Medical Research Methodology, 2024. **24**(1): p. 74.
24. Rubino, A., et al., *Association of the US Food and Drug Administration Antipsychotic Drug Boxed Warning With Medication Use and Health Outcomes in Elderly Patients With Dementia.* JAMA Network Open, 2020. **3**(4): p. e203630-e203630.
25. Belias, M., et al., *Statistical approaches to identify subgroups in meta-analysis of individual participant data: a simulation study.* BMC Medical Research Methodology, 2019. **19**(1): p. 183.
26. Nørgaard, A., et al., *Effect of antipsychotics on mortality risk in patients with dementia with and without comorbidities.* J Am Geriatr Soc, 2022. **70**(4): p. 1169-1179.
27. Dobson, A.J., et al., *Different estimates of the prevalence of dementia in Australia, 2021.* Med J Aust, 2023. **218**(7): p. 320-321.

APPENDIX A. Chapter 3 Supplementary Materials

Supplementary Figure S1. Risk of bias assessment

Supplementary Table S1. Trials characteristic

Supplementary Table S2. Details of variable in each dataset.

Supplementary Table S3. Mixed-effect logistic regression model of treatment effect in total populations in both datasets, measured by therapeutic response at week 4 and week 8.

Supplementary Table S4. Results of interaction terms between treatment effect and covariates. Table shows statistically significant interactions only.

Supplementary Table S5. Mixed-effect logistic regression model of therapeutic response among risperidone users in dataset B

Supplementary Table S6. Full mixed-effect linear regression models of Dataset A in all outcomes

Supplementary Table S7. Full mixed-effect linear regression models of Dataset B in all outcomes

Supplementary Table S8. Linear regression models for baseline variables in Dataset A (Full)

Supplementary Table S9. Linear regression models for baseline variables in Dataset B (Full)

Supplementary Document 1. BEHAVIORAL PATHOLOGY IN ALZHEIMER'S DISEASE (BEHAVE-AD)

Supplementary Table S1: Trial characteristics

	AUS-5	BEL-14	INT-24	USA-63	INT-83	USA-232
Trial design	Double-blind, Placebo-controlled Parallel-group trial	Double-blind, placebo-controlled trial	Placebo-controlled, Double-blind, Parallel-group trial	Double-Blind, Placebo-Controlled trial	A double-blind, placebo-controlled, parallel-group trial	Double-blind, Placebo-controlled Parallel-group trial
Duration of trials	12 weeks	4 weeks	12 weeks	12 weeks	8 weeks	8 weeks
Location	Australia and New Zealand	Belgium	8 countries	USA	USA, the U.K., Poland, Austria, Israel	USA
Number of participants at baseline						
Total	337	39	344	625	18	473
Placebo	170	19	114	163	8	238
Risperidone	167	20	115	462	10	235
Haloperidol	0	0	115	0	0	0
Inclusion criteria						
Age	>55	>65	>55	>55	>55	>55
Dementia diagnosis	Alzheimer's, vascular, or mixed dementia based on DSM-IV criteria, and with behavioural disturbances	Diagnosis of Senile Dementia of the Alzheimer Type (criteria of Berg et al) Staging of dementia of 1, 2 or 3 on the	Alzheimer's, vascular, or mixed dementia based on DSM-IV criteria, and with behavioural disturbances	Alzheimer's, vascular, or mixed dementia based on DSM-IV criteria, and with behavioural disturbances	Alzheimer's, vascular, or mixed dementia based on DSM-IV criteria, and with behavioural disturbances	Alzheimer's, vascular, or mixed dementia based on DSM-IV criteria, and with behavioural disturbances

		Clinical Dementia Rating scale.				
Functional Assessment Staging Tool (FAST) score for Alzheimer's Disease	4 or more	-	4 or more	4 or more	-	-
Mini-Mental State Examination (MMSE) score	23 or lower	-	23 or lower	23 or lower	5 to 23	5 to 23
Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) **total scores**	-	-	8 or more	8 or more	-	-
Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) **subscale scores**	2 or more on any subscale	-	-	-	2 or more on any subscale	2 or more on any subscale
Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) **global rating**	-	-	1 or more	1 or more	-	-
Cohen-Mansfield Agitation Inventory (CMAI) frequency score on aggressive items	Yes	-	-	-	-	-
Residents of an aged care facility	Yes	Yes	Yes	Yes	Yes	Yes
Exclusion criteria						
Neurological/Psychiatric conditions						

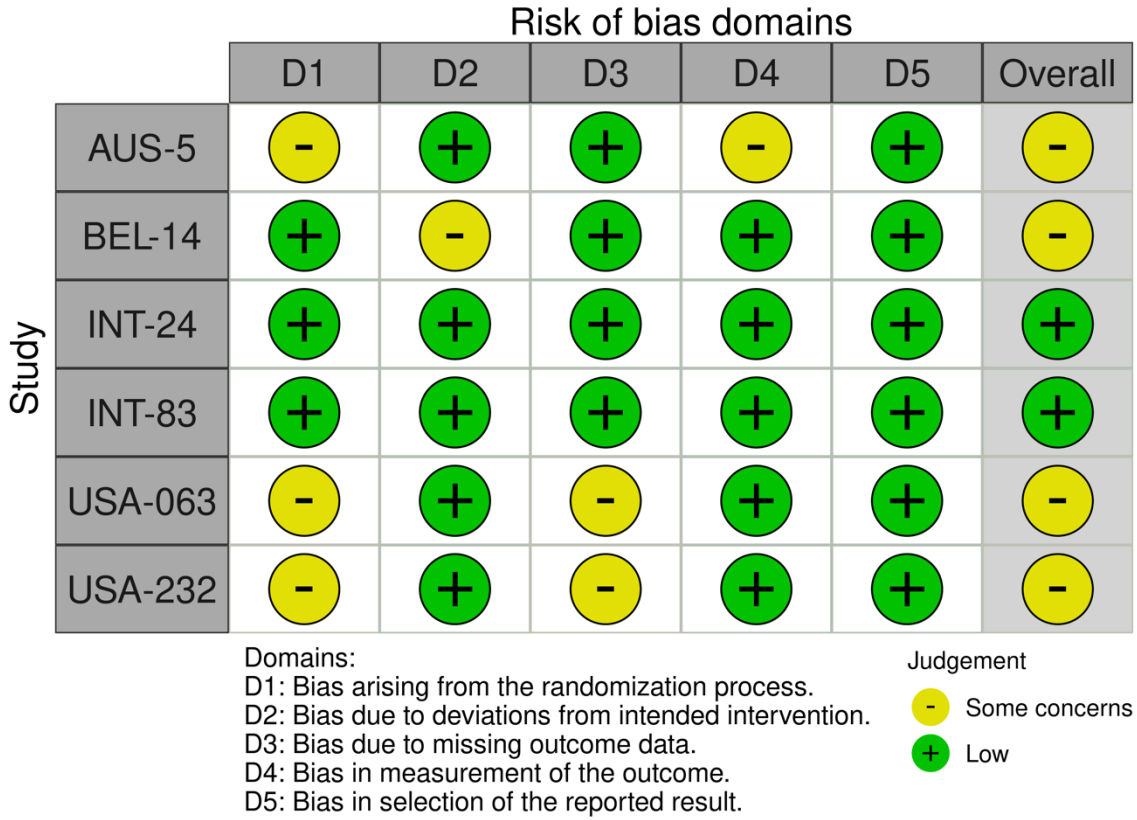
Medical/neurological conditions* other than dementia which diminish cognitive function	Yes	Yes	Yes	Yes	Yes	Yes
Other psychiatric disorders (major depression within the last 6 months, bipolar affective disorder, schizophrenia or schizoaffective disorder, delirium, etc)	Yes	Yes	Yes	Yes	Yes	Yes
Known by other causes of dementia (pure vascular dementia, human immunodeficiency virus) or reversible causes of dementia	No	Yes	No	Yes	Yes	Yes
Other medical conditions						
Clinically relevant or history of tardive dyskinesia	Yes	-	No	No	No	No
Clinically uncontrolled medical conditions	Yes	-	No	Yes	Yes	Yes
Clinically significant laboratory or electrocardiogram (ECG) findings.	Yes	-	Yes	Yes	Yes	Yes
Hypersensitivity or Immune mediated reaction to antipsychotics/risperidone or history of Neuroleptic Malignant Syndrome (NMS)	Yes	-	Yes	Yes	Yes	Yes
Seizure disorder requiring medication	Yes	-	No	Yes	Yes	Yes
Female subjects of childbearing potential without adequate contraception	No	-	No	Yes	No	Yes
Carcinoma in the past five years/Malignant melanoma	No	-	No	Yes	No	Yes

Medication use						
Substance-induced dementia (alcohol, etc.); Psychoactive Substance (including alcohol) Abuse or Dependence	Yes	-	Yes	Yes	Yes	Yes
History use of depot injection antipsychotics within 1 or 2 treatment cycle	Within 2 treatment cycles	-	Within 1 treatment cycle	Within 1 treatment cycle	Within 1 treatment cycle	Within 1 treatment cycle
Participants of other trials within 4 weeks	Yes	-	Yes	Yes	Yes	Yes
Received concomitant medications for chronic conditions for less than 30 days (expect OTC drugs and antibiotics)	No	-	No	Yes	Yes †	Yes
Expected to continue treatment with antipsychotics, antidepressants, lithium, carbamazepine, trazodone and/or valproic acid or other anticonvulsants during the trial.	No	-	No	Yes	Yes	Yes
History or risk of engaging in behavior that could harm themselves or others.	No	-	No	Yes	Yes	Yes
Intervention						
Dose	A flexible dose from 0.5 mg to 2 mg/day	A flexible dose from 1 mg to 4 mg/day	A flexible dose from 0.5 mg to 4 mg/day	A fixed-dose regimens of 0.5 mg, 1 mg, or 2 mg/day	A flexible dose from 1 mg to 1.5 mg/day	A flexible dose from 1 mg to 1.5 mg/day
Efficacy assessment						
Cohen-Mansfield Agitation Inventory (CMAI)	Yes	-	Yes	Yes	-	-

Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD) rating scale	Yes	Yes	Yes	Yes	Yes	Yes

*Including, but not limited to: drug overdose, severe liver, kidney, lung or heart dysfunction, severe anaemia, untreated hypothyroidism, vitamin B12 or folic acid deficiency, uncontrolled diabetes, Parkinson's disease, Huntington's disease, Huntington's chorea, progressive supranuclear paralysis, toxic confusional state, brain tumor, subdural hematoma, multiple sclerosis, brain trauma, Creutzfeldt-Jakob disease, Lewy Body dementia, and other conditions such as electrolyte imbalance, sepsis syndrome, and mental retardation.

† And those receiving Cognex® or Hydergine® and are not willing to discontinue use during the study period.



Supplementary Figure S1. Risk of bias assessment

Supplementary Table S2. Details of variable in each dataset.

Dataset 1*	Dataset 2*	Variables	Description	Types	Unit
x	x	TRIAL	Name of trials	Categorical	USA-5; BEL-14; INT-24; INT-83; USA-063; USA-232
x	x	AGE	Age	Continuous	Years
x	x	AGE_G	Age group	Categorical	<75; 75-85; >85
x	x	SEX	Gender	Categorical	Male/Female
x	x	BMI	BMI	Continuous	Weight/Height^2
x	x	BMI_group	Body weight of adults classified by BMI Less than 18.5: Underweight 18.5 to 24.9: Normal weight 25 or more: Overweight/Obese	Categorical	Underweight Normal weight Overweight/Obese
x	x	MMSE	Mini-mental state examination (MMSE) score	Continuous	
x	x	MMSE_stage	Severity of cognitive impairment (MMSE ≥21: Normal/Mild; 10 ≤ MMSE < 20: Moderate; MMSE < 10: Severe)	Categorical	NORMAL/MILD; MODERATE; SEVERE
x	x	BETO_B	BEHAVE-AD total score at baseline	Continuous	
x	x	N05B_B	Anxiolytic use (ATC code N05B) at baseline	Dichotomous	Yes/No
x	x	N05C_B	Hypnotic and sedative use (ATC code N05C) at baseline	Dichotomous	Yes/No
x	x	N06A_B	Antidepressant use (ATC code N06A) at baseline	Dichotomous	Yes/No
x	x	N06D_B	Anti-dementia use (ATC code N06D) at baseline	Dichotomous	Yes/No
x	x	N05B	Anxiolytic use (ATC code N05B) during trial	Dichotomous	Yes/No
x	x	N05C	Hypnotic and sedative use (ATC code N05C) during trial	Dichotomous	Yes/No
x	x	N06A	Antidepressant use (ATC code N06A) during trial	Dichotomous	Yes/No

x	x	N06D	Anti-dementia use (ATC code N06D) during trial	Dichotomous	Yes/No
x	x	Mean_Dose	Mean dose of Risperidone in each week	Continuous	
x	x	Psychosis	Presence of psychosis symptom at baseline	Dichotomous	Yes/No
x	x	Activity	Presence of activity disturbances symptom at baseline	Dichotomous	Yes/No
x	x	Aggressive	Presence of aggression symptom at baseline	Dichotomous	Yes/No
x	x	Sleep	Presence of sleep symptom at baseline	Dichotomous	Yes/No
x	x	Affective	Presence of affective disturbances symptom at baseline	Dichotomous	Yes/No
x	x	Anxiety	Presence of anxieties and phobias symptom at baseline	Dichotomous	Yes/No
x		RAC	Race	Categorical	Caucasian, Black, Other
x		CKD_stage	Renal function (eGFR) calculated by CKD-EPI formula[1]; and categorised into the following stages: eGFR > 90: Normal/Stage 1 60 < eGFR ≤ 90: CKD stage 2 45 < eGFR ≤ 60: CKD stage 3a eGFR ≤ 45: CKD stage 3b or higher	Categorical	CKD Normal/Stage 1 CKD stage 2 CKD stage 3a CKD stage 3b or higher
x		DIAGNOSIS	Demetia diagnosis	Categorical	Alzheimer's disease Vascular dementia Mixed type dementia
x		C_CAVAS	Any cardiovascular disease at baseline	Dichotomous	Yes/No
x		C_END	Any endocrine disease at baseline	Dichotomous	Yes/No
x		C_NEU	Any neurological disease at baseline	Dichotomous	Yes/No

**Dataset 1 included data from only 3 trials: AUS-5; USA-63 and USA-232; Dataset 2 included data from all 6 trials.*

[1]Levey, A. S., Stevens, L. A., Schmid, C. H., Zhang, Y. L., Castro, A. F., 3rd, Feldman, H. I., Kusek, J. W., Eggers, P., Van Lente, F., Greene, T., Coresh, J., & CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) (2009). A new equation to estimate glomerular filtration rate. Annals of internal medicine, 150(9), 604–612.

Supplementary Table S3. Mixed-effect logistic regression model of treatment effect in total populations in both datasets, measured by therapeutic response at week 4 and week 8.

Treatment effects	Dataset A		Dataset B		Dataset A		Dataset B	
	WEEK 4		WEEK 4		WEEK 8		WEEK 8	
	N = 1264; Trials = 6		N = 1061; Trials = 3		N = 1088; Trials = 5		N = 940; Trials = 3	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Risperidone group (Reference: Placebo group)	1.25 (0.98-1.58)	0.0668	1.18 (0.91-1.53)	0.2215	1.3 (1.01-1.67)	0.0455	1.35 (1.02-1.79)	0.0387
Age	1.01 (1-1.03)	0.1632	1.01 (0.99-1.03)	0.4167	1.01 (1-1.03)	0.1275	1.01 (0.99-1.03)	0.4892
Male (Reference: Female)	1 (0.77-1.3)	0.9966	0.98 (0.73-1.32)	0.9181	1.06 (0.79-1.41)	0.7048	1.08 (0.78-1.48)	0.6452
BMI	0.99 (0.96-1.01)	0.2646	0.97 (0.95-1)	0.057	1.01 (0.98-1.03)	0.6273	1 (0.97-1.04)	0.7487
MMSE	1 (0.98-1.02)	0.9956	1 (0.98-1.03)	0.6759	1.01 (0.99-1.03)	0.2662	1.02 (0.99-1.04)	0.1566
Use of psychotropic medications at baseline								
Anxiolytics	1.29 (0.78-2.13)	0.3151	1.54 (0.82-2.89)	0.1762	1.21 (0.67-2.18)	0.5293	1.05 (0.52-2.11)	0.8893
Hypnotic and sedatives	0.92 (0.61-1.39)	0.696	0.58 (0.35-0.95)	0.0305	0.74 (0.47-1.16)	0.1853	0.55 (0.32-0.96)	0.0353
Antidepressants	0.78 (0.44-1.37)	0.3836	0.73 (0.41-1.31)	0.2889	1.32 (0.71-2.45)	0.3799	1.27 (0.67-2.41)	0.4679
Anti-dementias	1.31 (0.85-2.03)	0.2176	1.3 (0.83-2.04)	0.2582	1.04 (0.65-1.66)	0.8665	0.96 (0.6-1.54)	0.867
BEHAVE-AD total score at baseline	1.01 (0.99-1.03)	0.2667	1.01 (0.99-1.03)	0.4549	1.03 (1.01-1.05)	0.0075*	1.02 (1-1.05)	0.0629
Presence of BPSD symptom at baseline (Reference: No symptom)								
Psychosis	1.25 (0.93-1.68)	0.1438	1.23 (0.88-1.72)	0.2327	0.89 (0.64-1.24)	0.4964	0.93 (0.65-1.32)	0.675
Activity disturbances	1.18 (0.83-1.69)	0.3475	1.24 (0.85-1.81)	0.2726	0.79 (0.53-1.19)	0.2597	0.81 (0.53-1.23)	0.3207
Aggression	0.86 (0.58-1.3)	0.4792	1 (0.65-1.55)	0.9997	0.93 (0.6-1.45)	0.7576	1.02 (0.64-1.61)	0.9461
Affective disturbance	0.87 (0.68-1.12)	0.2797	0.8 (0.61-1.06)	0.1269	0.89 (0.68-1.17)	0.403	0.82 (0.61-1.1)	0.1874
Sleep disturbances	1.08 (0.85-1.38)	0.5298	1.27 (0.96-1.68)	0.0928	0.97 (0.75-1.27)	0.8433	1.03 (0.77-1.39)	0.8366
Anxieties and phobias	1.01 (0.78-1.32)	0.9167	1.09 (0.82-1.46)	0.5534	1.01 (0.76-1.34)	0.938	1.18 (0.87-1.61)	0.2808
Race (Reference: Caucasian)								
Other			1.15 (0.64-2.07)	0.6285			1.79 (0.95-3.36)	0.0695

Black		1.07 (0.66-1.74)	0.7841		1.19 (0.71-1.97)	0.5087
Having currently active comorbidities at baseline (Reference: No disease)						
Cardiovascular diseases		1.39 (1.02-1.9)	0.036		1.3 (0.93-1.82)	0.1297
Endocrine diseases		0.89 (0.67-1.19)	0.4362		0.92 (0.68-1.25)	0.608
Neurological diseases		0.83 (0.62-1.11)	0.2079		0.97 (0.71-1.34)	0.8722
Dementia type (Reference: Alzheimer's disease)						
Mixed type dementia		0.95 (0.57-1.57)	0.8344		1.08 (0.63-1.85)	0.7909
Vascular dementia		1.09 (0.77-1.56)	0.6226		0.72 (0.49-1.05)	0.0897
Renal impairment						
Stage 2		1.12 (0.64-1.96)	0.6855		1.4 (0.77-2.54)	0.269
Stage 3a		1.16 (0.64-2.09)	0.6302		1.13 (0.6-2.13)	0.71
Stage 3b or higher		1.42 (0.75-2.7)	0.281		1.83 (0.93-3.61)	0.0822

*Values are significant results at each Bonferroni correction in therapeutic response at week 4 and week 8 (p<0.025 = 0.05/2)

Supplementary Table S4. Results of interaction terms between treatment effect and covariates. Table shows statistically significant interactions only.

Outcome*	WEEK 4		WEEK 8	
	SMD (95% CI)	**p**	**SMD (95% CI)**	**p**
BEHAVE-AD total score				
†Risperidone x BMI	0.02 (0 to 0.04)	0.024		
‡Risperidone x Any neurological disease (Yes)			-0.25 (-0.5 to 0)	0.048
BEHAVE-AD Global rating scale				
†Risperidone x Sex (Male)	-0.29 (-0.52 to -0.06)	0.012		
BEHAVE-AD Aggression subscale				
‡Risperidone x Any Endocrine diseases (Yes)			0.42 (0.16 to 0.68)	0.002

BEHAVE-AD Activity disturbances subscale				
‡Risperidone x cardiovascular diseases	-0.24 (-0.46 to -0.02)	0.032		
†Risperidone x BMI	0.02 (0 to 0.04)	0.032		
BEHAVE-AD Affective disturbances subscale				
‡Risperidone x cardiovascular diseases			0.31 (0.05 to 0.57)	0.018
BEHAVE-AD Anxiety disturbances subscale				
‡Risperidone x Race (Black)			0.48 (0.04 to 0.92)	0.029
‡Risperidone x Race (Other)			0.57 (0.06 to 1.08)	0.033
BEHAVE-AD Sleep disturbances subscale				
†Risperidone x BMI	0.03 (0.01 to 0.05)	0.005		
†Risperidone x MMSE score at baseline	0.02 (0.01 to 0.03)	0.048	0.02 (0 to 0.04)	0.030
†Risperidone x Sex (Male)			0.28 (0.03 to 0.53)	0.034

*Mixed-effect linear regression model
†Tested in dataset A
‡Tested in dataset B

Supplementary Table S5. Mixed-effect logistic regression model of therapeutic response among risperidone users in dataset B

Predictors of therapeutic response	**WEEK 4**		**WEEK 8**	
	N = 518; Trial = 2		**N = 461; Trials = 2**	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Model 1				
Age	1,01 (0,98; 1,04)	0,500	0,99 (0,97; 1,02)	0,617
Male (Reference: Female)	1,04 (0,7; 1,55)	0,830	0,95 (0,63; 1,45)	0,815
BMI (kg/m2)	0,95 (0,92; 0,99)	0,012	0,99 (0,95; 1,04)	0,766

MMSE	1,01 (0,98; 1,04)	0,630	1 (0,97; 1,03)	0,814
Use of psychotropic medications at baseline				
Anxiolytics	1,59 (0,67; 3,78)	0,294	1,2 (0,48; 2,98)	0,696
Hypnotic and sedatives	0,46 (0,23; 0,92)	0,027	2,41 (1,23; 4,72)	0,011
Antidepressants	1,11 (0,51; 2,44)	0,796	0,4 (0,16; 1,01)	0,053
Anti-dementias	1,9 (0,97; 3,71)	0,061	1,15 (0,58; 2,27)	0,695
BEHAVE-AD total score at baseline	1,14 (0,9; 1,46)	0,284	0,76 (0,58; 0,99)	0,040
Presence of BPSD symptom at baseline (Reference: No symptom)				
Psychosis	1,12 (0,5; 1,19)	0,239	1,05 (0,67; 1,65)	0,836
Activity disturbances	1,08 (0,66; 1,78)	0,758	1,1 (0,64; 1,88)	0,738
Aggression	1,01 (0,58; 1,77)	0,962	1,02 (0,57; 1,85)	0,937
Affective disturbance	0,82 (0,57; 1,18)	0,282	1,02 (0,66; 1,41)	0,845
Sleep disturbances	1,15 (0,79; 1,66)	0,473	0,91 (0,61; 1,36)	0,652
Anxieties and phobias	1,08 (0,74; 1,57)	0,686	0,78 (0,53; 1,16)	0,222
Race (Reference: Caucasian)				
Other	1,03 (0,47; 2,24)	0,945	0,72 (0,32; 1,66)	0,447
Black	0,97 (0,53; 1,78)	0,930	0,66 (0,35; 1,25)	0,198
Having currently active comorbidities at baseline (Reference: No disease)				
Cardiovascular diseases	1,36 (0,91; 2,03)	0,129	0,82 (0,54; 1,23)	0,334

	Endocrine diseases	0,92 (0,63; 1,33)	0,648	1,26 (0,85; 1,88)	0,247
	Neurological diseases	0,77 (0,53; 1,14)	0,190	0,76 (0,51; 1,14)	0,186
Dementia type (Reference: Alzheimer's disease)					
	Mixed type dementia	1,07 (0,56; 2,05)	0,836	1,1 (0,54; 2,24)	0,785
	Vascular dementia	1,36 (0,85; 2,19)	0,200	1,41 (0,86; 2,31)	0,168
eGFR (ml/min)		1 (0,99; 1,01)	0,880	1 (0,99; 1,02)	0,446
Number of observations		**637**		**570**	
Number of trials		**3**		**3**	
Model 2					
Early response (Reference: No response)		8.69 (5.57-13.54)	<0.001*	5.05 (3.24; 7.87)	<0.001*
Age		0.99 (0.96-1.03)	0,683	1 (0.96; 1.03)	0,833
Male (Reference: Female)		0.92 (0.56-1.53)	0,752	0.87 (0.52; 1.45)	0,592
BMI (kg/m2)		0.93 (0.89-0.98)	0,006	1.01 (0.96; 1.06)	0,701
MMSE		1.01 (0.97-1.06)	0,497	1.01 (0.97; 1.05)	0,658
Use of psychotropic medications at baseline					
	Anxiolytics	0.67 (0.18-2.48)	0,549	1.6 (0.38; 6.72)	0,523
	Hypnotic and sedatives	0.59 (0.1-3.33)	0,547	0.19 (0.03; 1.15)	0,071
	Antidepressants	1.05 (0.38-2.88)	0,927	1.85 (0.65; 5.22)	0,247
	Anti-dementias	1.94 (0.85-4.42)	0,114	0.76 (0.34; 1.67)	0,490

BEHAVE-AD total score at baseline	0.99 (0.95-1.03)	0,670	0.99 (0.95; 1.04)	0,785
Concomitant use of psychotropic medications				
Anxiolytics	1.01 (0.44-2.31)	0,985	0.72 (0.31; 1.67)	0,449
Hypnotics and sedatives	0.62 (0.18-2.14)	0,453	1.16 (0.39; 3.5)	0,789
Mean dose of risperidone	0.98 (0.62-1.57)	0,949	1.26 (0.82; 1.96)	0,293
Presence of BPSD symptom at baseline (Reference: No symptom)				
Psychosis	1.53 (0.86-2.73)	0,146	1.06 (0.61; 1.86)	0,826
Activity disturbances	0.79 (0.42-1.48)	0,463	0.78 (0.41; 1.49)	0,451
Aggression	1.47 (0.76-2.87)	0,252	1.4 (0.71; 2.74)	0,327
Affective disturbance	0.58 (0.36-0.92)	0,020	1.01 (0.63; 1.6)	0,981
Sleep disturbances	1.23 (0.76-1.98)	0,407	1.34 (0.81; 2.21)	0,253
Anxieties and phobias	1.34 (0.84-2.14)	0,225	1.7 (1.06; 2.74)	0,028
Race (Reference: Caucasian)				
Other	0.7 (0.27-1.84)	0,471	1.15 (0.45; 2.95)	0,776
Black	0.95 (0.47-1.92)	0,882	1.72 (0.84; 3.51)	0,138
Having currently active comorbidities at baseline (Reference: No disease)				
Cardiovascular diseases	1.67 (0.99-2.8)	0,054	1.7 (1; 2.89)	0,050
Endocrine diseases	0.76 (0.48-1.2)	0,243	0.57 (0.36; 0.91)	0,019
Neurological diseases	0.73 (0.45-1.16)	0,184	1.39 (0.86; 2.25)	0,183

Dementia type (Reference: Alzheimer's disease)				
Mixed type dementia	0.73 (0.3-1.76)	0,481	0.8 (0.32; 2.02)	0,637
Vascular dementia	1.68 (0.87-3.22)	0,121	0.67 (0.35; 1.27)	0,223
eGFR (ml/min)	1 (0.99-1.02)	0,807	1 (0.98; 1.01)	0,469
Number of observations	**518**		**461**	
Number of trials	**2**		**2**	

Model 1 includes baseline variables only. Model 2 includes baseline variables and treatment-emergent variables. Model 2 does not include AUS-5 trial as the BEHAVE-AD total score was not captured at week 2.

*Values are significant results after Bonferroni correction (p value <0.05/44 = 0.00113)

Supplementary Table S6. Full mixed-effect linear regression models of Dataset A in all outcomes

Predictors of BPSD score	BEHAVE-AD total score		Psychosis		Activity disturbances		Aggressiveness		Sleep disturbances		Affective disturbances		Anxieties and phobias		Global rating	
	MD (95% CI)	p	MD (95% CI)	p	MD (95% CI)	p	MD (95% CI)	p	MD (95% CI)	p	MD (95% CI)	p	MD (95% CI)	p	MD (95% CI)	p
4-WEEK OUTCOME																
Early reduction in rating score																
BEHAVE-AD total score	-0,09 (-0,1; -0,08)	<0.001#	-	-	-	-	-	-	-	-	-	-	-	-	-	-
BEHAVE-AD Psychosis subscale score	-	-	-0,2 (-0,21; -0,19)	<0.001#	-	-	-	-	-	-	-	-	-	-	-	-
BEHAVE-AD activity disturbances subscale	-	-	-	-	-0,32 (-0,35; -0,29)	<0.001#	-	-	-	-	-	-	-	-	-	-
BEHAVE-AD Aggression subscale score	-	-	-	-	-	-	-0,26 (-0,28; -0,24)	<0.001#	-	-	-	-	-	-	-	-
BEHAVE-AD sleep disturbance subscale	-	-	-	-	-	-	-	-	-0,94 (-1; -0,88)	<0.001#	-	-	-	-	-	-
BEHAVE-AD affective disturbance subscale	-	-	-	-	-	-	-	-	-	-	-0,58 (-0,63; -0,54)	<0.001#	-	-	-	-
BEHAVE-AD anxieties and phobias subscale	-	-	-	-	-	-	-	-	-	-	-	-	-0,33 (-0,36; -0,29)	<0.001#	-	-
BEHAVE-AD Global rating subscale score	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0,77 (-0,83; -0,71)	<0.001#

Age	0 (-0,01; 0)	0.586	0 (0; 0,01)	0.491	0 (-0,01; 0)	0.3102	-0,01 (-0,01; 0)	0.0691	0 (-0,01; 0,01)	0.9426	-0,01 (-0,01; 0)	0.032	0,01 (0; 0,01)	0.1254	0 (-0,01; 0)	0.2277
Male (Reference: Female)	-0,02 (-0,13; 0,09)	0.723	-0,05 (-0,14; 0,04)	0.2717	0,11 (-0,01; 0,23)	0.0629	0,07 (-0,04; 0,18)	0.209	0,08 (-0,03; 0,18)	0.1425	-0,2 (-0,3; -0,09)	<0.001#	-0,02 (-0,13; 0,1)	0.7596	-0,08 (-0,19; 0,04)	0.2031
BMI	-0,01 (-0,02; 0)	0.287	0 (-0,01; 0,01)	0.4838	0 (-0,01; 0,01)	0.6957	0,01 (0; 0,02)	0.2495	0,01 (0; 0,01)	0.2822	0 (-0,01; 0,01)	0.476	-0,01 (-0,02; 0)	0.2637	0,01 (0; 0,02)	0.1932
MMSE	-0,01 (-0,02; -0,01)	0.013#	0,02 (0,01; 0,02)	<0.001#	-0,01 (-0,02; -0,01)	0.011#	-0,02 (-0,03; -0,02)	<0.001#	0 (-0,01; 0)	0.3255	0 (-0,01; 0,01)	0.783	0,02 (0,01; 0,03)	<0.001#	-0,01 (-0,02; 0)	0.0027#
Use of psychotropic medications at baseline	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anxiolytics	-0,19 (-0,45; 0,08)	0.1705	-0,08 (-0,29; 0,14)	0.4784	-0,16 (-0,44; 0,12)	0.2741	0,08 (-0,18; 0,34)	0.5411	0,03 (-0,21; 0,27)	0.7939	0,24 (-0,01; 0,49)	0.0598	-0,06 (-0,33; 0,22)	0.6799	-0,11 (-0,39; 0,16)	0.4184
Hypnotic and sedatives	-0,11 (-0,44; 0,21)	0.4972	0,1 (-0,16; 0,37)	0.4541	-0,06 (-0,41; 0,29)	0.7394	0,24 (-0,08; 0,56)	0.1426	-0,07 (-0,37; 0,23)	0.6454	-0,07 (-0,38; 0,24)	0.6551	-0,26 (-0,59; 0,07)	0.1237	0,02 (-0,32; 0,36)	0.9224
Antidepressants	0,02 (-0,22; 0,25)	0.8979	-0,06 (-0,25; 0,13)	0.5327	-0,13 (-0,37; 0,12)	0.3053	0 (-0,23; 0,22)	0.9825	0,05 (-0,16; 0,26)	0.6111	0,09 (-0,13; 0,31)	0.4226	0,15 (-0,08; 0,39)	0.2067	-0,03 (-0,27; 0,21)	0.7853
Anti-dementias	-0,03 (-0,21; 0,15)	0.7331	0,2 (0,05; 0,35)	0.0107	-0,01 (-0,21; 0,19)	0.9103	-0,28 (-0,46; -0,1)	0.0026#	-0,09 (-0,25; 0,07)	0.2746	-0,14 (-0,32; 0,03)	0.115	-0,05 (-0,23; 0,13)	0.5658	-0,18 (-0,37; 0,02)	0.0741
Concomitant use of psychotropic medications	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anxiolytics	0,27 (0,09; 0,44)	0.0024#	-0,02 (-0,16; 0,12)	0.7414	0,14 (-0,04; 0,32)	0.1343	0,05 (-0,12; 0,22)	0.5406	-0,08 (-0,24; 0,07)	0.3039	-0,05 (-0,21; 0,11)	0.5425	0,15 (-0,03; 0,32)	0.1037	0,06 (-0,12; 0,24)	0.5201
Hypnotics and sedatives	0,08 (-0,18; 0,35)	0.5468	-0,05 (-0,27; 0,16)	0.6375	0,07 (-0,22; 0,35)	0.6492	-0,26 (-0,52; 0)	0.053	0,12 (-0,13; 0,36)	0.3429	0,06 (-0,19; 0,32)	0.6173	0,14 (-0,14; 0,41)	0.3296	0,03 (-0,25; 0,31)	0.8202

Mean dose of risperidone	0,05 (-0,05; 0,16)	0.330 3	0,07 (-0,02; 0,16)	0.121 9	-0,04 (-0,15; 0,08)	0.529 1	-0,03 (-0,14; 0,07)	0.534	0 (-0,1; 0,09)	0.946 4	-0,01 (-0,11; 0,09)	0.824 2	0 (-0,11; 0,11)	0.943 3	0,01 (-0,1; 0,12)	0.843 4
Presence of BPSD symptom at baseline (Reference: No symptom)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Psychosis	0,66 (0,55; 0,78)	<0.001#	0,46 (0,36; 0,56)	<0.001#	-0,25 (-0,38; -0,12)	<0.001#	-0,34 (-0,46; -0,22)	<0.001#	-0,08 (-0,19; 0,03)	0.1712	-0,11 (-0,22; 0,01)	0.070 7	-0,13 (-0,26; -0,01)	0.041 6	-0,14 (-0,27; -0,01)	0.038 4
Activity disturbances	0,4 (0,27; 0,54)	<0.001#	-0,12 (-0,24; -0,01)	0.034 8	0,93 (0,78; 1,08)	<0.001#	-0,43 (-0,57; -0,29)	<0.001#	-0,1 (-0,22; 0,03)	0.148 9	-0,1 (-0,23; 0,04)	0.147 9	-0,05 (-0,19; 0,1)	0.519 7	-0,05 (-0,19; 0,1)	0.532 3
Aggression	0,67 (0,53; 0,82)	<0.001#	-0,4 (-0,53; -0,28)	<0.001#	-0,18 (-0,34; -0,02)	0.027 9	0,85 (0,7; 1)	<0.001#	-0,12 (-0,26; 0,02)	0.081 2	-0,18 (-0,32; -0,03)	0.017	0 (-0,15; 0,16)	0.960 1	0,12 (-0,04; 0,28)	0.126 3
Affective disturbance	0,35 (0,25; 0,45)	<0.001#	-0,07 (-0,15; 0,01)	0.102 2	-0,25 (-0,36; -0,14)	<0.001#	-0,17 (-0,27; -0,06)	0.001 3#	-0,04 (-0,13; 0,06)	0.427 7	1,31 (1,19; 1,42)	<0.001#	-0,05 (-0,16; 0,05)	0.327 8	-0,16 (-0,27; -0,05)	0.003 1#
Sleep disturbances	0,38 (0,28; 0,48)	<0.001#	-0,13 (-0,22; -0,05)	0.001 5#	0 (-0,11; 0,11)	0.979 6	-0,23 (-0,33; -0,13)	<0.001#	1,64 (1,52; 1,75)	<0.001#	-0,04 (-0,14; 0,05)	0.374 7	-0,02 (-0,13; 0,08)	0.656 4	0,01 (-0,09; 0,12)	0.789 1
Anxieties and phobias	0,36 (0,26; 0,46)	<0.001#	-0,1 (-0,18; -0,02)	0.020 7	-0,14 (-0,25; -0,03)	0.015 5	-0,37 (-0,48; -0,27)	<0.001#	-0,01 (-0,11; 0,08)	0.783 1	0 (-0,1; 0,1)	0.979 1	0,89 (0,78; 1,01)	<0.001#	-0,05 (-0,16; 0,06)	0.378 4
BEHAVE-AD total score at baseline	-	-	0,85 (0,78; 0,91)	<0.001#	0,49 (0,41; 0,57)	<0.001#	0,7 (0,62; 0,77)	<0.001#	0,14 (0,07; 0,2)	<0.001#	0,28 (0,21; 0,35)	<0.001#	0,38 (0,3; 0,46)	<0.001#	0,42 (0,34; 0,5)	<0.001#
Number of observations	627		627		627		627		627		627		627		627	
Number of trials	5		5		5		5		5		5		5		5	
8-WEEK OUTCOME																
Early reduction in rating score																

BEHAVE-AD total score	-0,08 (-0,09; -0,08)	<0.001#	-	-	-	-	-	-	-	-	-	-	-	-	-	-
BEHAVE-AD Psychosis subscale score	-	-	-0,2 (-0,21; -0,19)	<0.001#	-	-	-	-	-	-	-	-	-	-	-	-
BEHAVE-AD activity disturbances subscale	-	-	-	-	-0,31 (-0,35; -0,28)	<0.001#	-	-	-	-	-	-	-	-	-	-
BEHAVE-AD Aggression subscale score	-	-	-	-	-	-	-0,27 (-0,29; -0,25)	<0.001#	-	-	-	-	-	-	-	-
BEHAVE-AD sleep disturbance subscale	-	-	-	-	-	-	-	-	-0,99 (-1,07; -0,92)	<0.001#	-	-	-	-	-	-
BEHAVE-AD affective disturbance subscale	-	-	-	-	-	-	-	-	-	-	-0,6 (-0,65; -0,54)	<0.001#	-	-	-	-
BEHAVE-AD anxieties and phobias subscale	-	-	-	-	-	-	-	-	-	-	-	-	-0,34 (-0,37; -0,3)	<0.001#	-	-
BEHAVE-AD Global rating subscale score	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0,77 (-0,83; -0,71)	<0.001#
Age	0 (-0,01; 0,01)	0.63	0 (0; 0,01)	0.1533	-0,01 (-0,01; 0)	0.2063	-0,01 (-0,02; 0)	0.0357	0 (-0,01; 0,01)	0.8691	-0,01 (-0,01; 0)	0.0809	0,01 (0; 0,01)	0.0839	0 (-0,01; 0)	0.2475
Male (Reference: Female)	0 (-0,12; 0,13)	0.9473	-0,06 (-0,16; 0,04)	0.2398	0,05 (-0,09; 0,18)	0.4761	0,11 (0; 0,23)	0.0552	0,11 (0; 0,23)	0.0553	-0,14 (-0,26; -0,03)	0.0153	0,01 (-0,12; 0,13)	0.9214	-0,01 (-0,14; 0,11)	0.843
BMI	-0,01 (-0,02; 0)	0.0668	0 (-0,01; 0,01)	0.9681	0 (-0,01; 0,02)	0.6385	0,01 (-0,01; 0,02)	0.3548	0 (-0,01; 0,01)	0.6439	-0,01 (-0,02; 0)	0.171	-0,01 (-0,03; 0)	0.0224	0 (-0,01; 0,01)	0.665

MMSE	-0,01 (-0,02; -0,01)	0.002 1[#]	0,02 (0,01; 0,03)	<0.001[#]	-0,01 (-0,02; 0)	0.0046	-0,03 (-0,04; -0,02)	<0.001[#]	-0,01 (-0,02; 0)	0.0843	0 (-0,01; 0,01)	0.7703	0,02 (0,01; 0,03)	<0.001[#]	-0,01 (-0,02; 0)	0.0091
Use of psychotropic medications at baseline	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anxiolytics	-0,15 (-0,46; 0,16)	0.3347	-0,09 (-0,34; 0,16)	0.4716	-0,39 (-0,72; -0,05)	0.0253	0,08 (-0,22; 0,37)	0.6066	0,01 (-0,29; 0,3)	0.9632	0,27 (-0,03; 0,56)	0.0745	-0,01 (-0,33; 0,31)	0.9443	-0,17 (-0,48; 0,14)	0.2944
Hypnotic and sedatives	0 (-0,33; 0,33)	0.9895	0,04 (-0,23; 0,31)	0.7518	0,03 (-0,33; 0,4)	0.853	0,37 (0,06; 0,69)	0.0211	0,02 (-0,29; 0,34)	0.8818	0,09 (-0,23; 0,41)	0.5799	-0,1 (-0,45; 0,24)	0.5541	-0,06 (-0,39; 0,28)	0.7446
Antidepressants	0,02 (-0,23; 0,26)	0.9046	-0,05 (-0,25; 0,15)	0.6402	-0,18 (-0,46; 0,09)	0.1899	-0,09 (-0,33; 0,15)	0.4555	0,04 (-0,19; 0,28)	0.7248	-0,05 (-0,29; 0,18)	0.6653	0,14 (-0,12; 0,4)	0.2888	-0,09 (-0,34; 0,16)	0.4984
Anti-dementias	-0,02 (-0,21; 0,18)	0.8681	0,24 (0,08; 0,4)	0.0041	-0,01 (-0,23; 0,21)	0.9306	-0,31 (-0,5; -0,13)	<0.001[#]	-0,08 (-0,27; 0,1)	0.3669	-0,11 (-0,3; 0,09)	0.2798	-0,04 (-0,25; 0,17)	0.7176	-0,15 (-0,35; 0,05)	0.1401
Concomitant use of psychotropic medications	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anxiolytics	0,23 (0,05; 0,41)	0.0128	-0,05 (-0,19; 0,1)	0.5451	0,18 (-0,02; 0,38)	0.0836	0,04 (-0,13; 0,21)	0.6445	-0,04 (-0,21; 0,13)	0.6571	-0,04 (-0,22; 0,14)	0.657	0,24 (0,05; 0,43)	0.0141	0,11 (-0,07; 0,3)	0.2248
Hypnotics and sedatives	0,09 (-0,17; 0,34)	0.4934	0,08 (-0,13; 0,28)	0.4513	0 (-0,28; 0,28)	0.9927	-0,35 (-0,59; -0,11)	0.0051	0,13 (-0,12; 0,37)	0.3034	-0,06 (-0,31; 0,18)	0.6007	0,06 (-0,2; 0,33)	0.6473	0,03 (-0,23; 0,29)	0.8343
Mean dose of risperidone	0,03 (-0,08; 0,14)	0.557	0,05 (-0,04; 0,14)	0.249	-0,09 (-0,2; 0,03)	0.161	-0,1 (-0,2; 0)	0.0594	-0,01 (-0,11; 0,1)	0.8827	-0,06 (-0,16; 0,05)	0.2933	0,04 (-0,07; 0,15)	0.4721	-0,05 (-0,16; 0,06)	0.3629
Presence of BPSD symptom at baseline (Reference: No symptom)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Psychosis	0,64 (0,51; 0,76)	<0.001[#]	0,49 (0,38; 0,6)	<0.001[#]	-0,25 (-0,4; -0,1)	0.0011[#]	-0,38 (-0,51; -0,25)	<0.001[#]	-0,1 (-0,22; 0,03)	0.147	-0,14 (-0,27; -0,01)	0.0351	-0,1 (-0,24; 0,05)	0.1853	-0,13 (-0,26; 0,01)	0.0699

Activity disturbances	0,42 (0,26; 0,57)	<0.001[#]	-0,04 (-0,17; 0,09)	0.5213	0,91 (0,73; 1,09)	<0.001[#]	-0,49 (-0,65; -0,34)	<0.001[#]	-0,06 (-0,21; 0,09)	0.4344	-0,09 (-0,24; 0,06)	0.2464	-0,07 (-0,24; 0,09)	0.3948	-0,04 (-0,2; 0,12)	0.6153
Aggression	0,6 (0,44; 0,76)	<0.001[#]	-0,41 (-0,54; -0,27)	<0.001[#]	-0,16 (-0,34; 0,03)	0.0913	0,86 (0,7; 1,03)	<0.001[#]	-0,12 (-0,29; 0,04)	0.1312	-0,22 (-0,38; -0,06)	0.0081	0,06 (-0,12; 0,23)	0.5156	0,16 (-0,01; 0,33)	0.0687
Affective disturbance	0,36 (0,26; 0,47)	<0.001[#]	-0,07 (-0,16; 0,02)	0.1262	-0,3 (-0,43; -0,18)	<0.001[#]	-0,21 (-0,32; -0,1)	<0.001[#]	0 (-0,11; 0,11)	0.9551	1,33 (1,2; 1,45)	<0.001[#]	0,03 (-0,08; 0,15)	0.585	-0,16 (-0,28; -0,05)	0.005
Sleep disturbances	0,35 (0,24; 0,46)	<0.001[#]	-0,15 (-0,24; -0,05)	0.001 7[#]	0,02 (-0,11; 0,14)	0.8129	-0,25 (-0,36; -0,14)	<0.001[#]	1,72 (1,58; 1,85)	<0.001[#]	-0,02 (-0,13; 0,09)	0.6982	-0,04 (-0,16; 0,07)	0.4598	0,02 (-0,09; 0,14)	0.7082
Anxieties and phobias	0,36 (0,25; 0,47)	<0.001[#]	-0,09 (-0,18; 0)	0.062	-0,1 (-0,23; 0,02)	0.104	-0,38 (-0,49; -0,27)	<0.001[#]	-0,06 (-0,17; 0,05)	0.2654	0 (-0,11; 0,1)	0.9337	0,92 (0,79; 1,04)	<0.001[#]	-0,03 (-0,15; 0,08)	0.5526
BEHAVE-AD total score at baseline	-	-	0,81 (0,74; 0,88)	<0.001[#]	0,51 (0,41; 0,6)	<0.001[#]	0,73 (0,65; 0,81)	<0.001[#]	0,11 (0,03; 0,19)	0.0049	0,29 (0,21; 0,37)	<0.001[#]	0,37 (0,28; 0,46)	<0.001[#]	0,37 (0,28; 0,45)	<0.001[#]
Number of observations	541		541		541		541		541		541		541		539	
Number of trials	4		4		4		4		4		4		4		4	

BEHAVE-AD, Behavioural pathology in Alzheimer's disease; SMD, Standardised mean difference; BPSD, Behaviours and psychological symptoms of dementia

[#]Values are significant results after Bonferroni correction (p value <0.05/44 = 0.00113)

Supplementary Table S7. Full mixed-effect linear regression models of Dataset B in all outcomes

Predictors of BEHAVE-AD total score and its components	BEHAVE-AD total score		Psychosis		Activity disturbances		Aggressiveness		Sleep disturbances		Affective disturbances		Anxieties and phobias		Global rating	
	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p
4-WEEK OUTCOME																
Early reduction in rating score																
BEHAVE-AD total score	-0,09 (-0,1; -0,08)	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-
BEHAVE-AD Psychosis subscale score	-	-	-0,2 (-0,21; -0,19)	0	-	-	-	-	-	-	-	-	-	-	-	-
BEHAVE-AD activity disturbances subscale	-	-	-	-	-0,32 (-0,36; -0,29)	0	-	-	-	-	-	-	-	-	-	-
BEHAVE-AD Aggression subscale score	-	-	-	-	-	-	-0,26 (-0,28; -0,24)	0	-	-	-	-	-	-	-	-
BEHAVE-AD sleep disturbance subscale	-	-	-	-	-	-	-	-	-0,96 (-1,02; -0,89)	0	-	-	-	-	-	-
BEHAVE-AD affective disturbance subscale	-	-	-	-	-	-	-	-	-	-	-0,58 (-0,64; -0,53)	0	-	-	-	-
BEHAVE-AD anxieties and phobias subscale	-	-	-	-	-	-	-	-	-	-	-	-	-0,33 (-0,37; -0,29)	0	-	-
BEHAVE-AD Global rating subscale score	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0,77 (-0,84; -0,71)	0
Age	0 (-0,01; 0)	0.2559	0 (-0,01; 0,01)	0.7169	0 (-0,01; 0,01)	0.6535	-0,01 (-0,02; 0)	0.0431	0 (-0,01; 0,01)	0.7605	-0,01 (-0,01; 0)	0.1072	0 (0; 0,01)	0.3112	-0,01 (-0,01; 0)	0.1361

Male (Reference: Female)	-0,02 (-0,15; 0,11)	0.751 6	-0,07 (-0,17; 0,03)	0.188 9	0,14 (0,01; 0,27)	0.031 5	0,09 (-0,03; 0,22)	0.137 7	0,05 (-0,07; 0,16)	0.422 8	-0,21 (-0,33; -0,09)	<0.001	-0,02 (-0,16; 0,11)	0.723 2	-0,02 (-0,15; 0,11)	0.791
BMI (kg/m2)	-0,01 (-0,02; 0,01)	0.345 5	0,01 (0; 0,02)	0.158 8	0 (-0,01; 0,02)	0.536 5	0 (-0,01; 0,01)	0.989 4	0 (-0,01; 0,01)	0.603	0 (-0,01; 0,01)	0.839 5	-0,01 (-0,02; 0,01)	0.389 8	0,01 (-0,01; 0,02)	0.258 7
MMSE	-0,02 (-0,03; -0,01)	<0.001	0,02 (0,01; 0,02)	0	-0,01 (-0,02; -0,01)	0.002	-0,03 (-0,03; -0,02)	0	-0,01 (-0,02; 0)	0.083	0 (-0,01; 0,01)	0.754 6	0,02 (0,01; 0,03)	0	-0,01 (-0,02; 0)	0.002 4
Use of psychotropic medications at baseline	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anxiolytics	-0,11 (-0,46; 0,24)	0.539 5	-0,14 (-0,42; 0,14)	0.322 7	-0,23 (-0,57; 0,12)	0.192	0,08 (-0,26; 0,42)	0.636 9	0,05 (-0,25; 0,36)	0.728 7	0,06 (-0,26; 0,39)	0.703 6	0,07 (-0,29; 0,43)	0.704 5	-0,23 (-0,59; 0,13)	0.206 8
Hypnotic and sedatives	0,08 (-0,34; 0,5)	0.706 4	0,17 (-0,16; 0,51)	0.309 7	0,18 (-0,24; 0,59)	0.404 3	0,1 (-0,31; 0,5)	0.639 6	-0,11 (-0,48; 0,26)	0.548 8	0,02 (-0,38; 0,41)	0.932 2	-0,09 (-0,53; 0,34)	0.675 4	0,23 (-0,2; 0,66)	0.296 3
Antidepressants	-0,03 (-0,27; 0,22)	0.836 5	-0,01 (-0,21; 0,19)	0.908 7	-0,08 (-0,33; 0,16)	0.502 9	-0,01 (-0,24; 0,23)	0.966 4	0,03 (-0,18; 0,25)	0.760 1	0,14 (-0,09; 0,37)	0.237 5	0,12 (-0,13; 0,37)	0.355 1	-0,01 (-0,27; 0,24)	0.920 8
Anti-dementias	-0,03 (-0,22; 0,16)	0.757 9	0,2 (0,05; 0,36)	0.011 6	0,04 (-0,15; 0,23)	0.657 2	-0,27 (-0,46; -0,09)	0.003 9	-0,08 (-0,25; 0,09)	0.349 9	-0,13 (-0,32; 0,05)	0.163 3	-0,12 (-0,32; 0,08)	0.233	-0,21 (-0,41; -0,01)	0.039 8
Concomitant use of psychotropic medications	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anxiolytics	0,25 (0,04; 0,46)	0.019 3	0,06 (-0,11; 0,22)	0.520 2	0,04 (-0,17; 0,25)	0.710 2	0,06 (-0,15; 0,26)	0.581 6	-0,04 (-0,23; 0,14)	0.661 3	-0,04 (-0,24; 0,16)	0.662 8	0,09 (-0,13; 0,31)	0.414	0,09 (-0,13; 0,3)	0.443 4
Hypnotics and sedatives	0,02 (-0,28; 0,33)	0.872 5	-0,03 (-0,28; 0,21)	0.783 2	-0,01 (-0,31; 0,3)	0.966 8	-0,33 (-0,62; -0,03)	0.030 8	0,12 (-0,15; 0,39)	0.388	0,1 (-0,19; 0,39)	0.492 7	0,18 (-0,14; 0,49)	0.275 1	-0,09 (-0,4; 0,23)	0.588 7
	0,04 (-0,08; 0,16)	0.524 6	0,06 (-0,04; 0,15)	0.218 6	-0,07 (-0,19; 0,04)	0.217 7	0 (-0,11; 0,11)	0.989 9	0,03 (-0,08; 0,13)	0.614 4	-0,01 (-0,12; 0,1)	0.835 5	-0,02 (-0,14; 0,1)	0.733 4	0 (-0,12; 0,12)	0.962 2
Mean dose of risperidone																

Presence of BPSD symptom at baseline (Reference: No symptom)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Psychosis	0,69 (0,56; 0,81)	0	0,44 (0,32; 0,56)	0	-0,27 (-0,41; -0,13)	<0.001	-0,32 (-0,45; -0,18)	0	-0,07 (-0,2; 0,05)	0.264	-0,13 (-0,26; 0,01)	0.0629	-0,1 (-0,25; 0,04)	0.1742	-0,15 (-0,29; 0)	0.04745
Activity disturbances	0,36 (0,2; 0,51)	0	-0,14 (-0,26; -0,01)	0.0348	0,85 (0,69; 1,01)	0	-0,41 (-0,56; -0,25)	0	-0,05 (-0,19; 0,09)	0.4522	-0,08 (-0,23; 0,07)	0.3131	-0,02 (-0,18; 0,15)	0.8443	-0,08 (-0,24; 0,09)	0.36111
Aggression	0,62 (0,46; 0,78)	0	-0,43 (-0,56; -0,29)	0	-0,19 (-0,36; -0,02)	0.026	0,81 (0,65; 0,98)	0	-0,14 (-0,29; 0,01)	0.0722	-0,17 (-0,33; -0,01)	0.037	0,03 (-0,15; 0,2)	0.7759	0,12 (-0,05; 0,3)	0.17224
Affective disturbance	0,34 (0,23; 0,45)	0	-0,11 (-0,21; -0,02)	0.0189	-0,24 (-0,35; -0,12)	<0.001	-0,17 (-0,28; -0,05)	0.0036	-0,04 (-0,15; 0,06)	0.3957	1,37 (1,24; 1,5)	0	-0,05 (-0,17; 0,07)	0.4336	-0,17 (-0,29; -0,06)	0.00422
Sleep disturbances	0,45 (0,34; 0,57)	0	-0,13 (-0,23; -0,03)	0.0081	0,05 (-0,07; 0,17)	0.4368	-0,24 (-0,35; -0,12)	<0.001	1,65 (1,53; 1,78)	0	-0,07 (-0,19; 0,04)	0.2021	-0,06 (-0,18; 0,07)	0.3849	-0,02 (-0,14; 0,11)	0.799
Anxieties and phobias	0,37 (0,25; 0,48)	0	-0,1 (-0,2; -0,01)	0.0326	-0,16 (-0,28; -0,04)	0.0075	-0,38 (-0,49; -0,26)	0	0 (-0,11; 0,1)	0.9366	0 (-0,12; 0,11)	0.9356	0,92 (0,79; 1,06)	0	-0,07 (-0,19; 0,06)	0.28119
Race (Reference: Caucasian)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Black	-0,17 (-0,41; 0,07)	0.1631	-0,06 (-0,25; 0,13)	0.545	-0,1 (-0,34; 0,13)	0.3854	-0,06 (-0,29; 0,17)	0.6043	0,12 (-0,1; 0,33)	0.2787	0,13 (-0,1; 0,36)	0.2588	0,14 (-0,11; 0,38)	0.2827	-0,18 (-0,43; 0,07)	0.15555
Other	-0,01 (-0,19; 0,17)	0.891	0,01 (-0,14; 0,15)	0.9363	-0,12 (-0,29; 0,06)	0.2052	0,01 (-0,17; 0,18)	0.9231	0,01 (-0,15; 0,17)	0.9353	0,02 (-0,15; 0,19)	0.8081	0,08 (-0,11; 0,27)	0.3971	-0,01 (-0,2; 0,18)	0.9222
Any currently active diseases at baseline (Reference: No disease)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cardiovascular disease	-0,01 (-0,14; 0,13)	0.927 9	-0,04 (-0,14; 0,07)	0.4817	-0,07 (-0,21; 0,06)	0.264	0,03 (-0,1; 0,15)	0.7016	0,01 (-0,1; 0,13)	0.828	-0,12 (-0,24; 0)	0.0581	0,08 (-0,06; 0,21)	0.2748	0,06 (-0,07; 0,2)	0.3666

Endocrine disease	-0,07 (-0,18; 0,05)	0.271	-0,04 (-0,13; 0,06)	0.436 4	-0,11 (-0,23; 0)	0.056 7	0,09 (-0,02; 0,2)	0.126 1	0,01 (-0,09; 0,12)	0.786 3	0 (-0,11; 0,11)	0.965 7	0,09 (-0,03; 0,21)	0.153 3	0,06 (-0,06; 0,18)	0.312 1
Neurological disease	0,07 (-0,05; 0,19)	0.258 2	-0,05 (-0,14; 0,04)	0.297 8	-0,02 (-0,14; 0,1)	0.747 1	0,1 (-0,01; 0,21)	0.082 7	0,07 (-0,03; 0,18)	0.174 7	-0,03 (-0,14; 0,08)	0.615 8	-0,02 (-0,14; 0,1)	0.744 3	-0,01 (-0,13; 0,11)	0.865 8
Dementia diagnosis (Reference: Alzheimer's disease)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vascular dementia	-0,05 (-0,28; 0,17)	0.641 9	-0,01 (-0,19; 0,17)	0.910 3	-0,08 (-0,3; 0,14)	0.473 5	-0,08 (-0,3; 0,14)	0.472	0,05 (-0,15; 0,25)	0.622 6	0,16 (-0,05; 0,38)	0.128 5	0,19 (-0,05; 0,42)	0.114 3	-0,05 (-0,28; 0,19)	0.698 4
Mixed type dementia	0,1 (-0,05; 0,26)	0.196 5	0,1 (-0,03; 0,23)	0.129 9	-0,11 (-0,27; 0,05)	0.178 3	-0,01 (-0,17; 0,14)	0.867 8	-0,08 (-0,22; 0,06)	0.247 7	0,01 (-0,14; 0,16)	0.849 6	-0,02 (-0,18; 0,15)	0.846 5	-0,06 (-0,22; 0,11)	0.492 9
eGFR (ml/min)	0 (0; 0)	0.861 9	0 (0; 0)	0.788 2	0 (0; 0)	0.505 9	0 (-0,01; 0)	0.038 1	0 (0; 0)	0.256	0 (0; 0,01)	0.194	0 (0; 0)	0.978 7	0 (0; 0)	0.874 8
BEHAVE-AD total score at baseline	-	-	0,86 (0,79; 0,93)	0	0,48 (0,39; 0,56)	0	0,7 (0,61; 0,79)	0	0,11 (0,03; 0,18)	0.059	0,29 (0,21; 0,37)	0	0,39 (0,3; 0,48)	0	0,44 (0,35; 0,52)	0
Number of observations	523		523		523		523		523		523		523		523	
Number of trials	2		2		2		2		2		2		2		2	
8-WEEK OUTCOME																
Early reduction in rating score																
BEHAVE-AD total score	-0,09 (-0,09; -0,08)	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-
BEHAVE-AD Psychosis subscale score	-	-	-0,2 (-0,21; -0,18)	0	-	-	-	-	-	-	-	-	-	-	-	-
BEHAVE-AD activity disturbances subscale	-	-	-	-	-0,33 (-0,37; -0,29)	0	-	-	-	-	-	-	-	-	-	-

BEHAVE-AD Aggression subscale score	-	-	-	-	-	-	-0,27 (-0,29; -0,25)	0	-	-	-	-	-	-	-	-
BEHAVE-AD sleep disturbance subscale	-	-	-	-	-	-	-	-	-1,01 (-1,09; -0,94)	0	-	-	-	-	-	-
BEHAVE-AD affective disturbance subscale	-	-	-	-	-	-	-	-	-	-	-0,58 (-0,64; -0,52)	0	-	-	-	-
BEHAVE-AD anxieties and phobias subscale	-	-	-	-	-	-	-	-	-	-	-	-	-0,34 (-0,38; -0,3)	0	-	-
BEHAVE-AD Global rating subscale score	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0,78 (-0,85; -0,71)	0
Age	0 (-0,01; 0,01)	0.467	0 (0; 0,01)	0.2942	0 (-0,01; 0,01)	0.7992	-0,01 (-0,02; 0)	0.064	0 (0; 0,01)	0.4113	-0,01 (-0,01; 0)	0.2201	0,01 (0; 0,02)	0.1059	0 (-0,01; 0,01)	0.371
Male (Reference: Female)	0,02 (-0,12; 0,16)	0.7583	-0,09 (-0,19; 0,02)	0.1242	0,11 (-0,04; 0,26)	0.1413	0,12 (-0,01; 0,25)	0.073	0,07 (-0,06; 0,19)	0.313	-0,16 (-0,29; -0,03)	0.0175	0 (-0,14; 0,15)	0.9591	0,02 (-0,12; 0,16)	0.7962
BMI (kg/m2)	-0,01 (-0,02; 0)	0.0894	0 (-0,01; 0,01)	0.6139	0,01 (-0,01; 0,02)	0.4414	0 (-0,01; 0,01)	0.9532	0 (-0,01; 0,01)	0.8847	-0,01 (-0,02; 0,01)	0.3441	-0,01 (-0,03; 0)	0.0757	0 (-0,01; 0,02)	0.65529
MMSE	-0,02 (-0,03; -0,01)	<0.001	0,02 (0,01; 0,03)	0	-0,02 (-0,03; -0,01)	0.0032	-0,03 (-0,04; -0,02)	0	-0,01 (-0,02; 0)	0.0449	0 (-0,01; 0,01)	0.7959	0,02 (0,01; 0,03)	0	-0,01 (-0,02; 0)	0.0581
Use of psychotropic medications at baseline	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anxiolytics	-0,15 (-0,53; 0,24)	0.456	-0,14 (-0,45; 0,16)	0.3588	-0,23 (-0,64; 0,19)	0.2809	0,04 (-0,33; 0,41)	0.8479	0,03 (-0,33; 0,39)	0.8621	-0,01 (-0,36; 0,35)	0.9712	0,06 (-0,34; 0,47)	0.7544	-0,15 (-0,55; 0,24)	0.4521
Hypnotic and sedatives	0,18 (-0,24; 0,59)	0.4048	0,16 (-0,17; 0,49)	0.3471	0,23 (-0,21; 0,68)	0.3054	0,14 (-0,26; 0,54)	0.5037	-0,16 (-0,54; 0,23)	0.4222	0,15 (-0,24; 0,54)	0.4473	0 (-0,43; 0,44)	0.9889	0,06 (-0,37; 0,49)	0.7803

Antidepressants	-0,02 (-0,28; 0,24)	0.865	-0,01 (-0,21; 0,2)	0.9587	-0,19 (-0,47; 0,08)	0.1691	-0,08 (-0,33; 0,17)	0.5492	0,02 (-0,22; 0,26)	0.8721	0,04 (-0,21; 0,28)	0.7718	0,09 (-0,18; 0,36)	0.5255	-0,08 (-0,34; 0,19)	0.5849
Anti-dementias	-0,01 (-0,22; 0,19)	0.8895	0,25 (0,08; 0,41)	0.003	0,01 (-0,21; 0,23)	0.9096	-0,26 (-0,46; -0,06)	0.0096	-0,06 (-0,25; 0,13)	0.5524	-0,07 (-0,26; 0,13)	0.4982	-0,13 (-0,34; 0,08)	0.2358	-0,14 (-0,36; 0,08)	0.1995
Concomitant use of psychotropic medications	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anxiolytics	0,2 (-0,02; 0,42)	0.074	0,03 (-0,15; 0,2)	0.7681	0,05 (-0,19; 0,29)	0.6721	0,04 (-0,18; 0,25)	0.7369	-0,06 (-0,26; 0,15)	0.5884	-0,03 (-0,24; 0,18)	0.7707	0,24 (0,01; 0,47)	0.0445	0,09 (-0,15; 0,32)	0.4691
Hypnotics and sedatives	0,1 (-0,18; 0,37)	0.4998	0,11 (-0,11; 0,33)	0.3386	0,05 (-0,25; 0,35)	0.7441	-0,37 (-0,63; -0,1)	0.0075	0,17 (-0,09; 0,43)	0.1906	-0,03 (-0,29; 0,23)	0.8329	0,05 (-0,24; 0,34)	0.7162	-0,05 (-0,34; 0,24)	0.7227
Mean dose of risperidone	0,03 (-0,09; 0,14)	0.6253	0,04 (-0,05; 0,14)	0.3469	-0,09 (-0,21; 0,03)	0.1555	-0,07 (-0,19; 0,04)	0.1913	0,02 (-0,09; 0,12)	0.7754	-0,04 (-0,15; 0,07)	0.4432	0,04 (-0,08; 0,16)	0.5592	-0,05 (-0,17; 0,07)	0.4326
Presence of BPSD symptom at baseline (Reference: No symptom)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Psychosis	0,65 (0,51; 0,79)	0	0,46 (0,34; 0,58)	0	-0,24 (-0,4; -0,08)	0.004	-0,36 (-0,5; -0,21)	0	-0,11 (-0,25; 0,02)	0.105	-0,17 (-0,32; -0,03)	0.0155	-0,08 (-0,23; 0,08)	0.3366	-0,12 (-0,27; 0,04)	0.1476
Activity disturbances	0,37 (0,2; 0,54)	0	-0,08 (-0,21; 0,06)	0.2651	0,88 (0,69; 1,07)	0	-0,46 (-0,63; -0,3)	0	-0,03 (-0,19; 0,13)	0.7509	-0,08 (-0,24; 0,08)	0.3247	-0,06 (-0,24; 0,12)	0.5017	-0,03 (-0,21; 0,15)	0.7419
Aggression	0,57 (0,4; 0,74)	0	-0,44 (-0,58; -0,29)	0	-0,16 (-0,36; 0,03)	0.0965	0,84 (0,66; 1,01)	0	-0,12 (-0,29; 0,05)	0.1574	-0,18 (-0,35; -0,02)	0.032	0,08 (-0,11; 0,26)	0.4192	0,15 (-0,04; 0,33)	0.1224
Affective disturbance	0,37 (0,25; 0,49)	0	-0,09 (-0,19; 0,01)	0.0634	-0,28 (-0,41; -0,14)	<0.001	-0,22 (-0,34; -0,1)	<0.001	-0,01 (-0,12; 0,11)	0.9276	1,38 (1,24; 1,51)	0	0,07 (-0,06; 0,2)	0.3161	-0,19 (-0,32; -0,07)	0.0032
Sleep disturbances	0,4 (0,28; 0,53)	0	-0,13 (-0,23; -0,03)	0.0118	0,01 (-0,12; 0,15)	0.8542	-0,28 (-0,41; -0,16)	0	1,71 (1,57; 1,86)	0	-0,02 (-0,14; 0,1)	0.702	-0,07 (-0,21; 0,06)	0.2908	0,01 (-0,12; 0,14)	0.8641

Anxieties and phobias	0,37 (0,25; 0,49)	0	-0,09 (-0,19; 0,01)	0.078 7	-0,12 (-0,25; 0,02)	0.086 8	-0,4 (-0,52; -0,28)	0	-0,06 (-0,18; 0,05)	0.275 7	0 (-0,12; 0,12)	0.975 3	0,93 (0,78; 1,07)	0	-0,03 (-0,16; 0,1)	0.692 7
Race (Reference: Caucasian)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Black	-0,13 (-0,39; 0,12)	0.299 4	-0,08 (-0,28; 0,13)	0.458 1	-0,08 (-0,35; 0,19)	0.573 3	0 (-0,25; 0,24)	0.977 3	0,2 (-0,04; 0,44)	0.101 1	0,13 (-0,11; 0,37)	0.298 4	0,19 (-0,07; 0,46)	0.157 8	-0,19 (-0,46; 0,07)	0.149 7
Other	-0,03 (-0,22; 0,16)	0.751 8	0 (-0,15; 0,15)	0.996 6	-0,11 (-0,31; 0,1)	0.302 7	0,01 (-0,17; 0,19)	0.934 2	-0,02 (-0,19; 0,16)	0.864 4	0,02 (-0,16; 0,19)	0.852 9	0,07 (-0,13; 0,26)	0.492 5	0 (-0,19; 0,19)	0.991 7
Any currently active diseases at baseline (Reference: No disease)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cardiovascular disease	-0,05 (-0,19; 0,09)	0.485 4	-0,08 (-0,19; 0,03)	0.145 7	-0,12 (-0,27; 0,03)	0.123 3	0,07 (-0,07; 0,2)	0.341 6	-0,06 (-0,19; 0,07)	0.387 2	-0,07 (-0,21; 0,06)	0.262	-0,06 (-0,21; 0,08)	0.401 7	0,06 (-0,08; 0,21)	0.391 6
Endocrine disease	-0,03 (-0,15; 0,09)	0.639 4	-0,01 (-0,11; 0,09)	0.881 2	-0,08 (-0,21; 0,05)	0.245	0,11 (-0,01; 0,23)	0.065	0,02 (-0,09; 0,14)	0.677 2	-0,03 (-0,15; 0,08)	0.568 8	0,11 (-0,02; 0,24)	0.089 4	0,06 (-0,07; 0,19)	0.335 8
Neurological disease	0,04 (-0,08; 0,17)	0.491 5	-0,08 (-0,18; 0,02)	0.1	-0,02 (-0,16; 0,11)	0.736 5	0,07 (-0,05; 0,19)	0.283 4	0,03 (-0,09; 0,15)	0.617 6	-0,01 (-0,12; 0,11)	0.919 5	-0,09 (-0,23; 0,04)	0.155 5	-0,05 (-0,18; 0,08)	0.486 9
Dementia diagnosis (Reference: Alzheimer's disease)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vascular dementia	-0,11 (-0,35; 0,13)	0.373 9	0 (-0,19; 0,19)	0.990 6	-0,06 (-0,32; 0,2)	0.631 3	-0,07 (-0,3; 0,16)	0.548 9	0,02 (-0,21; 0,24)	0.879 6	0,06 (-0,17; 0,29)	0.594 2	0,07 (-0,18; 0,32)	0.583 2	0,04 (-0,22; 0,29)	0.784 5
Mixed type dementia	0,17 (0; 0,34)	0.051 5	0,15 (0,01; 0,28)	0.034	-0,06 (-0,24; 0,12)	0.515 9	0,07 (-0,1; 0,23)	0.416 2	-0,1 (-0,25; 0,06)	0.236 1	-0,05 (-0,21; 0,11)	0.544 4	0,04 (-0,14; 0,22)	0.642 7	0 (-0,17; 0,18)	0.956 7
eGFR (ml/min)	0 (0; 0)	0.777 9	0 (0; 0)	0.780 8	0 (0; 0,01)	0.503 3	0 (-0,01; 0)	0.349 9	0 (0; 0)	0.362	0 (0; 0,01)	0.066 1	0 (0; 0)	0.578 9	0 (0; 0)	0.783 8

BEHAVE-AD total score at baseline	-	-	0,82 (0,75; 0,9)	0	0,49 (0,4; 0,59)	0	0,75 (0,66; 0,84)	0	0,1 (0,02; 0,18)	0.018 2	0,29 (0,21; 0,37)	0	0,39 (0,29; 0,48)	0	0,38 (0,29; 0,48)	0
Number of observations	465		465		465		465		465		465		465		463	
Number of trials	2		2		2		2		2		2		2		2	

BEHAVE-AD, Behavioural pathology in Alzheimer's disease; SMD, Standardised mean difference; BPSD, Behaviours and psychological symptoms of dementia

[#]Values are significant results after Bonferroni correction (p value <0.05/44 = 0.00113)

Supplementary Table S8_Linear regression models for baseline variables in Dataset A (Full)

Predictors of BPSD score	BEHAVE-AD total score		Psychosis		Activity disturbances		Aggressiveness		Sleep disturbances		Affective disturbances		Anxieties and phobias		Global rating	
	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p
4-WEEK OUTCOME																
Age	-0,01 (-0,01; 0)	0,2081	-0,01 (-0,02; 0)	0,1329	-0,01 (-0,02; 0)	0,0408	0 (-0,01; 0,01)	0,8886	0 (-0,01; 0,01)	0,7457	0 (-0,01; 0,01)	0,878	0 (-0,01; 0,01)	0,5511	0 (-0,01; 0,01)	0,904
Male (Reference: Female)	0,02 (-0,12; 0,15)	0,7977	-0,01 (-0,16; 0,13)	0,8397	0,15 (0,01; 0,3)	0,0406	0,06 (-0,09; 0,21)	0,4258	0,19 (0,04; 0,34)	0,0136	-0,18 (-0,32; -0,04)	0,0128	-0,12 (-0,25; 0,02)	0,0964	-0,05 (-0,2; 0,11)	0,5653
BMI	0,01 (0; 0,02)	0,1171	0,01 (0; 0,02)	0,1661	0 (-0,01; 0,02)	0,8828	0,01 (-0,01; 0,02)	0,243	0,02 (0,01; 0,04)	0,0059	0,01 (-0,01; 0,02)	0,313	0 (-0,01; 0,01)	0,9079	0,01 (-0,01; 0,02)	0,306
MMSE	0 (-0,01; 0,01)	0,8675	0,01 (0; 0,03)	0,0043	-0,01 (-0,02; 0)	0,0116	-0,02 (-0,03; -0,01)	<0.001#	0 (-0,01; 0,01)	0,7903	0 (-0,01; 0,01)	0,6107	0,02 (0,01; 0,03)	0,0029	-0,01 (-0,02; 0)	0,0404
Use of psychotropic medications at baseline																
Anxiolytics	-0,05 (-0,32; 0,21)	0,6858	-0,18 (-0,45; 0,1)	0,2056	-0,07 (-0,35; 0,22)	0,6452	0,08 (-0,21; 0,37)	0,6089	-0,01 (-0,31; 0,29)	0,9567	0,1 (-0,18; 0,37)	0,4952	0,06 (-0,21; 0,33)	0,6542	-0,11 (-0,41; 0,2)	0,4974
Hypnotic and sedatives	0,13 (-0,08; 0,35)	0,2349	0,03 (-0,19; 0,26)	0,7733	0,15 (-0,07; 0,38)	0,1855	0,15 (-0,08; 0,39)	0,1924	0,18 (-0,06; 0,41)	0,145	0,04 (-0,18; 0,26)	0,7038	0,09 (-0,12; 0,31)	0,4053	0,19 (-0,06; 0,44)	0,1297

Antidepressants	0,03 (-0,26; 0,32)	0,828	0,07 (-0,23; 0,37)	0,6306	-0,22 (-0,53; 0,08)	0,1543	0,07 (-0,24; 0,39)	0,6498	-0,16 (-0,49; 0,16)	0,323	0,31 (0,01; 0,61)	0,041	0,01 (-0,28; 0,3)	0,9409	-0,01 (-0,34; 0,32)	0,962
Anti-dementias	-0,08 (-0,33; 0,16)	0,5021	0,13 (-0,12; 0,39)	0,316	-0,02 (-0,28; 0,24)	0,866	-0,3 (-0,57; -0,04)	0,025	-0,08 (-0,36; 0,19)	0,545	-0,09 (-0,34; 0,17)	0,518	-0,11 (-0,36; 0,13)	0,369	-0,16 (-0,45; 0,12)	0,262
Presence of BPSD symptom at baseline (Reference: No symptom)																
Psychosis	-0,05 (-0,2; 0,11)	0,515	0,1 (-0,05; 0,26)	0,203	-0,15 (-0,31; 0,01)	0,069	-0,15 (-0,31; 0,02)	0,079	-0,07 (-0,24; 0,1)	0,393	0,04 (-0,12; 0,19)	0,613	-0,05 (-0,2; 0,1)	0,504	-0,15 (-0,32; 0,03)	0,101
Activity disturbances	0,02 (-0,16; 0,19)	0,861	-0,04 (-0,23; 0,14)	0,650	0,64 (0,46; 0,83)	<0.001#	-0,24 (-0,43; -0,05)	0,013	-0,09 (-0,29; 0,11)	0,375	-0,21 (-0,39; -0,03)	0,023	-0,06 (-0,24; 0,12)	0,506	0,01 (-0,19; 0,22)	0,891
Aggression	0,11 (-0,09; 0,31)	0,274	-0,11 (-0,32; 0,1)	0,291	-0,07 (-0,28; 0,15)	0,549	0,53 (0,32; 0,75)	<0.001#	-0,13 (-0,35; 0,09)	0,259	-0,05 (-0,26; 0,16)	0,629	0,1 (-0,1; 0,3)	0,323	0,17 (-0,06; 0,4)	0,149
Affective disturbance	0,05 (-0,08; 0,17)	0,466	0,07 (-0,06; 0,2)	0,285	-0,19 (-0,33; -0,06)	0,005	-0,03 (-0,17; 0,1)	0,620	-0,01 (-0,15; 0,13)	0,900	0,65 (0,52; 0,78)	<0.001#	-0,07 (-0,19; 0,06)	0,316	-0,11 (-0,26; 0,03)	0,132
Sleep disturbances	0 (-0,12; 0,13)	0,992	-0,05 (-0,18; 0,08)	0,448	0,05 (-0,09; 0,19)	0,463	-0,16 (-0,3; -0,02)	0,025	0,64 (0,5; 0,78)	<0.001#	-0,04 (-0,17; 0,1)	0,586	0,06 (-0,07; 0,19)	0,353	-0,08 (-0,22; 0,07)	0,295
Anxieties and phobias	0,02 (-0,11; 0,15)	0,791	-0,03 (-0,16; 0,11)	0,699	-0,08 (-0,23; 0,06)	0,239	-0,21 (-0,36; -0,07)	0,003	0,16 (0,02; 0,31)	0,028	0,08 (-0,05; 0,22)	0,232	0,49 (0,36; 0,63)	<0.001#	0,05 (-0,1; 0,2)	0,526
BEHAVE-AD total score at baseline	0,54 (0,45; 0,63)	<0.001#	0,47 (0,38; 0,56)	<0.001#	0,32 (0,23; 0,42)	<0.001#	0,39 (0,29; 0,48)	<0.001#	0,17 (0,07; 0,27)	<0.001#	0,19 (0,1; 0,28)	<0.001#	0,27 (0,19; 0,36)	<0.001#	0,28 (0,18; 0,38)	<0.001#

Number of observations	627		627		627		627		627		627		627		627	
Number of trials	5		5		5		5		5		5		5		5	
8-WEEK OUTCOME																
Age	0 (-0,01; 0,01)	0,4097	0 (-0,01; 0,01)	0,7773	-0,01 (-0,02; 0)	0,0557	-0,01 (-0,02; 0,01)	0,3439	0,01 (0; 0,02)	0,2267	0 (-0,01; 0,01)	0,5963	0 (-0,01; 0,01)	0,4718	-0,01 (-0,02; 0)	0,267
Male (Reference: Female)	0 (-0,14; 0,15)	0,9623	-0,06 (-0,2; 0,09)	0,4344	0,05 (-0,11; 0,21)	0,5372	0,1 (-0,07; 0,26)	0,2499	0,19 (0,02; 0,36)	0,0266	-0,05 (-0,21; 0,11)	0,5123	-0,13 (-0,28; 0,02)	0,0989	-0,12 (-0,29; 0,05)	0,1571
BMI	0 (-0,02; 0,01)	0,8791	0 (-0,01; 0,02)	0,7794	0 (-0,01; 0,02)	0,7913	0 (-0,02; 0,01)	0,6936	0 (-0,01; 0,02)	0,552	0 (-0,02; 0,02)	0,9851	-0,01 (-0,02; 0)	0,1718	0,01 (-0,01; 0,02)	0,4726
MMSE	0 (-0,01; 0,01)	0,8143	0,02 (0,01; 0,03)	<0.001	-0,02 (-0,03; -0,01)	0,0043	-0,02 (-0,03; -0,01)	0,0028	0 (-0,01; 0,01)	0,8128	-0,01 (-0,02; 0,01)	0,3386	0,02 (0,01; 0,03)	<0.001[#]	-0,01 (-0,02; 0)	0,0789
Use of psychotropic medications at baseline																
Anxiolytics	0,03 (-0,27; 0,34)	0,8254	-0,2 (-0,5; 0,1)	0,1848	-0,19 (-0,52; 0,14)	0,2546	0,2 (-0,13; 0,53)	0,2425	0,01 (-0,33; 0,35)	0,9534	0,38 (0,06; 0,71)	0,0192	0,34 (0,04; 0,65)	0,029	0,03 (-0,31; 0,36)	0,8803
Hypnotic and sedatives	0,27 (0,04; 0,5)	0,0232	0,15 (-0,08; 0,37)	0,1953	0,33 (0,08; 0,57)	0,0086	0,24 (-0,02; 0,49)	0,0673	0,18 (-0,07; 0,43)	0,1662	0,04 (-0,21; 0,29)	0,7748	0,15 (-0,09; 0,39)	0,2252	0,2 (-0,06; 0,46)	0,1237
Antidepressants	-0,22 (-0,53; 0,09)	0,1644	-0,13 (-0,43; 0,17)	0,4046	-0,28 (-0,61; 0,06)	0,1075	-0,12 (-0,46; 0,22)	0,4908	-0,2 (-0,55; 0,16)	0,2742	0,01 (-0,32; 0,34)	0,949	-0,13 (-0,45; 0,18)	0,4126	-0,23 (-0,57; 0,12)	0,1932

Anti-dementias	-0,02 (-0,29; 0,24)	0,865 3	0,24 (-0,01; 0,5)	0,0638	0 (-0,27; 0,28)	0,9968	-0,37 (-0,65; -0,08)	0,0119	0,05 (-0,24; 0,33)	0,754	-0,02 (-0,31; 0,26)	0,878	-0,05 (-0,32; 0,23)	0,7363	-0,17 (-0,46; 0,13)	0,2719
Presence of BPSD symptom at baseline (Reference: No symptom)																
Psychosis	-0,04 (-0,2; 0,13)	0,656 5	0,11 (-0,05; 0,27)	0,169	-0,08 (-0,25; 0,1)	0,403 1	-0,17 (-0,35; 0,01)	0,071 5	-0,08 (-0,26; 0,11)	0,418 5	-0,08 (-0,25; 0,1)	0,382 6	0 (-0,17; 0,17)	0,987 3	0,01 (-0,18; 0,19)	0,929 8
Activity disturbances	0,12 (-0,07; 0,32)	0,212 7	0,05 (-0,14; 0,25)	0,585 8	0,66 (0,45; 0,88)	<0.001	-0,15 (-0,37; 0,07)	0,171 8	0,06 (-0,16; 0,29)	0,578	-0,09 (-0,3; 0,12)	0,385	-0,02 (-0,22; 0,18)	0,824 9	0,18 (-0,04; 0,4)	0,1088
Aggression	0,18 (-0,04; 0,39)	0,114 5	-0,1 (-0,31; 0,12)	0,375 3	0,07 (-0,17; 0,31)	0,581	0,54 (0,3; 0,78)	<0.001#	0,06 (-0,19; 0,31)	0,663 2	-0,19 (-0,42; 0,04)	0,1101	0,19 (-0,03; 0,41)	0,095 7	0,39 (0,14; 0,63)	0,0019
Affective disturbance	-0,09 (-0,23; 0,05)	0,204 7	-0,07 (-0,21; 0,06)	0,294	0,2 (0,05; 0,35)	0,009 1	0,05 (-0,1; 0,2)	0,529 4	-0,06 (-0,22; 0,1)	0,438 1	-0,74 (-0,88; -0,59)	<0.001#	-0,1 (-0,24; 0,04)	0,172 5	0,06 (-0,1; 0,21)	0,4738
Sleep disturbances	-0,02 (-0,16; 0,12)	0,798 6	-0,06 (-0,19; 0,08)	0,414 2	0,04 (-0,11; 0,19)	0,611 8	-0,14 (-0,29; 0,01)	0,074 7	0,63 (0,47; 0,79)	<0.001#	-0,09 (-0,24; 0,05)	0,207 8	0,02 (-0,12; 0,17)	0,739 5	0,01 (-0,15; 0,16)	0,923 1
Anxieties and phobias	-0,05 (-0,19; 0,09)	0,518 7	-0,01 (-0,15; 0,13)	0,887 3	-0,02 (-0,18; 0,14)	0,794 7	0,2 (0,05; 0,36)	0,011 5	-0,14 (-0,3; 0,02)	0,091 8	-0,06 (-0,21; 0,09)	0,436 1	-0,45 (-0,6; -0,31)	<0.001#	-0,14 (-0,3; 0,01)	0,0746
BEHAVE-AD total score at baseline	0,38 (0,29; 0,48)	<0.001#	0,36 (0,27; 0,45)	<0.001#	0,21 (0,11; 0,31)	<0.001#	0,29 (0,19; 0,39)	<0.001#	0,03 (-0,07; 0,14)	0,553 4	0,19 (0,09; 0,29)	<0.001#	0,18 (0,09; 0,28)	<0.001#	0,06 (-0,05; 0,16)	0,2764
Number of observations	541		541		541		541		541		541		541		539	
Number of trials	4		4		4		4		4		4		4		4	

BEHAVE-AD, Behavioural pathology in Alzheimer's disease; SMD, Standardised mean difference; BPSD, Behaviours and psychological symptoms of dementia

[#]Values are significant results after Bonferroni correction (p value <0.05/44 = 0.00113)

Supplementary Table S9_Linear regression models for baseline variables in Dataset B (Full)

Predictors of BEHAVE-AD total score and its components	BEHAVE-AD total score		Psychosis		Activity disturbances		Aggressiveness		Sleep disturbances		Affective disturbances		Anxieties and phobias		Global rating	
	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p	SMD (95% CI)	p
4-WEEK OUTCOME																
Age	-0,01 (-0,02; 0)	0,1188	-0,01 (-0,02; 0)	0,0683	-0,01 (-0,02; 0)	0,032	0 (-0,01; 0,01)	0,4815	0 (-0,01; 0,01)	0,9641	0,01 (-0,01; 0,02)	0,3182	0 (-0,01; 0,01)	0,7563	0 (-0,01; 0,01)	0,5539
Male (Reference: Female)	0,01 (-0,15; 0,16)	0,9239	-0,05 (-0,21; 0,12)	0,5817	0,15 (-0,01; 0,31)	0,0658	0,09 (-0,08; 0,25)	0,2906	0,18 (0,01; 0,35)	0,0374	-0,19 (-0,35; -0,03)	0,0186	-0,12 (-0,28; 0,03)	0,1219	0,01 (-0,16; 0,19)	0,8961
BMI (kg/m2)	0,01 (0; 0,03)	0,1382	0,01 (0; 0,03)	0,1141	0 (-0,01; 0,02)	0,7176	0,01 (-0,01; 0,02)	0,5013	0,02 (0; 0,03)	0,0266	0,01 (-0,01; 0,03)	0,2022	0 (-0,01; 0,02)	0,9511	0,01 (-0,01; 0,03)	0,2484
MMSE	0 (-0,01; 0,01)	0,648	0,01 (0; 0,03)	0,0189	-0,01 (-0,02; 0)	0,0191	-0,02 (-0,04; -0,01)	<0.001	-0,01 (-0,02; 0,01)	0,3892	-0,01 (-0,02; 0)	0,2361	0,02 (0; 0,03)	0,0056	-0,01 (-0,02; 0)	0,0639
Use of psychotropic medications at baseline																
Anxiolytics	-0,22 (-0,55; 0,1)	0,1815	-0,31 (-0,65; 0,03)	0,0764	-0,32 (-0,65; 0,02)	0,0653	-0,03 (-0,38; 0,32)	0,8622	0,11 (-0,25; 0,46)	0,5486	-0,05 (-0,39; 0,28)	0,7509	0,06 (-0,27; 0,4)	0,7141	-0,08 (-0,45; 0,29)	0,6675
Hypnotic and sedatives	0,3 (0,03; 0,56)	0,0274	0,09 (-0,18; 0,36)	0,5181	0,39 (0,13; 0,65)	0,003	0,29 (0,01; 0,57)	0,0416	0,21 (-0,07; 0,5)	0,1419	0,12 (-0,14; 0,39)	0,3638	0,21 (-0,06; 0,47)	0,1237	0,36 (0,06; 0,65)	0,0168
Antidepressants	0,09 (-0,21; 0,4)	0,5548	0,13 (-0,19; 0,45)	0,4266	-0,12 (-0,44; 0,19)	0,4323	0,07 (-0,26; 0,39)	0,6888	-0,17 (-0,5; 0,16)	0,3162	0,33 (0,02; 0,65)	0,0389	0,05 (-0,26; 0,36)	0,7518	-0,03 (-0,37; 0,32)	0,8837

Anti-dementias	-0,06 (-0,32; 0,2)	0,632	0,15 (-0,12; 0,42)	0,2749	0,03 (-0,22; 0,29)	0,7987	-0,28 (-0,55; 0)	0,0479	-0,12 (-0,4; 0,16)	0,4029	-0,08 (-0,34; 0,19)	0,5641	-0,15 (-0,42; 0,11)	0,2523	-0,18 (-0,47; 0,11)	0,2229
Presence of BPSD symptom at baseline (Reference: No symptom)																
Psychosis	0,05 (-0,12; 0,22)	0,565	-0,06 (-0,23; 0,12)	0,5383	0,19 (0,02; 0,37)	0,0293	0,08 (-0,1; 0,27)	0,3753	0,09 (-0,1; 0,27)	0,3568	-0,05 (-0,23; 0,13)	0,5696	0,03 (-0,15; 0,2)	0,7657	0,14 (-0,05; 0,34)	0,1414
Activity disturbances	-0,01 (-0,2; 0,19)	0,9314	-0,06 (-0,26; 0,15)	0,5826	0,57 (0,37; 0,77)	<0.001#	-0,26 (-0,47; -0,06)	0,013	-0,1 (-0,31; 0,11)	0,3605	-0,2 (-0,4; 0)	0,053 7	-0,02 (-0,22; 0,18)	0,8289	-0,02 (-0,24; 0,2)	0,8399
Aggression	0,05 (-0,18; 0,27)	0,6844	-0,18 (-0,41; 0,05)	0,1216	-0,1 (-0,33; 0,12)	0,3687	0,48 (0,24; 0,71)	<0.001#	-0,18 (-0,42; 0,06)	0,1393	-0,02 (-0,25; 0,2)	0,8394	0,1 (-0,13; 0,32)	0,4048	0,12 (-0,13; 0,37)	0,3538
Affective disturbance	0,03 (-0,12; 0,17)	0,7159	0,03 (-0,12; 0,18)	0,6783	-0,18 (-0,33; -0,04)	0,0132	-0,04 (-0,19; 0,11)	0,5844	-0,05 (-0,2; 0,11)	0,5483	0,67 (0,53; 0,82)	<0.001#	-0,06 (-0,21; 0,08)	0,3869	-0,13 (-0,29; 0,03)	0,1072
Sleep disturbances	0,01 (-0,14; 0,15)	0,9024	-0,05 (-0,2; 0,1)	0,5092	0,1 (-0,05; 0,25)	0,1981	-0,13 (-0,29; 0,02)	0,0917	0,63 (0,47; 0,78)	<0.001	-0,11 (-0,26; 0,04)	0,1508	0,04 (-0,11; 0,19)	0,6094	-0,08 (-0,25; 0,08)	0,3313
Anxieties and phobias	0,02 (-0,13; 0,16)	0,8174	-0,02 (-0,17; 0,13)	0,8159	-0,12 (-0,27; 0,03)	0,1157	-0,21 (-0,36; -0,05)	0,0097	0,19 (0,03; 0,35)	0,0175	0,08 (-0,07; 0,24)	0,2735	0,49 (0,34; 0,64)	<0.001	0,04 (-0,12; 0,21)	0,6148
Race (Reference: Caucasian)																
Black	-0,15 (-0,46; 0,15)	0,3245	-0,14 (-0,46; 0,17)	0,3713	-0,17 (-0,48; 0,14)	0,2914	-0,29 (-0,61; 0,04)	0,0859	-0,13 (-0,47; 0,2)	0,4257	0,26 (-0,05; 0,58)	0,104	0,16 (-0,15; 0,47)	0,313	-0,22 (-0,56; 0,13)	0,2217
Other	-0,01 (-0,25; 0,23)	0,9588	0,12 (-0,13; 0,37)	0,3373	-0,23 (-0,47; 0,02)	0,0711	-0,11 (-0,36; 0,15)	0,4159	0,09 (-0,17; 0,35)	0,5092	0,01 (-0,24; 0,26)	0,93	0,05 (-0,19; 0,3)	0,6605	-0,17 (-0,44; 0,1)	0,2189

Any currently active diseases at baseline (Reference: No disease)																
Cardiovascular disease	-0,05 (-0,21; 0,11)	0,535 6	0,01 (-0,15; 0,17)	0,911 3	-0,2 (-0,35; -0,04)	0,013 3	-0,12 (-0,29; 0,04)	0,152 3	0,19 (0,02; 0,36)	0,029 3	0,02 (-0,14; 0,18)	0,825 9	0,04 (-0,12; 0,2)	0,623 1	-0,15 (-0,32; 0,03)	0,105 7
Endocrine disease	-0,03 (-0,17; 0,12)	0,733 3	-0,08 (-0,24; 0,07)	0,283 5	-0,1 (-0,25; 0,05)	0,186 9	0,11 (-0,05; 0,27)	0,170 6	-0,03 (-0,19; 0,13)	0,682 5	-0,03 (-0,18; 0,12)	0,704 4	0,04 (-0,11; 0,19)	0,598	0,11 (-0,05; 0,28)	0,179 7
Neurological disease	-0,01 (-0,16; 0,14)	0,938	-0,08 (-0,23; 0,08)	0,327 3	0 (-0,15; 0,15)	0,981 2	0,13 (-0,03; 0,29)	0,103 4	0,05 (-0,11; 0,22)	0,511 5	-0,07 (-0,22; 0,09)	0,399 4	-0,05 (-0,21; 0,1)	0,486 1	0,06 (-0,1; 0,23)	0,457
Dementia diagnosis (Reference: Alzheimer's disease)																
Mixed type dementia	-0,01 (-0,27; 0,24)	0,918 9	-0,02 (-0,29; 0,24)	0,872 8	-0,23 (-0,49; 0,03)	0,079 2	0,03 (-0,24; 0,3)	0,839 8	0,25 (-0,03; 0,52)	0,080 8	0,04 (-0,22; 0,3)	0,754 7	0,08 (-0,18; 0,34)	0,536 8	0,02 (-0,27; 0,3)	0,906 5
Vascular dementia	0,03 (-0,15; 0,21)	0,753	0,15 (-0,04; 0,34)	0,129 7	-0,11 (-0,3; 0,08)	0,241 5	-0,01 (-0,2; 0,19)	0,957	-0,18 (-0,37; 0,02)	0,082 8	-0,02 (-0,21; 0,17)	0,833 6	0,07 (-0,12; 0,26)	0,474 5	-0,08 (-0,29; 0,12)	0,426 4
eGFR (ml/min)	0 (0; 0)	0,994 9	0 (0; 0)	0,912 3	0 (0; 0)	0,836 7	0 (-0,01; 0)	0,232 8	0 (0; 0,01)	0,212	0,01 (0; 0,01)	0,002	0 (0; 0)	0,981	0 (-0,01; 0)	0,726 5
BEHAVE-AD total score at baseline	0,54 (0,44; 0,63)	<0.001[#]	0,49 (0,39; 0,59)	<0.001[#]	0,31 (0,21; 0,41)	<0.001[#]	0,36 (0,26; 0,46)	<0.001[#]	0,19 (0,09; 0,29)	<0.001[#]	0,2 (0,1; 0,3)	<0.001[#]	0,29 (0,19; 0,38)	<0.001[#]	0,28 (0,17; 0,39)	<0.001[#]
Number of observations	523		523		523		523		523		523		523		523	
Number of trials	2		2		2		2		2		2		2		2	
8-WEEK OUTCOME																
Age	0 (-0,01; 0,01)	0,653	0 (-0,01; 0,01)	0,808	-0,01 (-0,02; 0)	0,101 1	-0,01 (-0,02; 0,01)	0,377 4	0,01 (0; 0,02)	0,086 1	0 (-0,01; 0,01)	0,904 3	0,01 (-0,01; 0,02)	0,371 5	-0,01 (-0,02; 0,01)	0,287 2

Male (Reference: Female)	-0,01 (-0,18; 0,16)	0,908	-0,09 (-0,25; 0,08)	0,3066	0,06 (-0,12; 0,24)	0,512	0,11 (-0,07; 0,29)	0,2324	0,13 (-0,05; 0,32)	0,1561	-0,04 (-0,21; 0,14)	0,6776	-0,13 (-0,3; 0,04)	0,1441	-0,11 (-0,3; 0,07)	0,2401
BMI (kg/m2)	0 (-0,02; 0,02)	0,8964	0 (-0,01; 0,02)	0,641	0 (-0,01; 0,02)	0,7397	-0,01 (-0,02; 0,01)	0,5254	0 (-0,02; 0,02)	0,9834	0 (-0,02; 0,02)	0,9577	-0,01 (-0,03; 0,01)	0,206	0,01 (-0,01; 0,03)	0,4268
MMSE	0 (-0,01; 0,01)	0,7077	0,02 (0,01; 0,03)	0,0028	-0,02 (-0,03; -0,01)	0,005	-0,02 (-0,03; -0,01)	0,0035	0 (-0,02; 0,01)	0,5725	0 (-0,02; 0,01)	0,4491	0,02 (0,01; 0,04)	<0.001[#]	-0,01 (-0,02; 0)	0,1896
Use of psychotropic medications at baseline																
Anxiolytics	0,03 (-0,32; 0,38)	0,8705	-0,19 (-0,53; 0,16)	0,2929	-0,24 (-0,62; 0,14)	0,2135	0,17 (-0,21; 0,55)	0,3906	0 (-0,39; 0,4)	0,9896	0,32 (-0,05; 0,69)	0,0876	0,4 (0,03; 0,76)	0,0318	0,19 (-0,21; 0,58)	0,3536
Hypnotic and sedatives	0,43 (0,16; 0,7)	0,0016	0,2 (-0,07; 0,47)	0,1389	0,45 (0,16; 0,73)	0,0023	0,45 (0,16; 0,74)	0,0026	0,16 (-0,14; 0,46)	0,2847	0,09 (-0,2; 0,38)	0,536	0,2 (-0,07; 0,47)	0,1521	0,28 (-0,03; 0,59)	0,0732
Antidepressants	-0,19 (-0,51; 0,13)	0,2445	-0,13 (-0,44; 0,19)	0,4353	-0,29 (-0,63; 0,06)	0,1028	-0,12 (-0,47; 0,23)	0,4946	-0,19 (-0,55; 0,17)	0,2982	0,06 (-0,28; 0,39)	0,7434	-0,1 (-0,43; 0,23)	0,5469	-0,3 (-0,66; 0,06)	0,1069
Anti-dementias	-0,01 (-0,28; 0,25)	0,9272	0,23 (-0,04; 0,5)	0,099	0,03 (-0,25; 0,32)	0,8146	-0,39 (-0,68; -0,1)	0,0086	0,04 (-0,26; 0,34)	0,7908	-0,02 (-0,31; 0,27)	0,8729	-0,08 (-0,35; 0,19)	0,5468	-0,18 (-0,49; 0,13)	0,2504
Presence of BPSD symptom at baseline (Reference: No symptom)																
Psychosis																
Activity disturbances	0,11 (-0,1; 0,33)	0,2982	0,03 (-0,18; 0,24)	0,7676	0,65 (0,42; 0,88)	<0.001	-0,13 (-0,36; 0,1)	0,2679	0,07 (-0,17; 0,31)	0,5581	-0,08 (-0,31; 0,14)	0,4628	-0,02 (-0,24; 0,2)	0,8433	0,17 (-0,07; 0,41)	0,1643
Aggression	0,15 (-0,08; 0,38)	0,211	-0,14 (-0,37; 0,09)	0,2472	0,03 (-0,22; 0,29)	0,7999	0,54 (0,29; 0,79)	<0.001	0,07 (-0,19; 0,33)	0,6	-0,14 (-0,38; 0,11)	0,2725	0,19 (-0,05; 0,43)	0,12	0,33 (0,06; 0,59)	0,0146

Affective disturbance																
Sleep disturbances	-0,03 (-0,18; 0,13)	0,741 7	-0,05 (-0,21; 0,1)	0,502 6	0,01 (-0,16; 0,18)	0,885 5	-0,12 (-0,29; 0,05)	0,152 5	0,54 (0,37; 0,72)	<0.001	-0,12 (-0,28; 0,04)	0,147 8	0,01 (-0,15; 0,17)	0,916	0,02 (-0,15; 0,2)	0,804 4
Anxieties and phobias	0,04 (-0,12; 0,19)	0,651 2	0,01 (-0,14; 0,16)	0,917 3	0 (-0,17; 0,17)	0,996	-0,22 (-0,39; -0,05)	0,010 5	0,13 (-0,05; 0,3)	0,157 8	0,09 (-0,07; 0,25)	0,263 7	0,44 (0,29; 0,6)	<0.001[#]	0,16 (-0,01; 0,34)	0,065 8
Race (Reference: Caucasian)																
Black	0 (-0,32; 0,33)	0,985 7	-0,03 (-0,35; 0,29)	0,851 8	-0,05 (-0,4; 0,3)	0,796 6	-0,17 (-0,52; 0,18)	0,333 7	0,01 (-0,36; 0,37)	0,969 6	0,25 (-0,1; 0,59)	0,158 1	0,25 (-0,08; 0,58)	0,144 1	-0,19 (-0,55; 0,17)	0,305 2
Other	-0,01 (-0,26; 0,24)	0,934 6	0,08 (-0,17; 0,32)	0,538 4	-0,15 (-0,41; 0,12)	0,278 7	-0,05 (-0,32; 0,21)	0,695 2	0 (-0,28; 0,28)	0,998 8	-0,08 (-0,34; 0,18)	0,565 4	0,08 (-0,18; 0,33)	0,544 3	-0,13 (-0,41; 0,15)	0,368 4
Any currently active diseases at baseline (Reference: No disease)																
Cardiovascular disease	-0,05 (-0,22; 0,11)	0,528 7	-0,03 (-0,19; 0,13)	0,726 5	-0,22 (-0,39; -0,04)	0,015 6	0 (-0,18; 0,17)	0,978 3	0,13 (-0,05; 0,31)	0,159 1	0,12 (-0,06; 0,29)	0,179 7	-0,06 (-0,23; 0,1)	0,462	0,01 (-0,17; 0,2)	0,893
Endocrine disease	0,05 (-0,11; 0,21)	0,530 1	-0,04 (-0,2; 0,11)	0,574	-0,05 (-0,22; 0,12)	0,593	0,2 (0,03; 0,37)	0,02	0,1 (-0,07; 0,28)	0,257 4	-0,06 (-0,22; 0,11)	0,481 8	0,07 (-0,09; 0,23)	0,412 3	0,16 (-0,02; 0,34)	0,075 2
Neurological disease	-0,08 (-0,24; 0,08)	0,312	-0,11 (-0,27; 0,05)	0,165 2	0 (-0,17; 0,17)	0,975 6	0,07 (-0,11; 0,24)	0,450 5	-0,17 (-0,34; 0,01)	0,064 5	-0,03 (-0,2; 0,13)	0,702 1	-0,14 (-0,3; 0,02)	0,086	-0,04 (-0,22; 0,14)	0,676 1
Dementia diagnosis (Reference: Alzheimer's disease)																
Mixed type dementia	-0,08 (-0,36; 0,2)	0,578 5	0,07 (-0,21; 0,34)	0,630 4	-0,18 (-0,48; 0,12)	0,245 5	-0,13 (-0,43; 0,17)	0,386 6	0,02 (-0,29; 0,34)	0,879 1	-0,1 (-0,39; 0,19)	0,496 5	-0,03 (-0,31; 0,26)	0,862 1	0,05 (-0,26; 0,36)	0,747 3

Vascular dementia	0,19 (-0,01; 0,38)	0,0584	0,24 (0,05; 0,43)	0,0141	0,06 (-0,15; 0,27)	0,5592	0,17 (-0,04; 0,38)	0,108	-0,02 (-0,24; 0,2)	0,8577	-0,13 (-0,33; 0,08)	0,2174	0,07 (-0,13; 0,27)	0,4733	0,05 (-0,17; 0,27)	0,6668
eGFR (ml/min)	0 (0; 0,01)	0,552	0 (0; 0)	0,9163	0 (-0,01; 0)	0,5064	0 (0; 0)	0,9188	0 (0; 0,01)	0,1763	0,01 (0; 0,01)	0,0034	0 (0; 0,01)	0,7911	0 (0; 0,01)	0,8092
BEHAVE-AD total score at baseline	0,39 (0,29; 0,49)	<0.001#	0,38 (0,28; 0,48)	<0.001#	0,17 (0,06; 0,28)	0,0018	0,27 (0,17; 0,38)	<0.001#	0,07 (-0,04; 0,18)	0,2098	0,18 (0,08; 0,29)	<0.001#	0,19 (0,09; 0,3)	<0.001#	0,07 (-0,04; 0,18)	0,2317
Number of observations	465		465		465		465		465		465		465		463	
Number of trials	2		2		2		2		2		2		2		2	

BEHAVE-AD, Behavioural pathology in Alzheimer's disease; SMD, Standardised mean difference; BPSD, Behaviours and psychological symptoms of dementia

#Values are significant results after Bonferroni correction (p value <0.05/44 = 0.00113)

SUPPLEMENTARY DOCUMENT 1: BEHAVIORAL PATHOLOGY IN ALZHEIMER'S DISEASE (BEHAVE-AD)

A. Paranoid and Delusional Ideation (a delusion is a false conviction, not a misidentification)

1. "People are stealing things" delusion

(0) Not present.

(1) Delusion that people are hiding objects.

(2) Delusion that people are coming into the home and hiding or stealing objects.

(3) Talking and listening to people coming into the home

2. "One's house is not one's home" delusion.

(0) Not present.

(1) Conviction that the place in which one is residing is not one's home (e.g., packing to go home, complaints while at home of "take me home").

(2) Attempt to leave domiciliary to go home.

(3) Violence in response to attempts to forcibly restrict exit.

3. "Spouse (or other caregiver) is an imposter" delusion.

(0) Not present.

(1) Conviction that spouse (or another caregiver) is an imposter.

(2) Anger towards spouse (or another caregiver) for being an imposter.

(3) Violence towards spouse (or another caregiver) for being an imposter.

4. Delusion of abandonment (e.g.: to an institution).

(0) Not present.

(1) Suspicion of caregiver plotting abandonment or institutionalization (e.g., on the telephone).

(2) Accusation of a conspiracy to abandon or institutionalize.

(3) Accusation of impending or immediate desertion or institutionalization.

5. Delusion of infidelity (social and/or sexual unfaithfulness).

(0) Not present.

(1) Conviction that spouse, children, and/or other caregivers are unfaithful.

(2) Anger towards spouse, relative, or other caregiver for their infidelity.

(3) Violence toward spouse, relative, or other caregiver for their infidelity.

6. Suspiciousness/Paranoia other than above.

(0) Not present.

(1) Suspiciousness (e.g., hiding objects which they may later be unable to locate or a statement such as "I don't trust you”).

(2) Paranoid (i.e., fixed conviction with respect to suspicions and/or anger as a result of suspicions).

(3) Violence as a result of suspicions.

7. Delusions (non-paranoid) other than above.

(0) Not present.

(1) Delusional.

(2) Verbal or emotional manifestations as a result of delusions.

(3) Physical actions or violence as a result of delusions.

B. Hallucinations

8. Visual hallucinations.

(0) Not present.

(1) Vague not clearly defined.

(2) Clearly defined hallucinations of objects and persons (e.g., sees other people at the table).

(3) Verbal or physical actions or emotional responses to the hallucinations.

9. Auditory hallucinations.

(0) Not present.

(1) Vague not clearly defined.

(2) Clearly defined hallucinations of words and phrases.

(3) Verbal or physical actions or emotional responses to the hallucinations.

10. Olfactory hallucinations.

(0) Not present.

(1) Vague not clearly defined.

(2) Clearly defined hallucinations (e.g., smells a fire or "something burning").

(3) Verbal or physical actions or emotional responses to the hallucinations.

11. Haptic (sense of touch) hallucinations.

(0) Not present.

(1) Vague not clearly defined.

(2) Clearly defined hallucinations (e.g., "something is crawling on my body').

(3) Verbal or physical actions or emotional responses to the hallucinations.

12. Other hallucinations.

(0) Not present.

(1) Vague not clearly defined.

(2) Clearly defined hallucinations.

(3) Verbal or physical actions or emotional responses to the hallucinations.

C. Activity Disturbances.

13. Wandering (e.g. away from home or caregiver).

(0) Not present.

(1) Somewhat, but not sufficient as to require restraint.

(2) Sufficient as to require restraint.

(3) Verbal or physical actions or emotional responses to attempts to prevent wandering.

14. Purposeless activity (cognitive abulia).

(0) Not present.

(1) Repetitive, purposeless activity (e.g., opening and closing pocketbook, packing and unpacking clothing, repeatedly puffing on and removing clothing, insistent repeating of demands or questions).

(2) Pacing or other purposeless activity sufficient to require restraint.

(3) Abrasions or physical harm resulting from purposeless activity.

15. Inappropriate activity.

(0) Not present.

(1) Inappropriate activities (e.g., storing and hiding objects in inappropriate places, such as throwing clothing in wastebasket or putting empty plates in the oven, inappropriate sexual behavior such as inappropriate exposure).

(2) Present and sufficient to require restraint.

(3) Present and sufficient to require restraint and accompanied by anger or violence when restraint is used.

D. Aggressiveness.

16. Verbal Outbursts.

(0) Not present.

(1) Present (including unaccustomed use of foul or abusive language).

(2) Present and accompanied by anger.

(3) Present, accompanied by anger, and clearly directed at other persons.

17. Physical threats and/or violence.

(0) Not present.

(1) Threatening behaviour.

(2) Physical violence.

(3) Physical violence accompanied by vehemence.

18. Agitation (other than above).

(e.g. non-verbal anger; negativity including refusal to bathe, dress, continue walking, take medications, etc.; hyperventilation).

(0) Not present.

(1) Present.

(2) Present with emotional component.

(3) Present with emotional and physical component

E. Diurnal Rhythm Disturbances

19. Day/Night disturbance.

(0) Not present.

(1) Repetitive wakening during night (except for purpose of toileting).

(2) 50% to 75% of former sleep cycle at night.

(3) Complete disturbance of diurnal rhythm (less than 50% of former sleep cycle at night).

F. Affective Disturbance

20. Tearfulness (or whimpering or other "crying sounds”).

(0) Not present.

(1) Present.

(2) Present accompanied by a clear affective component.

(3) Present and accompanied by affective and physical component (e.g., wringing of hands or other gestures).

21. Depressed mood. other.

(0) Not present.

(1) Present (e.g., occasional statement "I wish I were dead," or "I'm going to kill myself," or "I feel like nothing," without clear affective concomitants).

(2) Present with clear concomitants (e.g., thoughts of death).

(3) Present with emotional and physical concomitants (e.g., suicidal gestures).

G. Anxieties and Phobias

22. Anxiety regarding upcoming events (Godot syndrome).

(0) Not present.

(1) Present with repeated queries and/or other activities regarding upcoming appointments and/or events (e.g., when are we going?).

(2) Present and disturbing to caregivers.

(3) Present and intolerable to caregivers.

23. Other anxieties.

(e.g., regarding money, the future, being away from home, health, memory, etc.; or generalized anxiety such as thinking everything is "terribly wrong").

(0) Not present.

(1) Present.

(2) Present and disturbing to caregivers.

(3) Present and intolerable to caregivers.

24. Fear of being left alone.

(0) Not present.

(1) Present with vocalized fear of being alone.

(2) Vocalized and sufficient to require specific action on the part of caregiver.

(3) Vocalized and sufficient to require patient to be accompanied at all times (e.g., patient must see the caregiver at all times).

25. Other phobias.

(e.g. fear of crowds, travel, darkness, people/strangers, bathing, etc.)

(0) Not present.

(1) Present

(2) Present and of sufficient magnitude to require specific action by caregiver.

(3) Present and sufficient to prevent patient activities.

APPENDIX B. HUMAN RESEARCH ETHICS APPROVAL

THE UNIVERSITY OF SYDNEY

RESEARCH INTEGRITY
& ETHICS ADMINISTRATION

HUMAN RESEARCH ETHICS APPROVAL

The University of Sydney confirms that this project meets the requirements of the National Statement on Ethical Conduct in Human Research.

Project identifier:	2024/HE000171
Project title:	Co-designing a personalised medicine calculator to improve antipsychotic prescribing in people living with dementia (Parts 1 & 2)
Application version:	2.01
Chief Investigator:	Dr Edwin Tan
Project team:	Professor Christine Lu Mr Edward Lau Mr Harry Le Professor Therese Low Professor Sarah Hilmer Mr Timothy Josh Tan Ms Weisi Chen Professor Yun-Hee Jeon
Project start date:	07 Mar 2024
Project end date:	07 Mar 2028
Date of issue:	Wednesday, 7 May, 2025

Project summary

There is limited guidance for clinicians and consumers around individualised antipsychotic prescribing in people living with dementia. This places patients at risk of adverse events or under-prescribing of treatment. This study will involve (i) analysis of national datasets so we understand why antipsychotics are used in Australia; (ii) interviews with clinicians and people living with dementia and their carers to understand their views on the usefulness and risks of antipsychotics; (iii) developing and testing statistical models to predict benefits and adverse outcomes of antipsychotic prescribing; (iv) using these findings to inform the codesign of a personalised antipsychotic calculator.

Summary of amendments

Manny Adaichi to be removed as analyst; Weisi (Sophie) Chen and Trong Hieu (Harry) Le to be added as analysts

Note

- Please ensure there is a version number and date displayed on all participant-facing documents.

Conditions of Approval for Clinical Trials

This letter constitutes ethical approval only. This project cannot proceed at any site until the necessary research governance authorisation is obtained.

- If your study is sponsored by the University or is to be conducted on a University of Sydney site, you must comply with additional University governance requirements prior to commencing at each site. Please contact Research Portfolio Clinical Trials Support at clinical-trials.research@sydney.edu.au.
- Clinical Trials must be registered on a clinical trials registry that complies with the International Committee of Medical Journal Editors (ICMJE). For trials conducted in Australia or New Zealand registration should be on the Australian New Zealand Clinical Trial Registry before recruitment of the first subject (http://www.anzctr.org.au/).
- If your trial is to be conducted under the Clinical Trials Notification (CTN) or Clinical Trials Approval (CTA) schemes should not commence until it has been notified to the Therapeutic Goods Administration (TGA).

Conditions of Approval

- Research must be conducted according to the approved proposal.
- An annual progress report must be submitted on or before the anniversary of approval and a final report on completion of the project.
- You must report as soon as practicable anything that might warrant review of ethical approval of the project including:
  - Serious or unexpected adverse events (which should be reported within 72 hours).
  - Unforeseen events that might affect continued ethical acceptability of the project.
- Any changes to the proposal must be approved prior to their implementation (except where an amendment is undertaken to eliminate *immediate* risk to participants).
- Researchers working on this project must be sufficiently qualified by education, training, and experience for their role, or adequately supervised. Changes to the project team must be reported and approved.
- Researchers must disclose any actual, potential of perceived conflicts of interest, including any financial or other interest or affiliation, as relevant to this project.
- Research data and primary materials must be retained and stored in accordance with relevant legislation and University guidelines.
- Ethics approval is dependent upon ongoing compliance of the research with the *National Statement on Ethical Conduct in Human Research*, the *Australian Code for the Responsible Conduct of Research*, applicable legal requirements, and with University policies, procedures, and governance requirements.

- If your research project is a clinical trial and is being sponsored by the University or is to be conducted on a University of Sydney site, you must comply with additional University governance requirements prior to commencing your Clinical Trial.
- The University may conduct audits on approved projects.
- The Chief Investigator has ultimate responsibility for the conduct of the research and is responsible for ensuring all others involved will conduct the research in accordance with the above.

Ethics Committee Representative

Chair

On behalf of the University of Sydney

The University of Sydney HRECs are constituted and operate in accordance with the National Statement on Ethical Conduct in Human Research and the Australian Code for the Responsible Conduct of Research (NHMRC). All personnel named on the project should be acquainted with these documents.

Research Integrity & Ethics Administration
Research Portfolio
Level 3, Michael Spence Building (F23)
The University of Sydney
NSW 2006 Australia

T +61 2 9036 9161
E human.ethics@sydney.edu.au
W Intranet.sydney.edu.au/ethics

ABN 15 211 513 464
CRICOS 00026A