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Long-Term Use of Medications with Anticholinergic Activity in Older Adults with Intellectual Disability: Prescribing Challenges and Impact on Health Outcomes

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Declaration

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Summary

Background: Older adults with intellectual disability are exposed to polypharmacy and a high anticholinergic burden due to the high prevalence of mental and neurological disorders. A cumulative anticholinergic burden has been associated with adverse effects such as daytime drowsiness, constipation, and poorer performance in activities of daily living, according to cross-sectional studies. Additionally, long-term exposure to anticholinergic burden has been associated with adverse effects in older adults in the general population, including cognitive decline, physical function deterioration, higher mortality rates, chronic constipation, increased risk of falls, and a higher likelihood of developing dementia or Alzheimer's disease. However, based on preliminary research, no studies have specifically examined the adverse effects of long-term exposure to medications with anticholinergic activity in older adults with intellectual disability.

Objectives: This thesis aimed to evaluate the factors associated with the use of medication with anticholinergic activity in older adults with intellectual disability by addressing the following key objectives: *i)* map and examine existing research on adverse effects of long-term use of medications with anticholinergic activity in this population (evidence gathering stage), *ii)* assess anticholinergic exposure at two timepoints over a ten-year period and investigate the associated outcomes (evidence gathering stage), *iii)* explore prescribers' perspectives on prescribing and deprescribing of medications with anticholinergic activity, identifying barriers and facilitators to deprescribing (theoretical development), and *iv)* data synthesis to assess the development of an intervention aimed at enhancing the prescribing and deprescribing of medications with anticholinergic activity among older adults with intellectual disability, based on both the theoretical foundation and the gathered evidence.

Methods: The Medical Research Council framework on complex interventions was used to provide the theoretical foundation for the design of an intervention aimed at optimising anticholinergic prescribing for older adults with intellectual disability. A scoping review was conducted to evaluate existing studies of the adverse effects of long-term anticholinergic burden in the population. A longitudinal cohort study using Data from Wave 1 and Wave 4 from the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing, which are ten years apart, was used to assess the Anticholinergic

Cognitive Burden (ACB), with ACB scores calculated for the same cohort at both timepoints. Multinomial logistic regression was used to analyse the factors associated with high ACB scores at Wave 4, while logistic regression was used to examine outcomes at Wave 4 associated with mild and high ACB at Wave 1. Semi-structured interviews were also conducted with healthcare professionals who prescribe medication for older adults with intellectual disability in Ireland. The Theoretical Domains Framework was applied to identify barriers and facilitators to the deprescribing of medications with anticholinergic activity from the prescribers' perspectives.

Results: The scoping review found no studies examined adverse effects associated with long-term anticholinergic activity exposure among older adults with intellectual disability. The longitudinal study found that approximately 70% of participants reported use of medications with anticholinergic activity at both timepoints, with no significant change in ACB scores between the two waves. Antipsychotics were the most common contributors to anticholinergic exposure, followed by anticholinergics, antiepileptics, and antidepressants at both timepoints. Mild and high ACB scores at Wave 1 were significantly associated with an increased risk of falls and mental health conditions after 10 years. The qualitative study identified several facilitators of deprescribing in different domains: environmental context and resources of medical records; prescriber Knowledge and Skills (knowledge of appropriate prescribing and deprescribing skills); social influences (carer/family involvement) and beliefs about consequences (positive impacts of deprescribing and use of non-pharmacological treatments). Identified barriers to deprescribe medications with anticholinergic activity included environmental context and resources; Knowledge and social influences.

Conclusion: Older adults with intellectual disability are exposed to a high anticholinergic burden and more likely for a sustained period of time, and this was significantly associated with a higher risk of falls and mental health conditions. The prescribing and deprescribing of medications with anticholinergic activity for older adults with intellectual disability is a complex process that requires an intervention to support prescribers in making informed decisions.

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Table of Abbreviations

Abbreviation	Term
AAIDD	American Association on Intellectual and Developmental Disabilities
AC	Anticholinergic
ACB	Anticholinergic Cognitive Burden scale
ADeN	Australian Deprescribing Network
ADLs	Activities of Daily Living
ADRs	Adverse Drug Reactions
ADS	Anticholinergic Drug Scale
ANS	Autonomic Nervous System
ANZCTR	Australian New Zealand Clinical Trials Registry
ARS	Anticholinergic Risk Scale
ATC	Anatomical Therapeutic Chemical
BCW	Behaviour Change Wheel
BI	Barthel Index
CADeN	Canadian Medication Appropriateness and Deprescribing Network
CAM	Complementary and Alternative Medicine
CAPI	Computer-Assisted Personal Interview
ChiCTR	Chinese Clinical Trial Registry
CI	Confidence Interval
CNS	Central Nervous Systems
COM-B	Capability, Opportunity and Motivation for Behaviour
COPD	Chronic Obstructive Pulmonary Disease
COREQ-32	Consolidated criteria for reporting qualitative research
COX-inhibitor	Cyclooxygenase inhibitor
CTRI	Clinical Trials Registry-India
DBI	Drug Burden Index
DPRA	Data Protection Risk Assessment
ECG	Electrocardiogram

GEE	Generalized Estimating Equations
GLMM	Generalized Linear Mixed Models
GP	General Practitioner
HSE	Health Service Executive
IASSIDD	International Association for the Scientific Study of Intellectual and Developmental Disabilities
ICTRP	International Clinical Trials Registry Platform
IDS-TILDA	Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing
IQ	Intelligence Quotient
ISRCTN	International Standard Randomised Controlled Trial Number
MeSH	Medical Subject Heading
MMSE	Mini-Mental State Examination
MRC	Medical Research Council framework
NERD	Network of European Researchers in Deprescribing
NHI	National Health Institute
NHS	National Health Service
NIDD	National Intellectual Disability Database
NPT	Normalization Process Theory
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OPTIMA-ID	Optimising Pharmaco-Therapy and Improving Medication for Ageing with Intellectual Disability
OR	Odds Ratio
OTC	Over The Counter
PACTR	Pan African Clinical Trials Registry
PIMs	Potentially Inappropriate Medications
PIN	Personal Identification Number
PIP	Potentially Inappropriate Prescribing
PIQ	Pre-Interview Questionnaire
PPI	Participant and Public Involvement
PRISMA-ScR	Preferred Reporting Items for Systematic reviews and Meta-Analysis extension for Scoping Review

RCT	Randomized Controlled Trial
SAA	Serum Radioreceptor Anticholinergic Activity Assay
SmPC	Summary of Product Characteristics
SSRI	Selective Serotonin-Reuptake Inhibitor
TCA	Tricyclic Antidepressant
TCD	Trinity College Dublin
TDF	Theoretical Domain Framework
TILDA	The Irish Longitudinal Study on Ageing
TRIP	Turning Research into Practice
USDeN	United States Deprescribing Research Network
WHO	World Health Organisation

Presentations and Publications

Oral Presentation at national and internation conferences:

- **THEconf2023, Trinity College Dublin, Ireland, 7-9 March 2023**
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Chapter 1

Introduction

1.1 Intellectual Disability

1.1.1 Definition of Intellectual Disability

The definition of intellectual disability in this study is based on the criteria used by the primary data source, the Intellectual Disability Supplement to The Irish Longitudinal Study on Ageing (IDS-TILDA) (1). IDS-TILDA recruited its participants using the sampling frame from the National Intellectual Disability Database (NIDD) in Ireland (2). Consequently, the definition of intellectual disability in this aligns with that used by the NIDD, which adopts its definition from the World Health Organization's (WHO) Classification of Mental and Behavioural Disorders (ICD-10). The WHO defines intellectual disability (previously referred to as "mental retardation") as "a significantly reduced ability to understand new or complex information and to learn and apply new skills (impaired intelligence). This results in a reduced ability to cope independently (impaired social functioning) and begins before adulthood, with a lasting effect on development" (3). Intellectual Disability develops from birth or during early childhood. Individuals with this condition typically require support in daily activities throughout their lives due to difficulties with learning, understanding, retaining new information, and communicating. Diagnosis is determined by a standardized Intelligence Quotient (IQ) score below 70 and is classified into the following categories: mild (IQ score between 50 and 69), moderate (IQ score between 35 and 49), severe (IQ score between 20 and 34), and profound (IQ score estimated to be under 20).

Other organizations have their own definition for intellectual disability. The American Association on Intellectual and Developmental Disability (AAIDD) defines it as "a condition characterized by significant limitations in both intellectual functioning and adaptive behaviour before the age of 22" (4). Intellectual functioning refers to mental capacity, including the ability to learn, and solve problems. Adaptive behaviour is about the social, conceptual, and practical skills necessary for everyday life. Conceptual skills involve language, literacy, self-direction, and understanding concepts like time, money, and number. Social skills include interpersonal abilities, self-esteem, social responsibility, ability to follow the rules, and solving of social problems. Practical skills refer to daily activities such as transportation, personal care, healthcare, daily routines, use of telephone and money, safety and occupational skills.

According to the National Health Service (NHS), the term intellectual disability (also known as “learning disability”), is defined as “a global impairment of intellectual ability causing difficulty with learning and everyday activities. It affects someone for their whole life” (5). People with intellectual disability may experience difficulties in learning new information, adapting to new situations, problem solving, communication and developmental progression.

1.1.2 Aetiology of Intellectual Disability

Intellectual disability could be caused by one, or more, of three different factors. These are: 1) genetic factors (chromosomal or heredity), 2) acquired (congenital and/or developmental), 3) environmental and sociocultural (6). These are explained below.

1. The genetic factor:
    a. Chromosomal or hereditary disorders such as Down syndrome, Fragile X chromosome syndrome, Rett syndrome, Prader-Willi syndrome, neurofibromatosis, tuberous sclerosis, adrenoleukodystrophy, lesch-Nyhan syndrome and other very rare disorders.
    b. Heredity factors such as phenylketonuria, galactosemia, Tay-Sachs disease, glycogen deposit disease, Mowat-Wilson syndrome. Most of these are autosomal recessive conditions that could be associate with development of intellectual disability, motor dysfunction, verbal dyspraxia or hypogonadism.
2. The acquired factors
    a. Congenital factors could be metabolic such as neonatal hypothyroidism, infectious such as syphilis, simple herpes, toxoplasmosis, Cytomegalic Inclusion Body Disease or toxic such as foetal alcohol syndrome or lead poisoning.
    b. Developmental factors include prenatal complications such as uncontrolled diabetes, umbilical cord prolapses, vaginal haemorrhage, intrauterine malnutrition and placenta previa. There are also perinatal and birth complication asphyxia related to suffocation, prolonged suffering with neonatal anoxia, and inadequate application of high forceps. In addition to

postnatal complication including encephalopathy from hyperbilirubinemia, encephalitis, meningitis, and encephalic traumatism.

3. Environmental and sociocultural factors
    a. In developing countries, poverty has been linked with intellectual disability. There are a wide range of environmental and psychosocial factors that have an impact on developing intellectual disability and these include, poor prenatal, perinatal and postnatal healthcare, family instability, adolescent maternity, infant mistreatment, and level of education.

1.1.3 Prevalence of Intellectual Disability

According to the NIDD in Ireland, by end of 2017, the prevalence rate of people with intellectual disability was 5.96 per 1000 population based on the 2016 census population data (2). The prevalence rate of people with mild intellectual disability was 1.92 per 1000 compared to 3.49 per 1000 for moderate, severe or profound intellectual disability. The number of people aged 35 years or more with intellectual disability has increased from 28.5% in 1974 to 49.1% in 2017, indicating the extending of lifespan of people with intellectual disability in Ireland (2). A meta-analysis study which included 52 publications between 1981 and 2008, reported a worldwide prevalence of 10.37 per 1,000 population (7). A more recent systematic review that included publications from 1999 up to 2019, found that 107.62 million people globally had intellectual disability which equates to about 2% of the global population, with an annual percentage change of -0.80 (8). The same study reported a slightly higher prevalence of intellectual disability in males (1.42%) compared to female (1.37%). A lower prevalence was found in regions/countries with a high socio-demographic index (0.33%) compared to regions/countries with a low-middle socio-demographic index (2.42%). The prevalence rate of intellectual disability decreased with age, with a rate of 18.30 per 1,000 population (95% CI 15.17-21.43) in children and adolescent, compared to 4.94 in 1,000 population in adults (95% CI 3.66- 6.22) (7, 8).

1.1.4 Ageing and Life Expectancy among those with Intellectual Disability

Data from the NIDD, has shown that the mean age of death rose from 47.1 years in 2001 to 53.1 in 2016 in Ireland (9). Although there was an increase in the mean age of mortality in both sexes, females with intellectual disability had a higher mean age of death (55.9

years) compared to males (52.1 years) with intellectual disability in 2016 (9). Furthermore, the mean rate of deaths increased by over five- to eight-fold, from those with mild level of intellectual disability to those with profound level of intellectual disability, as illustrated in *Table 1.1-1.* Additionally, the mean rate of death is 48% higher for those living in community homes and 29% higher for those in residential settings compared to individual with intellectual disability living in family homes or independently (9). Another study in Ireland, conducted in 2015, compared mortality rates to the general population. It found that people with intellectual disability are dying 19 years earlier and have a mortality rate four times higher than the general population (10). Although the life expectancy of people with intellectual disability is rising, it remains lower than that of the general population, who have an average age at death of 66.1 years (11).

Table 1.1-1 Mean rate of death per 1,000 between 2009-2016 in people with intellectual disability based on the level of intellectual disability in Ireland (9).

Level of Intellectual Disability	Mean rate of death per 1,000	95%CI
Mild	4.79	(4.22–5.36)
Moderate	9.10	(8.17–10.03)
Severe	18.69	(16.57–20.81)
Profound	35.50	(30.41–40.59)

The average life expectancy of people with intellectual disability is based on the causes and aetiology of the conditions. For example, people with Fragile X and Down syndrome live longer compared to people with Tuberous Sclerosis, Rett, Williams and Cerebral Palsy (11). The increase in life expectancy among people with intellectual disability has occurred recently, resulting in limited data on disease patterns after middle age. It is not yet known if this increase in life expectancy will lead to a delay in the onset of age-related diseases. This increased in life expectancy in people with intellectual disability could be attributed to improvements in healthcare resulting in better medical intervention, especially treatment of respiratory infections and congenital heart conditions (11). For example, the life expectancy of people with Down syndrome has increased from 9 years in 1929 to over 70 years in 2013, primarily due to the introduction of antibiotics to treat respiratory infectious diseases in the 1950s. Due to the enhanced vulnerability of their immune

system, respiratory infections used to be a major cause of death in people with Down syndrome (11, 12). Deinstitutionalisation, (moving from institutional settings to community home settings) has been shown to have a positive impact on life expectancy among various European countries (11, 13). Countries at early stage of deinstitutionalization had reported higher prevalence of chronic bronchitis, gastric and duodenal ulcers, osteoporosis and myocardial infarction among people with intellectual disability compared to countries at advance level of deinstitutionalisation. For those living with families or independently, the provision of health services in Primary Care, such as medical checks, cancer screening and vaccination, was lower than for those in institutions (13).

1.1.5 Morbidity in People with Intellectual Disability

According to a study conducted in Ireland, more than 70% of people with intellectual disability reported multimorbidity (defined as two or more chronic conditions), and the most prevalent diseases are as follow; eye disease, mental health condition, neurological disorder, gastrointestinal disease, endocrine disorders, joint disease, hypertension, heart conditions, lung disorders, cancer, stroke and liver disease (14). The prevalence of eye diseases, mental health conditions, endocrine diseases, joint diseases, cancer, hypertension and stroke were all significantly associated with increased age. Furthermore, eye diseases, hypertension and joint diseases were significantly higher in females with intellectual disability compared to males with intellectual disability. The multimorbidity pattern was mental health conditions/neurological disorders in people with intellectual disability, compared to cardiovascular/metabolic diseases, and liver/lung/joint/eye diseases in people without intellectual disability (14).

There are a wide range of medical conditions associated with intellectual disability. These conditions could be classified as; primary health conditions or secondary health conditions (15). The primary health conditions indicate all medical conditions that are directly associated with the intellectual disability and these include mobility problems such as cerebral palsy, hearing and visual problems, epilepsy, psychosis, and mental health conditions, *etc,*. Syndrome-related conditions include medical conditions that co-occur or are genetically related to certain types of intellectual disability, for instance hypothyroidism in people with Down syndrome. The secondary medical conditions are

those occurring at higher rate in people with intellectual disability compared to general population. These condition are considered as preventable and it includes; constipation, gastro-oesophageal reflux disease, obesity, edentulous and untreated dental caries (15).

Older adults with intellectual disability have a higher burden of multimorbidity compared to older people in the general population (16). The early occurrence of multimorbidity contributes to early aging and frailty in people with intellectual disability. Multimorbidity is common across all age groups in people with intellectual disability compared to the general population where it is more prevalent in those aged 50 and over (16). In the Netherlands, at age 18, people with intellectual disability are more likely to have developed a chronic disease compared to those without intellectual disability (17). This study also found that males are more vulnerable to chronic disease and multimorbidity in comparison to females with intellectual disability.

The prevalence of multimorbidity among people aged 40 years and over with intellectual disability is 71.2% (14) compared to 58.6% for general population aged 65 or over (18). Dementia is a common condition with ageing people, both in the general population and in people with intellectual disability. However, it can present earlier in people with intellectual disability, particularly between the age of 51-56 in people with Down syndrome, compared to 65 years or older in the general population (19). Additionally, people with intellectual disability have higher incidence of mental health conditions (including bipolar disorder, depression and schizophrenia), neurological diseases (such as dementia and epilepsy), gastrointestinal disorders (including oesophageal reflux and peptic ulcer) and a lower incidence of cardiovascular diseases (16, 20).

In comparison to the general population, people with intellectual disability have poorer physical health and their health needs are often unrecognised and unmet (21, 22). The inequality in receiving health care is a concern for healthcare systems and people with intellectual disability and their families in developed countries. More than a third of deaths in people with intellectual disability are amenable to healthcare and consequently the proportion of avoidable deaths was higher (21). While many of the leading causes of death among people with intellectual disability are similar to those in the general population, there are notable differences. Respiratory diseases are one of the leading causes of death in people with intellectual disability, with significant contribution also coming from urinary and neurological diseases. These findings highlight opportunities to

improve care by enhancing the management of pneumonia, aspiration, urinary infections and seizures in individual with intellectual disability (21). As a result of the high rate of multimorbidity, medication use is significantly higher in people with intellectual disability to manage the associated disease burden (23-25).

1.1.6 Medication Use Among General Older Adults

People are living longer but not necessarily in better health (23). As noted above in section 1.1.5, multimorbidity can increase consumption of medication. Generally, as people age, various normal physiological changes take place that can impact how they process and respond to medication. For instance, reduction in body mass, blood flow, body water, gastric motility, hepatic and renal functions, all impact on the pharmacokinetics of medication (26-28) via changes in the absorption, distribution, metabolism and excretion of medications by the body (29). Additionally, pharmacodynamics, defined as the effect of medication on the body and their mechanism of action (29), is also affected by ageing. This results in greater sensitivity to various classes of medications and their associated adverse effects, including benzodiazepines, anticholinergics, and opioids (27, 30). These age-related changes in pharmacokinetics and pharmacodynamics may be heightened in older adults with frailty, making them particularly vulnerable to adverse effects of medication (31, 32). Furthermore, there are other age-related changes that should be considered while prescribing for older adults including difficulty swallowing, loss of vision, hearing difficulty and decrease in coordination. These might interfere with a patient's ability to administer and adhere to their prescribed medication regimen (27, 33-35). Older adults tend to have a higher consumption of over the counter (OTC) and complementary and alternative medication (CAM) compared to younger people (36-39). Due to the increase in medication and supplement use, older adults are at a potentially higher risk of drug interactions (40, 41).

Although older adults are prescribed medications at a high rate, there is insufficient evidence-based data on the safety and efficacy of medication use in this population. The insufficient clinical trials related to older adults resulted in limited evidence-base treatment and prescribing guidelines which make prescribing challenged for prescribers (42). It is well-established that older adults are often excluded or underrepresented in clinical trials (43-47). However, they can be excluded not only because of their age but also

due to multimorbidity and polypharmacy (defined as concurrent use of five or more medications), which increases the risk of drug-drug interactions, drug-related events, falls, hospitalisation and impact on quality of life (43, 48, 49). Furthermore, there have been encouraging development in trials inclusion, for instance, in 2019, the National Health Institute (NHI) amended its policy for all funded-NHI trials to include people of various ages (50). Additionally, in 2022, the Food and Drug Administration (FDA) issued guidance for the industry on the inclusion of older adults in cancer clinical trials (51).

1.1.7 Medication Use Among Older Adults with Intellectual Disability

People with intellectual disability are described as being among "the most medicated group in society", with a greater rate of prescription and polypharmacy compared to the general population (23-25). A nationally representative study, known as The Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA), was conducted among older adults aged 40 and over with intellectual disability in Ireland. Further details are provided later in this chapter, see section 1.2. Researchers from both IDS-TILDA and The Irish Longitudinal Study on Ageing (TILDA) examined the differences in medication use between older adults in the general population and older adults with intellectual disability aged 50 or more who live in the community (23). They found that the use of medications and supplements are much greater in people with intellectual disability. More interestingly, the rate of excessive polypharmacy (concomitant ingestion of 10 or more medications), is six times higher in people with intellectual disability compared to the general population (11.3% in people with intellectual disability versus 1.9% in the general population) (23). The use of supplements was twice as high in people with intellectual disability, however, they reported a smaller range of supplements compared to the general population. In both IDS-TILDA and TILDA, females reported higher medication and supplement use in comparison to men (23).

A Swedish study found that people with intellectual disability are more likely to be prescribed medications with anticholinergic activity, intermediate- and long-acting benzodiazepines, and antipsychotics in comparison to the general population (52). In contrast, people with intellectual disability were less likely to be prescribed Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) compared to the general population. Another study had investigated pain management medication and reported that people with intellectual

disability are more likely to be prescribed paracetamol or fentanyl for all types of pain diagnoses compared to the general population (53). Additionally, they were less likely to be prescribed COX, COX-2 inhibitors, weak opioids, migraine medication, and tricyclic antidepressants in comparison to the general population. People with intellectual disability are less likely to be diagnosed with headaches, musculoskeletal pain, pain related to respiratory system or circulatory system in comparison to the general population. However, they are more likely to report pain related to urinary system and visceral pain (53).

In older adults with intellectual disability, the complexity of polypharmacy, age-related risk of adverse effects and the presence of organic brain dysfunction are all compounded together and may result in idiosyncratic responses to drugs (54). In addition, the presence of organic brain dysfunction is considered as the cause of unpredictable response to psychotropic medications in this population. In many people with intellectual disability, brain damage is the main cause of the intellectual disability (55). The nature of the damage and the change that has occurred to the brain structure may result in an altered response and sensitivity to medications. This can therefore be a challenge to prescribers to determine an appropriate dose (55). Additionally, the difference in physical status may result in altered hepatic and renal capacity, and a change in the volume of distributions which can lead to uncertainty in how the body might respond to medication (55). Edentulous, poor oral health and difficulty swallowing are all factors that contribute to challenges in swallowing tablets in people with intellectual disability (56).

Polypharmacy and potentially inappropriate prescribing (PIP) in older adults with intellectual disability highlight several challenges. These include difficulties in obtaining consent for treatments, a lack of robust evidence due to the exclusion of individuals with intellectual disability from pharmacological randomized controlled trials (RCTs), challenges in communicating symptoms and adverse drug reactions (ADRs), and greater sensitivity to medication and their adverse effects due to organic dysfunction associated with individuals with intellectual disability (57). In comparison to the general population, there are much fewer studies on the prevalence of polypharmacy in people with intellectual disability. Instead, research has focused on polypharmacy within specific classes of medications, such as psychotropic drugs (58-62) and antiepileptic medications (63-65). In people with intellectual disability, higher rates of polypharmacy were

associated with mental health conditions, neurological diseases, living in institutional settings, and being female (66, 67). Different prescribing patterns were reported in people with intellectual disability compared to the general population. For example, among people with intellectual disability, antipsychotics medications, antiepileptics, antidepressants and laxatives are the most frequently reported medication classes (24, 67, 68). In contrast, cardiovascular medications, analgesics, gastrointestinal agents and antithrombotic medications are the most frequently reported therapeutic groups (69, 70).

1.1.8 Anticholinergic Medications

Anticholinergic medications are a type of medication that block acetylcholine receptors, of which are two main types of receptors: muscarinic and nicotinic receptors. Therefore, the term anticholinergics includes those with antimuscarinic and antinicotinic activity. There are two types of nicotinic receptors; N1 which is located in peripheral and muscle receptor type, and N2 which is mainly distributed centrally or neuronal receptor type (71). Muscarinic receptors are widely distributed in both the central nervous systems (CNS) and peripheral systems. In addition, there are five subtypes of muscarinic receptors (M1, M2, M3, M4 and M5) which have different functional responses and disease relevance as illustrated in *Table 1.1-2* (72, 73).

Table 1.1-2 Subtypes of muscarinic receptors, adapted from Brunton and Ritter *et al (2011).*

	M1	M2	M3	M4	M5
Functional Response	• Cognitive function • Seizure • Secretion • Dopamine release	• Heart rate • Smooth muscle contraction	• Smooth muscle contraction (mainly bladder) • Secretion (salivary glands) • Dopamine release • Food intake	• Analgesic • Cataleptic activity • Facilitate dopamine release	• Facilitate dopamine release • Drug-seeking behaviour and reward
Disease Relevance	• Cognitive dysfunction • Alzheimer's disease • Schizophrenia	• Cognitive dysfunction • Alzheimer's disease • Pain	• Urinary incontinence • Chronic obstructive pulmonary disease (COPD) • Irritable bowel syndrome	• Neuropathic pain • Schizophrenia • Parkinson's disease	• Schizophrenia • Parkinson's disease • Drug dependence

Anticholinergic medication can be classified into three categories; *i)* naturally occurring alkaloids (such as atropine and scopolamine), *ii)* semisynthetic derivatives alkaloids (such as ipratropium, tiotropium, tropicamide and homatropine) and, *iii)* synthetic derivatives (such as solifenacin and darifenacin) (73). In drug development, it is difficult to obtain selective muscarinic receptor antagonism due to the orthosteric sites which remain conserved across the receptor subtypes.

Anticholinergic activity can be identified both centrally and peripherally. The peripheral activity occurs by targeting the autonomic nervous system (ANS), which is mainly responsible for controlling heartbeat, contraction and relaxation of vascular and visceral smooth muscle, and energy metabolism. Some of the medication used for pupil dilatation, known as mydriasis and mainly used for ophthalmological examination. They are also used for management of Parkinson's disease, severe insomnia, obsessive-compulsive disorders, bipolar disorder, motion sickness, overactive bladder, asthma, chronic obstructive pulmonary disease (COPD), cardiovascular diseases, neuropathic pain, muscle spasm, and irritable bowel syndrome (71-74).

The adverse effects associated with the use of anticholinergics are divided into central and peripheral adverse effects depending on cholinergic receptors affected, and on their affinity for the cholinergic receptor. Medications with anticholinergic activity that can cross the blood-brain barrier and act centrally, are associated with adverse effects including decline in cognitive function, memory impairment, headache, behavioural disturbances, insomnia and anxiety (75, 76). Furthermore, when used at high doses the adverse effects include confusion, agitation, delirium and seizures. Peripheral anticholinergic adverse effects include hyperthermia, anhidrosis, tachycardia, arrhythmias, constipation, vomiting, dry mouth, dry eyes, urinary retention, blurred vision, mydriasis, narrow-angle glaucoma, potential vision loss and muscle relaxation (76, 77).

The higher anticholinergic exposure (defined in section 1.1.9 below), the higher risk of adverse effects (78-80). Older adults are at higher risk of exposure to anticholinergics due to medications prescribed to manage age-related health conditions. Additionally, age related conditions such as constipation, urinary dysfunction and dementia, may be worsened with anticholinergic exposure (81, 82). The use of medications with anticholinergic activity has been considered as potentially inappropriate in older and frail

adults (83, 84), including vulnerable older people and those with dementia (85). There are many medications that possess some level of anticholinergic activity, which is mainly not responsible for the therapeutic effect but it can contribute to the adverse-effect associated with the medication (86). For example, antipsychotics, tricyclic antidepressants, and diphenhydramine have anticholinergic activity despite not impacting on the therapeutic effects of the medication.

1.1.9 Measurement of Anticholinergic Exposure

The anticholinergic propriety of medication could be measured by three methods:

1. Serum Radioreceptor Anticholinergic Activity Assay (SAA).
2. In vitro measurement of drug affinity to muscarinic receptors.
3. Expert-based list of medications with anticholinergic activity (79).

The SAA method measures the cumulative anticholinergic burden caused by all medications and their metabolites (79). It measures both prescribed and OTC medications but reflects a transitional state outside the brain. Cognitive impairment has been reported with many medications despite normal SAA concentration. Additionally, many epidemiological studies reported no association between SAA and number of medications with anticholinergic activity taken by the patient.

The second method, *in vitro* measurement of drug affinity to muscarinic receptors, uses SAA method but includes an *in vitro* sample (79). It measures the direct anticholinergic effect through measuring medication binding into specific muscarinic receptor and measuring the antagonistic effect with a comparative cholinergic agonist. In clinical perspective, this method is limited to medication with a clear peripheral anticholinergic effect, and it has limitations in measuring central anticholinergic activity.

The third method, expert-based list of medications, is established based on opinions of clinicians, pharmacists and pharmacologists and researchers to combine their expertise, along with drug information available in the literature, to determine the anticholinergic activity of specific medications (79). This method is the most clinically relevant method however is considered as the least standardized one. A list of expert-based medications with anticholinergic activity and scales are described below. These are the Anticholinergic Cognitive Burden scale (79), the anticholinergic drug scale (87), the Anticholinergic Risk Scale (88), the Anticholinergic Burden Classification (89), the Anticholinergic Loading Scale

(90), the Clinical-rated Anticholinergic Score (91), and the Anticholinergic Activity Scale (86).

1. **Anticholinergic Cognitive Burden (ACB) Scale:** This is a tool developed by Boustani *et al.*, to identify the severity of anticholinergic negative effect on cognition of both prescribed and OTC medications (79). These negative cognitive effect includes delirium, mild cognitive impairment, cognitive decline and dementia. Each medication assigned a score based on their negative effect on cognition. The tool provides the clinician with a simple score that captures the cumulative anticholinergic cognitive burden resulting from all medication taken by the patient. This tool was developed by searching all published literature which measured the anticholinergic activity of medication and examining associated outcomes including cognitive decline in older adults. The authors provided a list of all studied medication, and the method used to measure the anticholinergic activity. The list was then reviewed by an expert multidisciplinary team which included geriatricians, geriatric psychiatrists, general physicians, geriatric pharmacist, geriatric nurse and ageing brain researchers. The expert multidisciplinary team had classified the medication into mild, moderate and severe cognitive anticholinergic negative effects. Additionally, they established a scoring system as presented in *Table 1.1-3* below. The total score for a patient was calculated by summing the score of all taken medication to determine the cumulative anticholinergic cognitive burden.

Table 1.1-3 Scoring system in the Anticholinergic Cognitive Burden Scale

Score	Medication Description
0	For all medication with no anticholinergic effects
1	For medication with possible anticholinergic effects (according to SAA and/or the in vitro affinity to muscarinic receptors but with no clinically relevant negative cognitive effects).
2 or 3	For medications with established and clinically relevant cognitive anticholinergic effects and based on their ability to cross the blood-brain barrier and causes delirium.

2. **Anticholinergic Drug Scale (ADS):** This tool was developed by Carnahan and colleagues to assist physicians identify the anticholinergic adverse effect among

older adults (87). The tool determines anticholinergic activity of medication based on their effects on the serum anticholinergic activity. Medication classified into score of 0 to 3, with 0 indicating no anticholinergic activity and 3 for significantly marked anticholinergic activity. They had found an association between the ADS and the SAA level, but it is not certain if there clinically significant outcomes associated with the SAA level and that is because there are some medications known to have a negative cognitive effect but reported normal level of SAA. Additionally, it had been reported by some studies, there was no association between the SAA level and the number of medications with anticholinergic activity taken by individual (87). The ADS did not involve expert review and did not focus on anticholinergic negative cognitive effects. Therefore, the ADS is better than ACB is measuring peripheral anticholinergic adverse effects. The team has found that total score of ADS was significantly associated with SAA among long-term care residents (79, 87).

3. **Anticholinergic Risk Scale (ARS):** The ARS tool was developed by Rudolph *et al.* (2008) and measures both central and peripheral anticholinergic effects (88). It was developed by studying the top 500 prescribed medication within a veteran health care system in Boston. The anticholinergic activity of the 500 medications was determined via literature search. Similarly to the ADS tool, medication was ranked from 0 to 3 based on the strength of anticholinergic effect. Higher ARS scales found to be associated with a higher rate of reporting anticholinergic adverse effects (88). In comparison to the ACB, the ARS focused on one healthcare system that serves mainly a male population, therefore it wasn't based on systematic evidence review of the literature. In addition, the ARS captured both peripheral and central anticholinergic adverse effects, and included falls, dizziness and confusion as central adverse effects. However, it did not use a standardized cognitive assessment for assessing confusion, for example Mini-Mental State Examination (MMSE) or the confusion assessment scale. Therefore, Boustani and colleague believe that categorization of ACB is more accurate to measure the anticholinergic negative effect on cognition compared to the ARS or the ADS scales.

However, all of the three scales noted above are easily applied to drug lists in both research or clinical settings to establish the total drug-related anticholinergic burden and do not require specialised laboratory testing (79).

4. **Anticholinergic Burden Classification:** This tool focuses on negative effect on cognition of medicines with anticholinergic activity, and it was developed based on the SAA and average estimated clinical effect of the medication (89) with medications scored on a scale from 0 to 3 based on the potency of their anticholinergic effects. The tool found a significant association between the long-term exposure to anticholinergics and a cognitive decline in older adults, similarly to a cognitive decline in young adults associated with scopolamine use (89).
5. **Anticholinergic Loading Scale:** Same as the Anticholinergic Burden Classification, this tool was developed in same method, with a similar scoring system, and focuses on cognitive decline. It had been reported that a higher Anticholinergic Loading Scale score was associated with slower response speed as a measure of cognitive function (90).
6. **Clinical-rated Anticholinergic Score:** This tool was established to assess association between the use of medications with anticholinergic activity and the severity of delirium in older adults (91). Like previous tools, this tool had same scoring system from 0 to 3, however the scoring values were selected by consensus of three geriatric psychiatrists' clinicians. The tool was studied among 544 older men and found an association between long-term use of anticholinergics and a decline in executive function and verbal memory (91).
7. **Chew *et al.,* (2008):** This group conducted a study on 107 medications with anticholinergic activity, most frequently used on older adults (86). They employed rodent forebrain and striatum homogenate to measure an *in vitro* drug binding affinity to muscarinic receptors. The 104 studied medications were the same included in other studies.
8. **Anticholinergic Activity Scale:** This scale was established based on findings of the work conducted Chew *et al.* (2008). Medication was scored from 0 to 4 based on their affinity to bind muscarinic receptors (86). Older adults with Parkinson disease was reporting a decline in cognitive function when exposed to anticholinergics (92).

1.1.10 Anticholinergic Exposure Among Older Adults with Intellectual Disability

People with intellectual disability experience a higher incidence of multimorbidity and higher prevalence of polypharmacy, and are exposed to high anticholinergic burden (67, 93). Additionally, the higher prevalence of mental and neurological diseases in people with intellectual disability was associated with a high exposure rate to medication with anticholinergic activity (94, 95). A Scottish study determined that high anticholinergic exposure was found in adults with intellectual disability, from 17 to 94 years old (93). However, the highest anticholinergic burden was reported in those aged 55 years or over; females had a higher exposure to anticholinergic burden in comparison to males. According to cross-sectional studies conducted in Ireland using IDS-TILA data, high anticholinergic exposure in older adults with intellectual disability was significantly associated with adverse effects such as constipation, daytime dozing, higher dependence level in activities of daily living based on Barthel Index, decline in physical function including timed up-and-go and grip strength, and multiple laxatives use (20, 67, 96).

The long-term exposure to anticholinergics had been studied among the general elderly population, and it has been associated with a decline in both physical function and cognitive function (91, 97-100), higher risk of dementia (101), and a higher mortality rate among elderly people discharged with a high score in Geriatric Depression Scale (102).

A scoping review on anticholinergic adverse effects following long-term use, conducted by this PhD candidate, highlighted a major gap in knowledge. This scoping review is presented in detail in *Chapter 2*.

1.2 The Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA)

1.2.1 IDS-TILDA Study Design

The IDS-TILDA is a national longitudinal study researching how older adults (aged 40 years or older) with intellectual disability in Ireland age (1). Each person with intellectual disability is assigned a personal identification number (PIN) when registered with the NIDD (1). The NIDD provided the sampling frame and facilitated the random selection of 1800 PINs of older adults with intellectual disability for IDS-TILDA. The study aims to identify the principal influences on successful ageing in people with intellectual disability and to compare those with the general population. Following expert input and comparison with TILDA, the conceptual framework of IDS-TILDA includes six main research areas with sub-categories in each section as illustrated in *Figure 1.2-1.* These are physical and behavioural health, mental and cognitive health, utilisation of healthcare services, social network and support, employment, retirement, day services and lifelong learning and quality of life experience (1).

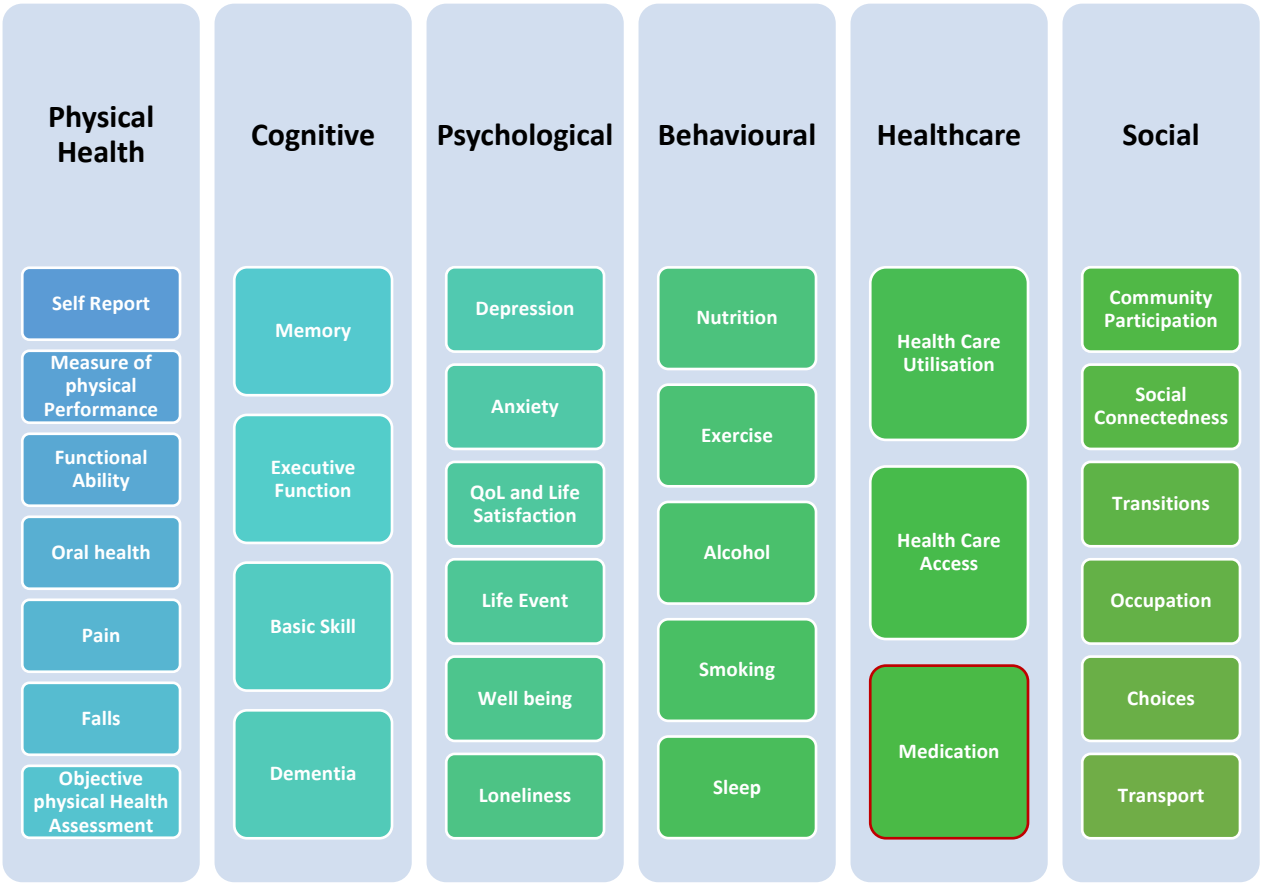

Figure 1.2-1 IDS-TILDA conceptual framework

To date, IDS-TILDA has completed data collection of five waves: Wave 1 (2009/2010), Wave 2 (2013/2014), Wave 3 (2016/2017), Wave 4 (2019/2020) and Wave 5 (2022/2023). *Figure 1.2-2* illustrates the sample involved in IDS-TILDA across the first four waves, as data from Wave 5 was not used for this thesis.

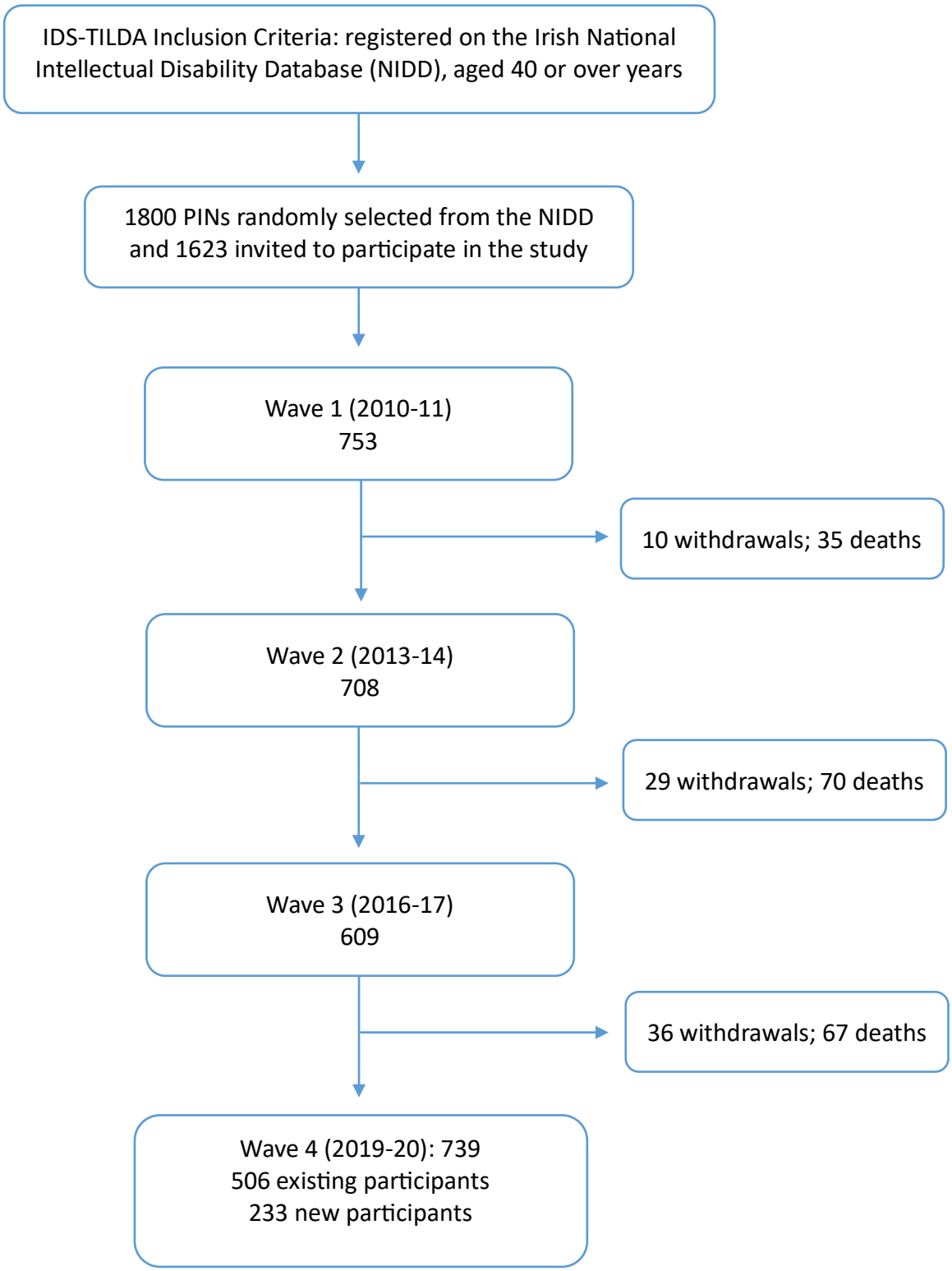

Figure 1.2-2 IDS-TILDA sample flow chart (Wave 1-Wave 4)

The development of IDS-TILDA included people with intellectual disability in the study design as well as a range of key stakeholders. IDS-TILDA developed an International Scientific Advisory Committee which was involved in the process of study protocol development and recruitment of people with intellectual disability (103). A Patient and Public Involvement (PPI) panel was established in IDS-TILDA to involve people with intellectual disability, as explained in *section 1.2.2* below.

1.2.2 Participants and Public Involvement in IDS-TILDA

PPI panel was established to include individuals with intellectual disability to actively participate in the early foundational stages of IDS-TILDA (103). They played a key role in designing the study's logo and took part in a National Photographic Exhibition, where they shared their thoughts and opinions on 'What ageing means to us.' Additionally, they have been involved in consultancy workshops aimed at enabling their input and advice on the study's protocol, processes, and accessible materials. They are also involved in developing easy-read materials and reports. Moreover, they contribute to prioritizing research areas by voting based on their opinions and perspectives. Individuals with intellectual disability, along with their families, carers, or service providers, have participated in developing and reviewing the study documents, including the study protocol, consent forms, Pre-Interview Questionnaires (PIQ), and Computer-Assisted Personal Interview questionnaires (CAPI). They have also contributed to designing accessible materials for dissemination, research reports, and the study's website.

1.2.3 Retention of Sample and Refresh Strategy

IDS-TILDA first started data collection in 2008, with 753 people with intellectual disability aged 40 years or older participating in Wave 1, representing 46% of the total invited sample (103). Followed by 708 of the 753 participated in Wave 2 and 609 continued to Wave 3. There was no new recruitment of new participants either at Wave 2 or Wave 3. However, the sample was refreshed in Wave 4 with 233 new participants. This ensured that the sample size remained sufficient to represent the population of people with intellectual disability aged 40 years and over living in Ireland. This has been presented above in *Figure 1.2-2*.

1.3 Research Objectives

The development of this thesis has been based on the Medical Research Council (MRC) framework on designing or evaluating complex interventions, which was first published in 2008 and revised in 2013 (104, 105). A complex intervention is defined as an intervention characterised by;

1. Involving several interacting components,
2. Where challenging behaviours are expected from individual delivering or receiving the intervention,
3. Targeting various organisations or groups,
4. Targeting many and variable outcomes (104).

The MRC framework provides guidance to facilitate the process of developing, implementing and evaluating an intervention to enhance health services (104). According to the MRC framework, the four integral components of a complex intervention include the *i*) process of development, *ii)* pilot and feasibility, *iii)* implementation and *iv)* evaluation of the intervention. However, this research thesis will involve only the first process which is component *i)* development of the intervention. This component is described in more detail below.

The MRC framework states that the best practice when developing an intervention is to use a systematic approach: define the best available evidence and related appropriate theory (104). There are three stages that the MRC framework incorporates in the development phase:

1. Identifying existing evidence

   In this stage, an existing high quality systematic review should be identified and if there is none, one should be conducted to identify what is already known about similar intervention(s).

2. Identifying and developing theory

   This stage is about the development of the rationale of the intervention and identifying the change needed and how this could be achieved based on the existing evidence and theory.

3. Modelling process and outcomes

The third stage focuses on modelling the intervention and this will provide information on the design of the intervention and the most appropriate evaluation process to implement. A series of studies might be needed to achieve the last design of the intervention.

High anticholinergic burden has been significantly associated with daytime dozing and constipation in studies conducted previously for Wave 1 participants in IDS-TILDA (67). However, in the same study, falls and edentulous was not statistically significant with high anticholinergic burden. In wave 2, a study was conducted to examine association between Drug Burden Index (DBI) and Barthel index (BI) and there was no association between anticholinergics use and BI (96). Additionally, another study was conducted to measure association between ACB and frailty in Wave 2 (106). The study concluded that ACB was not statistically significant associated with frailty. However, these studies only examined cross-sectional associations, and longitudinal studies were needed to examine the influence of ACB on long term health outcomes for older adults with intellectual disability. There has also been no mixed methods research to examine why these medications are prescribed, which is needed to target an intervention to optimise prescribing of anticholinergics. Therefore, this thesis has been designed to include the three main components recommended by the MRC framework for the development of an intervention as outlined in *Figure 1.3-1* and discussed below:

1. Evidence gathering

   The evidence gathering stage is conducted in two stages: scoping review and longitudinal study.

   a. Scoping Review to examine the existing literature on outcomes associated with long-term exposure to anticholinergics among older adults with intellectual disability, see *Chapter 2*.
   b. Longitudinal cohort study to investigate anticholinergic adverse effects associate with long-term exposure to high anticholinergic burden, using IDS-TILDA data, see *Chapter 3*.

2. Theoretical Foundation

   A qualitative study was conducted to identify the facilitators and barriers relevant to the theoretical foundation to assess the development of an intervention on improving anticholinergic prescribing for older adults with intellectual disability. A

qualitative interview study aimed to explore prescribers' view and perspectives on the prescribing and deprescribing of anticholinergic among older adults with intellectual disability. The Theoretical Domains Framework (TDF) was used to classify the barriers and facilitators, see *Chapter 3*.

3. Data synthesis was conducted, combining the provided evidence and theoretical foundation, to support the development of an intervention aimed at improving anticholinergic prescribing practices in older adults with intellectual disability, see *Chapter 5*.

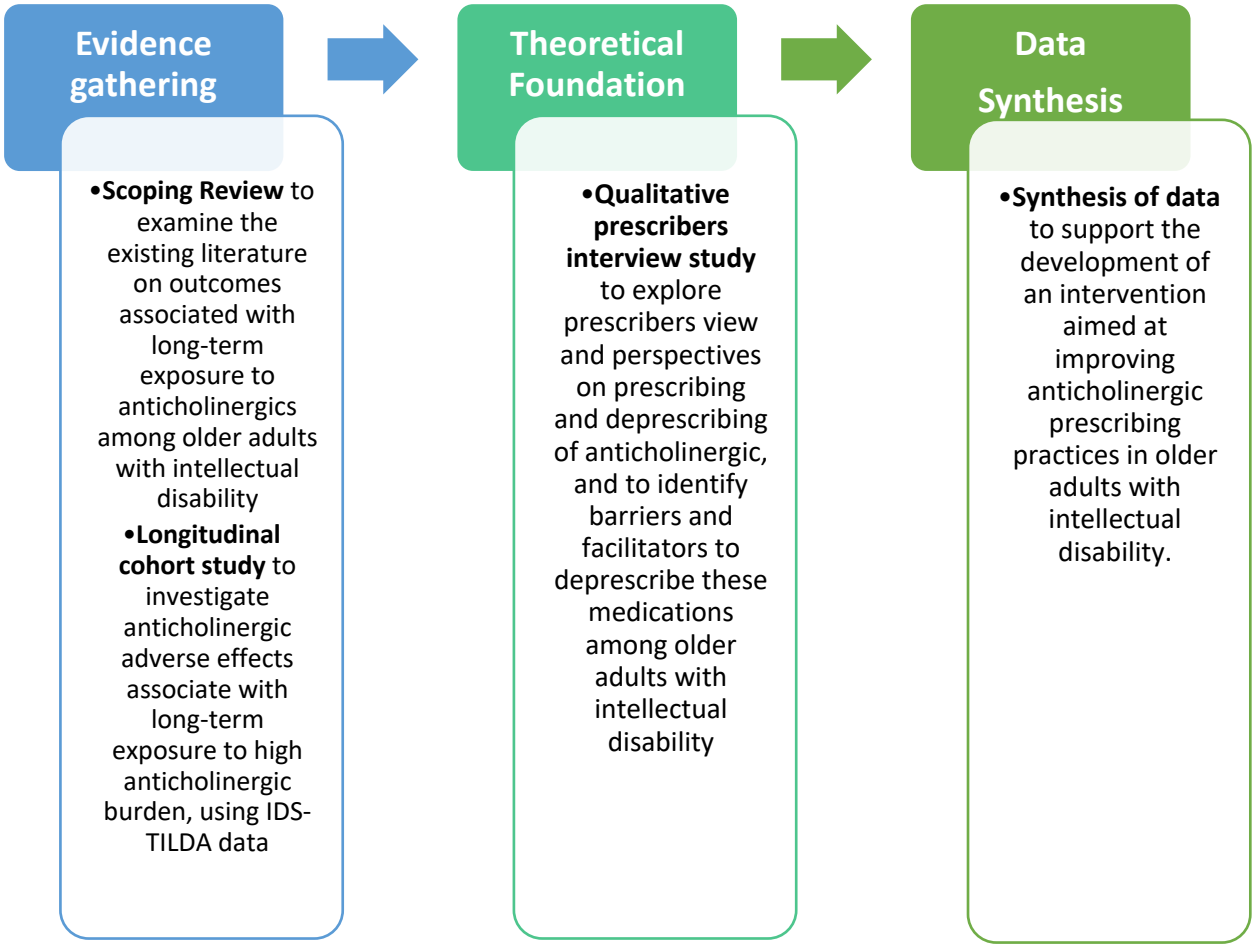

Figure 1.3-1 The three main components of the thesis based on the Medical Research Council (MRC) framework.

The aims of this thesis are as follow:

1. Map and examine the existing research literature on adverse effects associated with long-term exposure to anticholinergics among older adults with intellectual disability, presented in *Chapter 2.*
2. Examine outcomes associated with long-term exposure to anticholinergics amongst older adults with intellectual disability, presented in *Chapter 3.*
3. Explore prescriber's views and perspectives on prescribing and deprescribing of anticholinergics for older adults with intellectual disability, presented in *Chapter 4*.
4. Data synthesis in order to assess the development of an intervention aimed at enhancing the prescribing and deprescribing of anticholinergics among older adults with intellectual disability, as presented in *Chapter 5*.

The thesis aims and objectives and mapping these aims to the MRC stages and thesis chapters are illustrated in *Table 1.3-1.* Individual contribution to each study and chapters are provided is *Appendix 1.3-1*.

Table 1.3-1 Mapping aims of the thesis to the MRC and thesis chapter.

	MRC stage	Aim and Objectives	Thesis Chapter
Aim 1	**Evidence Gathering Stage**	Map and examine the existing research literature on adverse effects associated with long-term exposure to anticholinergics among older adults with intellectual disability.	**Chapter 2:** The adverse effects associated with long-term exposure to anticholinergics amongst older adults with intellectual disability: a scoping review **Chapter 5:** Discussion and Recommendations
Aim 2	**Evidence Gathering Stage**	**Aim:** to examine outcomes associated with long-term exposure to anticholinergics amongst older adults with intellectual disability. **Objectives:** 1. Examine the anticholinergic burden of people participated in Wave 1 and remined in the study at Wave 4 (linked cohort). 2. Compare the anticholinergic burden of the whole cohort at Wave 1 and Wave 4. 3. Identify and compare the most frequently reported medicines and classes of medicines contributing to anticholinergic burden in whole cohort of Wave 1 and Wave 4.	**Chapter 3:** Outcomes associated with long-term exposure to anticholinergics amongst adults aged 40 or over with intellectual disability: a longitudinal cohort study **Chapter 5:** Discussion and Recommendations

		4. Examine socio-demographic and health-related factors associated with anticholinergic burden at whole cohort in Wave 4.	
Aim 3	**Theoretical Foundation**	**Aim:** to explore prescriber's views and perspectives on prescribing and deprescribing of anticholinergics for older adults with intellectual disability. **Objectives:** 1- Recruit 8 – 10 participants involved in prescribing for older adults with intellectual disability. 2- Examine prescriber's knowledge on anticholinergic burden, anticholinergic adverse effects, tools used to quantify it 3- Identify barrier and facilitators of deprescribing of anticholinergics using the Theoretical Domain Framework (TDF) 4- Investigate prescriber's opinion on pharmacist role in deprescribing of anticholinergics	**Chapter 4:** Prescriber's view on anticholinergic deprescribing among older adults with intellectual disability: A qualitative study **Chapter 5:** Discussion and Recommendations
Aim 4	**Data synthesis for an intervention Development**	Synthesis of data to assess the development of an intervention aiming to enhance prescribing/deprescribing of anticholinergics among older adults with intellectual disability.	**Chapter 5:** Discussion and Recommendations

Chapter 2

The adverse effects associated with long-term exposure to medications with anticholinergic activity amongst older adults with intellectual disability: a scoping review

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Lamya Al Shuhaimi, Martin C Henman, Philip McCallion, Mary McCarron, Maire O'Dwyer
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2.1 Introduction

Medications with anticholinergic activity are used to manage a wide range of diseases, and they are inevitable and appropriate to treat certain psychiatric conditions and non-psychiatric disorders as explained in *Chapter 1, section 1.1.8*. Medications with anticholinergic activity have well-recognised peripheral and central adverse effects as illustrated in *Table 2.1-1* (76). Anticholinergic central adverse effects will be associated with medications capable of crossing the blood brain barrier, see *section 1.1.8*. in *Chapter 1.*

Table 2.1-1 Anticholinergic adverse effects

Central adverse effects	Peripheral adverse effects	Other adverse effects
Headache	Constipation, vomiting and dry mouth	Falls
Anxiety	Urinary retention	Higher Dependence level in daily activities
Insomnia	Blurred vision, narrow angle glaucoma, mydriasis	Frailty
Agitation	Hyperthermia and anhidrosis	
Delirium	Tachycardia, arrythmias and flushing	
Confusion	Reduced sweat	
Seizures		
Behavioural disturbance		
Reduced cognitive function		

As illustrated in *Chapter 1 section 1.1.10*, older adults with intellectual disability are exposed to a higher burden of medications with anticholinergic activity due to the high prevalence of multimorbidity, especially mental and neurological diseases. There are few observational cross-sectional studies which have examined the prevalence of high anticholinergic burden and measured the associated adverse effects among older adults with intellectual disability (20, 67, 93, 96, 106). In older adults with intellectual disability, it has been identified that high anticholinergic burden was significantly associated with daytime dozing, constipation, multiple laxatives use (67), higher dependence level using

Barthel index for measuring daily living activities (20) and decline in physical function including timed up-and-go measures and grip strength (96).

There are few longitudinal studies that have examined adverse effects associated with long-term exposure to high anticholinergic burden among the general geriatric population (91, 97-102), and people with cognitive impairments, Alzheimer's and dementia (107-111). These studies have reported that long-term exposure to a high burden of anticholinergic activity was associated with a decline in physical activity (91, 97, 98, 112), falls (113), decline in cognitive function (91, 97-100, 114), a higher incidence rate of dementia (101, 115), and Alzheimer's Disease (116) and lower health-related quality of life (117). Another study has reported that anticholinergic exposure was associated with higher mortality risk in elderly patients discharged from an acute care hospital carrying at least one dependency in basic activities of daily living (BADL) (118).

Based on the PhD candidate's preliminary research, there has been no or limited research exploring the adverse effects associated with long-term exposure to high anticholinergic burden among older adults with intellectual disability. Given that older adults with intellectual disability are expected to be more sensitive to anticholinergic central adverse effects due to their lifelong organic brain dysfunction which is associated with enhanced blood-brain barrier permeability and putative deficit in central cholinergic transmission (119). As a support of that, people with Down syndrome have genetically higher risk for developing dementia in Alzheimer's disease associated with a decline in concentration and function of central acetylcholine. Alzheimer disease is very common in the fourth decade in people with Down syndrome (120).

Therefore, the aim of this scoping review is to map and examine the existing research literature on adverse effects associated with long-term exposure to anticholinergics among older adults with intellectual disability.

2.2 Method

The scoping review followed the framework established by Arksey and O'Malley (121), further developed by Levac (122) and also guidance provided by the Joanna Briggs Institute (123). Additionally, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Review (PRISMA-ScR) was used as a reporting guideline for this review.

The framework consisted of six stages each of which are described below.

2.2.1 Identification of the Research Question

Based on the preliminary search, there are few published cross-sectional studies which have observed the burden of anticholinergics among people with intellectual disability and its associated adverse effects (20, 67, 93, 96).

To the knowledge of the PhD candidate, no research studies have examined the possible adverse effects associated with long term exposure to high anticholinergic burden among older adults with intellectual disability. Therefore, this scoping review aimed to examine these adverse effects and to answer the following research question:

What are the adverse effects associated with the long-term exposure to high anticholinergic burden among older adults with intellectual disability?

2.2.2 Identification of the Relevant Studies

The search was conducted using seven electronic databases: Cochrane library, PubMed, Medline, EMBASE, CINAHL Complete, PsycINFO and Science Direct. Additionally, grey literature, conferences papers and preliminary studies were searched through the following 12 grey literature data bases; ClininalTrials.gov; Open Grey; Google Scholar; EU Clinical Trial Register; The Turning Research into Practice (TRIP); International Standard Randomised Controlled Trial Number (ISRCTN); PROSPERO; the World Health Organisation International Clinical Trials Registry Platform search portal (ICTRP); Australian New Zealand Clinical Trials Registry (ANZCTR); Chinese Clinical Trial Registry (ChiCTR); Pan African Clinical Trials Registry (PACTR) and Clinical Trials Registry-India (CTRI).

The search included terms related to four main keywords which were 'intellectual disability', 'anticholinergic', 'adverse drug reaction' and 'long-term exposure'. The expanded search terms are listed below:

1. Intellectual Disability: 'cognitive impairment' OR 'developmental disabilities' OR 'learning disabilities' OR 'intellectual disabilities' OR 'mentally retarded' OR 'mentally disabled persons' OR 'handicap' OR 'Down Syndrome' OR 'mental retardation' OR 'persons with intellectual disability' OR 'mental deficiency' OR 'intellectual development disorders' OR 'psychosocial mental retardation' OR 'mentally disabled' OR 'mentally handicapped'
2. Anticholinergic: 'anticholinergic' OR 'anticholinergic Burden' OR 'anticholinergic agent' OR 'anticholinergic exposure' OR 'cholinergic antagonist' OR 'antimuscarinic' OR 'antimuscarinic drugs' OR 'antimuscarinic agent' OR 'muscarinic antagonist' OR 'cholinergic blocking agent' OR 'acetylcholine antagonist' OR 'cholinergic receptor antagonist' OR 'cholinergic antagonists' OR 'cholinolytics'. '
3. Adverse drug reaction: 'adverse outcomes' OR 'side effects' OR 'adverse effect' OR 'drug toxicity' OR 'drug related side effects' and 'adverse reactions' OR 'side effects of drugs' OR 'drug side effects' OR 'adverse drug event' OR 'adverse drug reactions' OR 'anticholinergic toxicity' OR 'anticholinergic syndrome' OR 'anticholinergic effect' OR 'central anticholinergic syndrome' OR 'peripheral anticholinergic syndrome' OR 'anticholinergic toxicity' OR 'anticholinergic effect' OR 'cognitive function' OR 'cognitive impairment' OR 'cognitive disorder' OR 'delirium' OR ' dementia' OR 'physical function' OR ' physical activity' OR 'frailty' OR 'accidental falls' OR 'falls' OR 'hip fracture' OR 'death' OR 'mortality' OR 'constipation' OR 'urinary incontinence'
4. Long-term exposure: 'long-term use' OR 'chronic use' OR '≥ 3 months'

The search strategy was adapted for each database, and it was conducted in May and June 2021 (2021-05-29, 2021-06-10, 2021-06-14), and it was re-run again in October 2021 (2021-10-08). The search strategy used for each database can be found in *Appendix 2.2*-1. The search strategy was developed in consultation with the subject librarian in Trinity College Dublin (TCD). Medical Subject Heading (MeSH) terms and Boolean operators were employed in each database search.

The search strategy was limited to articles in English language. There was no limitation or restriction on type of study, publishers, or place of publication. The search strategy was developed based on discussion within the research team which consist of five members.

2.2.3 Study Selection

The inclusion and exclusion criteria were developed following PICO which is a technique used to frame and answer a clinical research question (124). The acronym PICO formed by P of "patient or population", I for "intervention", C for "comparison or context" and O for "outcome". To be included in this scoping review, the study had to include adults with an intellectual disability aged 40 years or over (population), long-term exposure to anticholinergic burden (intervention), and reported and measured cognitive and physical adverse effects (outcome). The PhD candidate was aware of the limited literature in this area, and therefore any care setting was included (context).

A word document was designed to include all search records and details such as keywords, MeSH terms, search restriction, search results and number of studies fit to the stated inclusion criteria, for each database. The document was updated by the end of each search stage. Results retrieved from the searched databases were exported to EndNote 20, where duplicates were excluded. Studies were then screened based on the title and abstract to ensure eligibility to the stated inclusion criteria. This was completed independently by two members of the research team. Full articles were retrieved to assess their eligibility to fit the inclusion criteria.

The eligibility of the studies was assessed based on the following inclusion criteria.

1. **Study design:** there was no limitation of the study design.
2. **Population study:** people with intellectual disability defined as "a condition characterized by significant limitations in both intellectual functioning and adaptive behaviour that originates before the age of 22"(4).

   Generally, there is no specific age category or range used to described older adults with intellectual disability. Based on the preliminary search conducted, most of research studies consider older adults with intellectual disability are those aged ≥ 40 years (20, 67, 95, 96). Consequently, people with intellectual disability aged ≥ 40 years included to detect the largest possible number of studies. Moreover, no studies were excluded based on the level of intellectual disability of the study

population. This scoping review excluded studies with children or adults with intellectual disability aged less than 40 years old.

3. **Intervention:** the study had no limitation on tools used to quantify the anticholinergic burden. There is no specific definition for "anticholinergic long-term use" however, long-term use of benzodiazepines is considered as taking at least one benzodiazepine daily, or alternative days for at least 3 months (125). Therefore, the research team agreed to define "long-term use of anticholinergics" as the regular use of medications with anticholinergic activity for at least 3 months or more. Based on that, the scoping review included all studies which examined adverse effects associated with the use of anticholinergics for a period of 3 months or longer.

   The published studies examined the long-term anticholinergic adverse effects over a period of 1 – 20 years follow-up in general population (97, 101, 126-128).
4. **Context**: the scoping review included all studies involving older adults with intellectual disability living in all possible residence areas including, nursing homes, community group homes, independently or with family.
5. **Outcomes**: the scoping review included all published literature that examined all known anticholinergic adverse effects associated with the long-term exposure; these included peripheral and central adverse effects, as shown in *Table 2.1-1*.

   There was no restriction on tools used for assessing or reporting adverse effects.

   Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) is used for data reporting in this scoping review (129).

2.2.4 Data Charting

Relevant data was extracted from full-text articles using a pre-defined extraction framework, as shown in *Appendix 2.2-2*. Data extracted was sorted under the following headings:

1. Bibliography which included title, authors, journal, year of publication, country, aim and objectives
2. Design and settings included studied population, length of the study, reported outcomes and tools used
3. Results

4. Conclusion
5. Implication

The PhD candidate extracted all relevant data from the full-text articles using the data extraction framework. This was then reviewed independently by MO'D to check inclusion eligibility of these studies.

2.2.5 Collating, Summarising, and Reporting Results

This stage was not completed as there was no study included in the review.

2.2.6 Consultation

Stakeholders from Daughters of Charity Service, Royal College of Psychiatrists of Ireland (Intellectual disability subgroup), National Intellectual Disability Memory Service, Down Syndrome Ireland, The International Association for the Scientific Study of Intellectual and Developmental Disabilities (IASSIDD) and Tallaght Hospital, were contacted via email and consulted on the research question and to clarify any potential ongoing or relevant studies.

2.2.7 Ethics

Ethics was not required for this scoping review as it involved synthesising published research.

2.3 Results

2.3.1. Study Description

The search was conducted in 2021-10-08, resulting in 462 records retrieved from the seven electronic databases and 47 records from grey literature searches. After the removal of duplicates (n = 30), a total of 479 records remained. The titles and abstracts of these 479 records were independently screened by two members of the research team. At this stage, 473 records were excluded because they were non-longitudinal studies and, therefore, did not examine adverse effects associated with long-term exposure to anticholinergic burden, or involved a different population. Therefore, only six articles were retrieved for full-text review. These were assessed by two members of the research team (PhD candidate and MO'D). All six articles were excluded due to differences in the study population, such as general older adults or individuals with dementia, *i.e.* none of the six articles included older adults with intellectual disability. As a result, no studies were included in this scoping review. The PRISMA-ScR flowchart (*Figure 2.3-1*) illustrates the study selection process and the outcomes at each stage of the search.

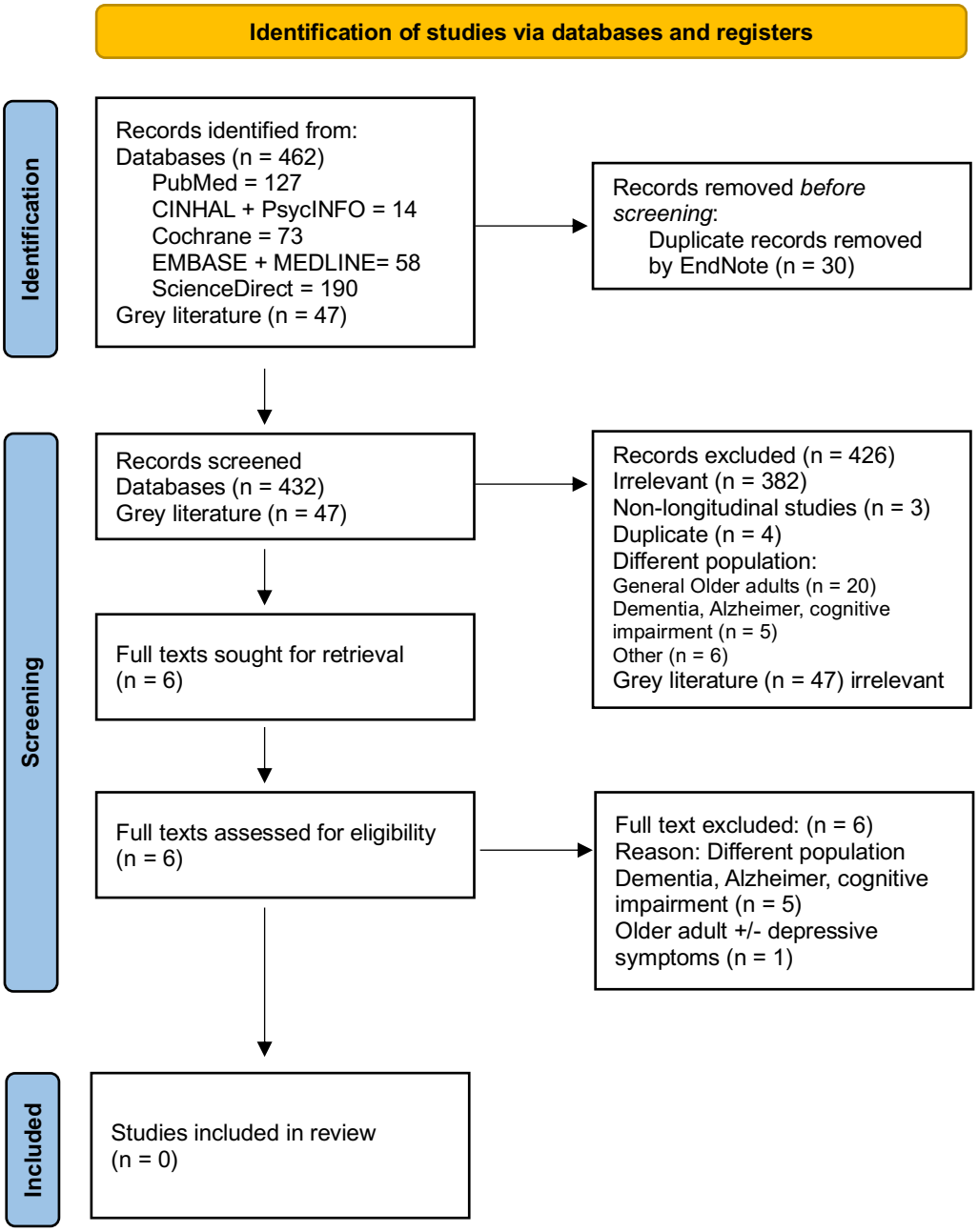

Figure 2.3-1 PRISMA-ScR Flow chart of the study selection and the results of each search process

2.3.2. Differences Between the Protocol and the Review

Stages 4 and 5 of the framework described in section 3.3, were not completed as none of the studies identified in the search met all the inclusion criteria. Therefore, there was no data to be charted, collated, summarized, and reported.

2.3.3. Findings of the Consultation Stage

Three stakeholders provided comments on the process and the findings of review, and these were Down Syndrome Ireland, The Royal College of Psychiatrists of Ireland (Intellectual disability subgroup) and the International Association for the Scientific Study of Intellectual and Developmental Disabilities (IASSIDD). The stakeholder from Down Syndrome Ireland had said *"In our experience, when an older adult with Down syndrome presents to a medical professional with a decline in cognitive function or deteriorating health, there is a presumption that it is a part of aging or dementia, often with little investigation of other causes. It is immensely worrying that medications could be causing these symptoms, and this is never considered"*. And additionally, *"However, until there are answers to your research question, older adults with intellectual disability may continue to be dismissed, receive inaccurate diagnosis and experience ill health and reduced quality of life needlessly, which is very concerning."* The stakeholder from the Royal College of Psychiatrists of Ireland had commented *"The reasons for overprescribing in adults with intellectual disability are myriad. We know up to 23% of the ID population can be prescribed antipsychotics for behavioural disturbances. Contributory socio-cultural factors include pressure from relatives/carers for immediate resolution of a problem*, *limited resources for changing the environment*, *lack of appropriately trained staff in residential facilities*, *shortfall of psychiatrists*, *lack of input from adequately resourced disability teams, psychology, OT, pharmacy, social work etc*. The IASSIDD stakeholder had commented " *For the scientific membership of IASSIDD, particularly our members working in the medicines area there is clearly a need to develop the studies that will address this gap and contribute to improving the lives of people with intellectual disabilities*. "

In summary of the stakeholder consultation, there were no concerns about the review findings, and they have highlighted the important role of such longitudinal studies, the necessity of research on this area, reasons for such prescribing and the possible risks for people with Down Syndrome.

The study protocol (130) and the scoping review (131) have been published in HRB Open Research database.

2.4 Discussion

This is the first scoping review to map the evidence and examine adverse effects associated with long-term use of medication with anticholinergic activity, among older adults with intellectual disability. No studies were deemed eligible for the scoping review resulting in an empty review.

It is not uncommon for reviews focusing on people with intellectual disability to not have any included studies. Research completed by Yaffe *et al.* (2012) found that out of 81 systematic reviews conducted with a population of people with intellectual disability, 15 resulted in empty reviews (132). This highlights that people with an intellectual disability are often excluded in research. Empty reviews highlight a huge gap in knowledge, and these should encourage research to be conducted in such a novel area.

There are two main obstacles faced by researches in undertaking epidemiological health research on older adults with intellectual disability, as identified by Thessa *et al.* (2011) (133). Many people with an intellectual disability are relatively independent, requiring limited supports and often able to make a range of decisions that impact on their lives. Others, particularly those within the severe to profound range of intellectual disability, require significant support from family or professional caregivers. Lack of support by the family or care providers can be a barrier to recruit a large-scale sample of participants.

Furthermore, lack of awareness on importance of research can result in challenge to recruit people with intellectual disability in research. Secondly, there are a lack of tools to measure health features in older adults with intellectual disability. Most health measurement tools used in general population involve neuropsychological tests, self-reported questionnaires and physical screening tests which may need a certain level of physical and cognitive abilities; these measurement tools may not be compatible with older adults with intellectual disability (133). Therefore, most of the published epidemiological research conducted on older adults with intellectual disability are based on proxy for example medical records/registers or observation of care providers and that could result on under-recognition of some health conditions or risk factors due to lack of appropriate diagnostic tools and communication barriers (133). Additionally, a smaller sample of participants will obstruct extrapolation of the results and may not provide an

extensive look at health characteristics and risks experienced by people with intellectual disability.

Although the life expectancy of older adults with intellectual disability is lengthening, there are still many avoidable deaths or deaths amenable to healthcare(94). People with intellectual disability have high prevalence of mental health diseases and epilepsy which increases their exposure to multiple high risks medicines such as sedatives and anticholinergics (94). Lack of research among this vulnerable population, resulted with a limited evidence base for safe and appropriate use of such medication. Therefore, longitudinal studies are required to explore possible adverse effects of high-risk medication such as anticholinergics. Then, development of an intervention or guidance would be needed to facilitate appropriate prescribing and deprescribing of anticholinergics among older adults with intellectual disability.

There are some challenges faced in conducting longitudinal studies to examine adverse effects associated with long-term use of anticholinergics amongst general elderly population. For instance, a systematic review conducted by Andre *et al.* (2019) identified and assessed 25 longitudinal studies examined cognitive impairment associated with long-term use of anticholinergic among people aged 50 or over (134), by searching only one database. The review highlighted the complexity to assess long-term cognitive impairments adverse effects and the heterogeneity of the published studies. However, most reliable, and recent studies have suggested poorer cognitive function associated with anticholinergic use. Additionally, a longitudinal cohort study illustrated that the association results varied based on scales used to quantify the anticholinergic exposure and the tools used to assess the cognitive function (135). These challenges could be overcome by identifying the appropriate methods used to quantify anticholinergic exposure and the appropriate instruments to assess the targeted outcomes.

Older adults with intellectual disability are living longer and this comes with an increased risk of having age-related health conditions such as Alzheimer, and dementia (136). Defining mild cognitive impairment in general population is challenging and more challenging for people with intellectual disability. Therefore, a clear and objective standard definition, assessment tool and diagnosis method for dementia and mild cognitive impairment is needed in practice. The early diagnosis will help to control the symptoms and avoid irreversible neuropathy.

Scoping reviews have been conducted on individuals with intellectual disabilities, encompassing articles from various fields and study types (137-139). Generally, longitudinal studies are considered challenging due to resources needed and sample retention; this could explain the lack of longitudinal studies amongst older adults with intellectual disability.

2.4.1 Strengths and Limitations

This is the first scoping review which aimed to map and explore available research on adverse effects associated with the long-term anticholinergic exposure among older adults with intellectual disability.

The use of certain centrally acting medication such as sedatives and anticholinergics for long-term could lead to further adverse effects compared to short-term use of those medication. Some of these adverse effects have been studied among the general population but older adults with intellectual disability are at higher risk to develop anticholinergic adverse effects compared to general population. Therefore, the research question could not be answered by examining different population or different age category such as children or adults with intellectual disability. This empty review highlights the necessity of including people with intellectual disability in clinical research to enhance safe prescribing and reduce medication-related adverse reactions. The subject librarian was involved in the process of developing the search terms and the searching of relevant databases which reduced the risk of missing relevant data. In addition, a list of stakeholders was consulted on the research question, search strategy and results. The review had no limitation on study types and therefore pilot, feasibility studies and grey literature of ongoing or unpublished research were included to identify research in early stages. PRISMA-ScR guidelines had been followed to report the finding of the review.

2.5 Conclusion

This review has concluded that no studies to date have examined the adverse effects associated with long-term exposure to medication with anticholinergic activity among older adults with intellectual disability. The review identified a large gap in literature (*i.e.*, there is no research that focuses on this area) given the high prevalence of anticholinergic exposure in this population. Longitudinal cohort studies are needed to identify the adverse effects associated with long term exposure to anticholinergic burden among older adults with intellectual disability. Much needed research will provide an evidence base required to enhance appropriate prescribing of these medications among this vulnerable group of the population.

Chapter 3

Outcomes associated with long-term exposure to medications with anticholinergic activity amongst adults aged 40 years or over with intellectual disability: a longitudinal cohort study

3.1 Introduction

The prevalence of multimorbidity and the patterns of diseases are distinct in people with intellectual disability compared to general population. Multimorbidity begins at an earlier age and is associated with poorer health outcomes in people with intellectual disability (16, 140, 141). Furthermore, the average lifespan of people with intellectual disability is 19 years less than the general population (10). One study has reported that 37% of deaths in people with intellectual disability were amenable to health care intervention, compared to 22% of deaths in general population (21).

As discussed in *Chapter 1*, older adults with intellectual disability are more likely to receive excessive polypharmacy (≥ 10 medications) and to be exposed to a higher anticholinergic burden (67). This is associated with adverse effects such as higher dependency level, constipation and daytime dosing. However, a scoping review reported in this thesis (*Chapter 2*) did not find any studies that examined adverse effects associated with long-term exposure to anticholinergics among older adults with intellectual disability (131).

One way of assessing the impact of long-term exposure to medications with anticholinergic activity would be to use data from a cohort study. The IDS-TILDA study had collected data from four waves over a ten-year period by 2019/2020 that could be used for this purpose. Therefore, this study was nested within the IDS-TILDA, specifically, data obtained in Waves 1 and 4. Further details on the IDS-TILDA were described in section 1.2 in *Chapter 1.*

3.2 Aim and Objectives

This study aimed to examine the outcomes associated with long-term exposure to anticholinergics amongst older adults with intellectual disability using data from IDS-TILDA.

Furthermore, the objectives of this study were to:

1. Examine the anticholinergic burden of people who participated in Wave 1 and remined in the study at Wave 4 (longitudinal cohort).
2. Compare the anticholinergic burden of the whole cohort at Wave 1 and the whole cohort at Wave 4.
3. Identify and compare the most frequently reported medicines and classes of medicines contributing to the anticholinergic burden in whole cohort of Wave 1 and Wave 4.
4. Examine socio-demographic and health-related factors associated with the anticholinergic burden of the whole cohort in Wave 4.

3.3 Method

This section describes the study methodology including study design and cohort, ethical approval, medication data collection, quantification of anticholinergic exposure and statistical analysis applied to examined longitudinal association between anticholinergic scores at Wave 1 and associated outcomes at Wave 4.

3.3.1 Study Design

This longitudinal study was nested within IDS-TILDA and examined data from the physical health, cognitive, psychological, healthcare and social framework domains (illustrated in *Chapter 1*). From the research question of this thesis: *What are the anticholinergic adverse effects associated with long-term exposure to anticholinergics in older adults with intellectual disability?* building on previous research using IDS-TILDA data (67, 106) and using data from Wave 1 (2009/10) and Wave 4 (2019/20), the study examined participants exposed over a 10 year interval. Data provided at Wave 1 was considered as baseline while Wave 4 data was considered as a follow-up time point.

3.3.2 Ethical Approval

IDS-TILDA ethical approval was granted from the Faculty of Health Sciences Research Ethics Committee in Trinity College Dublin and from 138 Intellectual Disability Service Providers in Ireland (1). This study used data obtained in Wave 1 and Wave 4, ethical approval for both waves was attained. See *Appendix 3.3-1* for approval letters.

3.3.3 Study Cohort

There were 753 older adults with intellectual disability who participated in Wave 1 (2009/20) and 736 (98%) provided medication data. A total of 739 older adults with intellectual disability participated in Wave 4 (2019/20) and 719 (97%) of them provided medication data. In Wave 4, there was a refreshment sample of 233 new participants included to obtain a sample of younger participants, *i.e.* those aged 40 – 49 years old. The flowchart of the study sample for this chapter is illustrated in *Figure 3.3-1*.

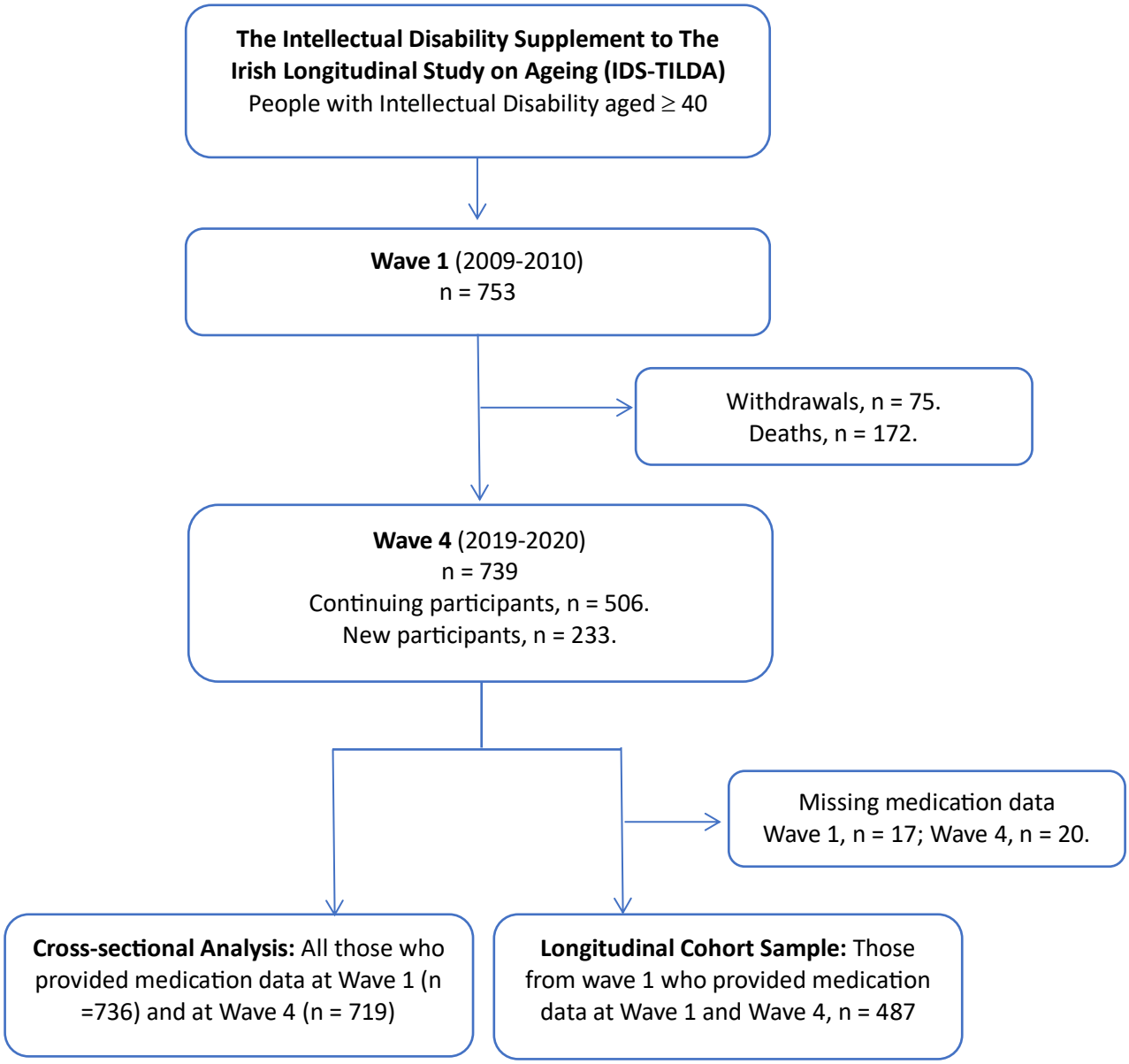

Figure 3.3-1 Flowchart of the study sample

There were 506 older adults with intellectual disability who participated in both waves (Wave 1 and Wave 4). 75 participants had withdrawn and 172 had died by the time of Wave 4 data collection. 487 (96%) of the 506 provided medication data at both waves (Wave 1 and Wave 4). This group constituted the longitudinal cohort sample (*Figure3.3-1*). For cross-sectional and comparison analysis, total number of participants who provided medication at each wave were included (Wave 1 n = 736, Wave 4 n = 719). In addition, the full sample in Wave 4 was used in multinomial regression analysis to examine socio-demographic and health related factors associated with mild and high anticholinergic exposure compared to those with no anticholinergic exposure. The

longitudinal cohort sample was used to examine longitudinal association between ACB scores at Wave 1 and anticholinergic adverse effects reported at Wave 4.

3.3.4 Medication Data Collection

At both waves, medication data was gathered as part of the Pre-interview Questionnaire (PIQs). Then, the provided medication data was confirmed at the face-to-face Computer Assisted Personal Interviews (CAPI). The gathered medication data included the information of all prescribed, over the counter (OTC) medication, herbal medication and supplements. For each medicine, the dosage forms, strength, doses, frequency and treatment duration were gathered. A template used for medication data collection in the PIQs was provided in *Appendix 3.3-2* for Wave 1 and Wave 4. The medication data was collected by staff trained by a pharmacist. After that, the data was inputted into SPSS for data analysis by the PhD candidate (SPSS template provided in *Appendix 3.3-3*). The medication data inputting included the name of the medicine, Anatomical Therapeutic Chemical (ATC) code, route of administration, dosage form, frequency, date prescribed. The ATC code is a medication coding system established by the World Health Organization (WHO)(142).

3.3.5 Anticholinergic Cognitive Burden

3.3.5.1 Medication Inventory for Anticholinergic Cognitive Burden

The Anticholinergic Cognitive Burden (ACB) scale was used in this study to quantify the anticholinergic burden, as the ACB scale was previously used to evaluate anticholinergic exposure of the same cohort at Wave 1 and Wave 2 of the study (67, 106). An inventory of the anticholinergic cognitive burden medication list was conducted twice by a research team member who studied and examined anticholinergic burden at Wave 1 and 2 in IDS-TILDA, prior to this study. The aim of the medications inventory was to ensure that the list included all the medications that possessed anticholinergic activity used by IDS-TILDA participants, and that the assigned ACB score for each medicine included was up to date.

First Medication Inventory for ACB scale: The original list of medication was obtained from the updated 2012 Anticholinergic Cognitive Burden Scale (143). The first medication inventory was conducted at wave 1 (2009/10), and it was completed by consulting

standard reference sources, other validated anticholinergic scales and the Summary of Product Characteristics Information (SmPC) to include medication with anticholinergic activity taken by IDS-TILDA participants and not included in the original ACB scale (144). The review and consultation of references was conducted independently by two pharmacists (MO'D and IM). Then, the amended list with the newly included medication and the assigned ACB score was reviewed by another pharmacist (MH). Based on the conducted medication inventory process and consensus, the original ACB scale was modified to include 22 medications with anticholinergic activity that are in use in Ireland (*Appendix 3.3-4*: Original ACB scale established at Wave 1).

Second Medication Inventory for ACB scale: After three years, the list of medication was reviewed and updated by another pharmacist (JO'C) at Wave 2 (2013/14)(145). The list was reassessed based on a systematic review conducted to develop an updated list of medications with anticholinergic activity over various anticholinergic scales (146). The review was conducted to identify other medications with anticholinergic activity that may not have been included in the ACB scale list established in Wave 1. The SmPC and a geriatric specialist pharmacist were consulted for the inclusion of the newly reported medicines. Oxycodone, morphine and dosulepin were added to the ACB inventory based on this review. The ACB scores for the new medicines were assigned based on similar medication from the same therapeutic category, scores assigned based on other scales and the Maudsley Prescribing guidelines (147). The PhD candidate was not involved in the first and second medication inventory.

Third Medication Inventory for ACB scale: For this current study, the second medication inventory list was reviewed by the PhD candidate, three senior pharmacists within the research team (MO'D, MH and IM) at Wave 4 (2019/20). A recent updated systematic review, and prescribing guidelines, were consulted in addition to the previous systematic review, SmPC and other case-control studies (57, 128, 148). This review concluded that there were no medications to be added but the score was changed for two medicines and new dosage forms of prednisone were added. *Table 3.3-1* illustrates the amendments carried out on the list of the ACB Scale at this stage. The final medication inventory list included 121 medicines that possess anticholinergic activity and full list of medications is illustrated in *Appendix 3.3-5* with the corresponding ACB scores.

Table 3.3-1 Amendments on Medication Inventory for Anticholinergic Cognitive Burden

Drug Name	ATC Code	ACB Score	New ACB Score	Note
Dosulepin	N06AA16	2	3	Not in Wave1 list
Lofepramine	N06AA07	1	3	Not in Wave 1 list
Prednisone nasal and enema/rectal foam	R01AD02 R01AD52 A07EA03 H02AB07	-	1	Not in previous lists
ACB: Anticholinergic Cognitive Burden				

3.3.5.2 Anticholinergic Cognitive Burden Scores

According to the ACB Scale, all medication was scored from 0 to 3 based on their anticholinergic activity. Medication with no anticholinergic activity were assigned a score of 0 and those with possible anticholinergic activity were scored as 1. Definite anticholinergics were scored 2 or 3 based on their cognitive adverse effect (143). Furthermore, the total anticholinergic burden was calculated by adding the total score of all the prescribed medications with anticholinergic activity for each participant. The total anticholinergic burden was categorised into three types of exposure as presented in *Table 3.2-2*. The total scoring categorisation has been used in previous studies using IDS-TILDA data (67, 106). A sensitivity analysis was conducted to examine the different exposure categorisation used in general population (such as high exposure = 3+) and no significant difference was observed.

Table 3.3-2 Classification of Anticholinergic Exposure Based on the total ACB Score

Total ACB Score	Classification of Anticholinergic Exposure
0	No anticholinergic exposure
1 – 4	Mild anticholinergic exposure
5+	High anticholinergic exposure
ACB: Anticholinergic Cognitive Burden	

3.3.5.3 Most Frequently Reported Medication and Therapeutic Classes of Medication with Anticholinergic Activity at Wave 1 and Wave 4

Medications were ranked based on the number of prescriptions in Wave 4. For Wave 1, the data was updated based on the updated medication list of ACB scale, and then comparison of results from the two waves was reported (144). These medications were then categorised into relevant therapeutic groups based on the medication category in the ATC (142), then the total number of prescriptions in each class of medication was reported.

3.3.5.4 Measures of Outcomes Associated with Long-term Exposure to Anticholinergics

Based on previous studies conducted in IDS-TILDA and the available reported measures in the study dataset for Wave 4, these were the measured anticholinergic adverse effects studied in this study:

1. Constipation
2. Falls
3. Edentulous
4. Barthel Index for Activity of Daily Living
5. Mental Health Condition
6. Dementia/ Alzheimer diseases or taking anti-dementia medication

Details of the questions asked for each outcome and the source of the information (PIQ or CAPI) are illustrated in *Table 3.3-3*. All models were adjusted for age, gender, level of intellectual disability, residence, epilepsy and polypharmacy. Models were adjusted for epilepsy because of its high prevalence and frequent use of anti-epileptic medication which have a major contribution to the level of anticholinergic exposure.

Table 3.3-3 Data requested and accessed

Wave	Pre-Interview Questionnaire (PIQ)	Computer Assisted Personal Interview (CAPI)
Wave 1	**Demographic Data: Gender:** Are you male or female? **Age:** What is your date of birth? **Level of intellectual disability:** What is your level of intellectual disability? (Not verified/ Mild/ Moderate/ Severe/ Profound/ Don't Know) **Medication Data:** Medication Name, Dosage, Frequency (Daily/ Weekly/ When required/ Don't know) **Epilepsy:** Has a doctor ever told you have epilepsy? (Yes/ No/ Don't Know) **Emotional, nervous or psychiatric conditions:** Has a doctor ever told you have an emotional, nervous or psychiatric condition? (Yes/ No/ Don't Know)	**Demographic Data:** Household residence: Where do you live most of the time? (independent/with family, community home, residential centre)
Wave 4	**Demographic Data:** Same as above. **Medication Data:** Medication Name, Dosage, Frequency (Daily/ Weekly/ When required/ Don't know), Route, Date first prescribed **Modified Barthel Index (Activity of daily living):** Details on questions are illustrated in Appendix 3.3-6	**Demographic Data:** Same as above. **Adverse effects: falls:** Have you fallen since your last interview? (Yes/ No/ Don't Know/ Refused to answer) **Edentulous:** Which best describes the teeth you have? (I have all my own teeth-none missing/ I have my own teeth/ no dentures-but some missing/ I have dentures as well as some of my own teeth/ I have full dentures/ I have no teeth or dentures/ unclear response/ don't know/ refused to answer) **Modified Barthel Index (Activity of daily living):** Details on questions are illustrated in *Appendix 3.3-6*

Table 3.3-3 Continued		
Wave 4		**Epilepsy:** Participants with previous diagnosis were asked to confirm or dispute the conditions: “last time you were interviewed, you told us that you had Epilepsy? If condition confirmed,” Do you still have epilepsy?" If condition disputed, “Can you confirm that you never had epilepsy or epilepsy was misdiagnosed?” “Since your last review, has a doctor ever told you have epilepsy? (Yes/ No/ Don’t Know)? If answered “yes”, participants asked” Do you still have epilepsy? ” yes/no. Participant with no previous diagnosis, asked “Since your last review, has a doctor ever told you have epilepsy? (Yes/ No/ Don’t Know)? If answered “yes”, participants asked” Do you still have epilepsy? ” yes/no. **Constipation:** Participants with previous diagnosis were asked to confirm or dispute the conditions: “last time you were interviewed, you told us that you had constipation? If constipation confirmed,” Do you still have constipation?" If constipation disputed, “Can you confirm that you never had constipation or constipation was misdiagnosed?”, “Since your last review, has a doctor ever told you have emotional, nervous or psychiatric problems? (Yes/ No/ Don’t Know)? If answered “yes”, participants asked” Do you still have emotional, nervous or psychiatric problems? ” yes/no. Participant with no previous constipation, asked “Since your last review, has a doctor ever told you have constipation? (Yes/ No/ Don’t Know)? If answered “yes”, participants asked” Do you still have constipation? ” yes/no. **Emotional, nervous or psychiatric conditions:** Participants with previous diagnosis were asked to confirm or dispute the condition: “last time you were interviewed, you told us that you had emotional, nervous or psychiatric problems? If condition confirmed,” Do you still have emotional, nervous or psychiatric problems?" If condition disputed, “Can you confirm that you never had emotional, nervous or psychiatric problems or it was misdiagnosed?” Since your last review, has a doctor ever told you have emotional, nervous or psychiatric problems? (Yes/ No/ Don’t Know)? If answered “yes”, participants asked” Do you still have emotional, nervous or psychiatric problems? ” yes/no. Participant with no previous emotional, nervous or psychiatric problems, asked “Since your last review, has a doctor ever told you have emotional, nervous or psychiatric problems? (Yes/ No/ Don’t Know)? If answered “yes”, participants asked” Do you still have emotional, nervous or psychiatric problems?” yes/no. Emotional, nervous or psychiatric condition includes; Hallucinations, Anxiety, Depression, Emotional problems, Schizophrenia, Psychosis, Mood swings, Manic depression, Post-traumatic stress disorder or “Something else”

Table 3.3-3 Continued		
Wave 4		**Dementia or Alzheimer:** Participants with previous diagnosis were asked to confirm or dispute the conditions: “last time you were interviewed, you told us that you had dementia, organic brain syndrome, senility or Alzheimer? If condition confirmed,” Do you still have dementia, organic brain syndrome, senility or Alzheimer?" If condition disputed, “Can you confirm that you never had dementia, organic brain syndrome, senility or Alzheimer or dementia, organic brain syndrome, senility or Alzheimer was misdiagnosed?” , “Since your last review, has a doctor ever told you have dementia, organic brain syndrome, senility or Alzheimer? (Yes/ No/ Don’t Know)? If answered “yes”, participants asked” Do you still have dementia, organic brain syndrome, senility or Alzheimer? Participant with no previous diagnosis, asked “Since your last review, has a doctor ever told you have dementia, organic brain syndrome, senility or Alzheimer? (Yes/ No/ Don’t Know)? If answered “yes”, participants asked” Do you still have dementia, organic brain syndrome, senility or Alzheimer? ” yes/no.

A Modified Barthel index (BI) for Activities of Daily Living (ADLs) was developed for use with IDS-TILDA data and gathered as part of the CAPI (149). The Barthel Index is a measure of the level of dependency for the activities of daily living of an individual. It is a scoring measure with a range from 0 to 20 for activities of daily living including; feeding, transfer, using stairs, dressing, grooming, bathing, toileting, bladder continence and bowel continence. Participants or a family member/carer rate their difficulty experienced each activity from 0 to 20. The total scores for an individual can be classified into 5 categories: (0-4) total dependence, (5-12) severe dependence, (13-18) moderate dependence, (19) mild dependence and (20) total independence. Therefore, the lower score indicates poorer physical function. The IDS-TILDA questions used to formulate a BI score are illustrated in *Appendix 3.3-6*.

For dentate status, participants were classified as "Dentate" if they answered (I have all my own teeth-none missing/ I have my own teeth/ no dentures-but some missing/ I have dentures as well as some of my own teeth) and classified as "Edentulous" if they answered with (I have full dentures/ I have no teeth or dentures). This classification has been used previously for a study conducted in IDS-TILDA (67).

3.3.6 Covariates

The socio-demographic covariates used for this study included gender (male or female), age categories (40 – 49 years, 50 – 64 years, 65+ years), type of residence (family/independent, community group home or residential care settings), and level of intellectual disability (mild, moderate or severe/profound). A community group home is where dedicated staff provide support for people with intellectual disability in a small group setting. In contrast, residential care settings are campus-based living arrangements or where 10 or more people share a single living unit, supported by services. Additionally, health-related covariates included ability to walk 100 yards (no/some difficulty, a lot of difficulty/cannot do at all), epilepsy (yes/no), multimorbidity (presence of two or more chronic conditions) and neurological condition (includes cerebral palsy, epilepsy, multiple sclerosis, Parkinson's disease, spina bifida, muscular dystrophy, Alzheimer's, dementia and memory impairment). A polypharmacy covariate was also included and it was created by excluding medications with anticholinergic activity as these were included in the ACB score. Polypharmacy was defined as taking five or more medication concurrently.

3.3.7 Statistical Analysis

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test the normality of the data. As the data was not normally distributed (*P*-value < 0.05), median and interquartile ranges were reported for discrete data. Descriptive analysis was reported as proportion and percentages of the total sample size (n, %). McNemar is a non-parametric test and was used to test marginal homogeneity in paired samples. Differences in proportion were tested using McNemar's test for dichotomous variables, such as the variable for sex, and the McNemar-Bowker test was used for variables with 3 or more subcategories such as the variable for the level of intellectual disability: mild, moderate and severe/profound (150, 151). To control for type I error (false positive results), a Holm-Bonferroni correction was applied and an adjusted *P*-value derived based on the number of comparisons (152). Therefore, statistical significance was set as 0.025 (0.05/2 comparison) for variables with two subcategories and 0.017 (0.05/3 comparison) for variables with three subcategories. Multinomial logistic regression was used to identify socio-demographic and health-related factors associated with mild and high anticholinergic exposure (ACB 1 – 4, 5+) compared to the reference category (ACB = 0). Logistic regression was used to examine longitudinal association between ACB scores at Wave 1 and adverse effects reported at Wave 4. The Model was adjusted for age, sex, level of intellectual disability, type of residence, epilepsy and polypharmacy. Odds Ratio (OR), 95% Confidence Interval (CI) and *P*-value were reported. Data analysis was conducted using *IBM SPSS V 28.0* and *P*-value > 0.05 was considered as significant. Multicollinearity between the independent factors was tested using two strategies: Spearman's correlation coefficients and Variance Inflation Factors (VIF). For the VIF, any variable with a value equal to or greater than 2 indicates collinearity associated with that variable, which might have an impact on the results (153). All values below 2 indicate no collinearity between the independent factors. Dany and Reidy's classification was used to interpret the correlation coefficient of the Spearman's test (154). Therefore, a correlation of ±1 indicates perfect correlation, whereas values between ± 0.7 and ± 0.9 are considered strong correlations, values between ± 0.4 and ± 0.6 are moderate correlations, values between ±0.1 and ±0.3 are weak correlations, and a value of zero indicates no correlation. All values of 0.4 and below were considered weak correlation. A

statistician was consulted on the study design and tests applied (CR). Experts from the same field of research were consulted and involved in study design (IM, PK, JOC).

3.4 Results

3.4.1 Demographic Characteristics

3.4.1.1 Longitudinal cohort

The socio-demographic and health-related covariates of the longitudinal cohort at Wave 1 and Wave 4 (n = 487) illustrated in *Table 3.4-1*.

Table 3.4-1 Demographic characteristics of the longitudinal cohort cohort at Wave 1 and Wave 4

	Wave 1, n (%), (N = 487)	Wave 4, n (%), (N = 487)	Differences in proportions (*P*-value)
Age (years)			
40-49	212 (43.5)	-	-
50-64	222 (45.6)	313 (64.3)	**<0.001**
65+	53 (10.9)	174 (35.7)	
Sex			
Male	213 (43.7)	213 (43.7)	NA
Female	274 (56.3)	274 (56.3)	
Residence *			
Independent/Family	74 (15.2)	60 (12.4)	**<0.001**
Community group home	185 (38.0)	227 (47.0)	
Residential care	228 (46.8)	196 (40.6)	
Missing	n = 0	n = 4	
Level of intellectual disability			
Mild	108 (24.1)	108 (24.1)	NA
Moderate	207 (46.1)	207 (46.1)	
Severe/Profound	134 (29.8)	134 (29.8)	
Missing	n = 38	n = 38	
Walking 100 yards			
No / some difficulty	422 (86.8)	338 (73.2)	**<0.001**
A lot of difficulty/ can't do at all	64 (13.2)	124 (26.8)	
Missing	n = 1	n = 25	
Epilepsy			
No	331 (68.4)	323 (66.3)	0.09
Yes	153 (31.6)	164 (33.7)	
Missing	n = 3	n = 0	
Chronic constipation			
No	405 (83.2)	248 (51.3)	**<0.001**
Yes	82 (16.8)	235 (48.7)	
Missing	n = 0	n = 4	
Falls			
No	349 (72.1)	332 (68.9)	0.239
Yes	135 (27.9)	150 (31.1)	
Missing	n = 3	n = 5	

Table 3.4-1 Continued			
Mental Health Condition No Yes Missing	 227 (48.4) 242 (51.6) n = 18	 231 (47.4) 256 (52.6) n = 0	 0.586
Dementia and Alzheimer's No Yes	 470 (96.5) 17 (3.5)	 456 (93.6) 31 (6.4)	 0.038
Barthel Index Mild dependence / total independence Moderate/ severe/ total dependence Missing	 155 (31.8) 321 (65.9) n = 11	 87 (18.6) 380 (81.4) n = 20	 **<0.001**
Dentate/ Edentulous Dentate Edentulous Missing	 387 (79.8) 98 (20.2) n = 3	 354 (72.8) 132 (27.2) n = 0	 **<0.001**
Multiple Laxative Use Not taking Taking 1 laxative Taking 2 or more	 316 (64.9) 91 (18.7) 80 (16.4)	 248 (50.9) 139 (28.5) 100 (20.5)	 **<0.001**
ACB Exposure No Exposure Mild Exposure High Exposure	 146 (30.0) 193 (39.6) 148 (30.4)	 139 (28.5) 219 (45.0) 129 (26.5)	 0.115
Polypharmacy excluding medications with anticholinergic activity No Yes	 318 (65.3) 169 (34.7)	 224 (46.0) 263 (54.0)	 **<0.001**
Multiple Antipsychotic Use None 1 antipsychotic 2 or more antipsychotics	 265 (54.4) 163 (33.5) 59 (12.1)	 273 (56.1) 168 (34.5) 46 (9.4)	 0.112
P-value derived from McNemar's and McNemar-Bowker test. Holm-Bonferroni correction applied (P-value of 0.025 for variables with two subcategories and 0.017 for variables with three subcategories) and all significant P-values are in bold.			

The level of intellectual disability and sex are time independent covariates. From Wave 1 to Wave 4, there was a significant change in residence setting with an increase in people living in community group homes by 9% and a reduction in people living in residential care settings and independent/or with family by 6.2% and 2.8%, respectively.

There was a significant increase in reporting chronic constipation, multiple laxative use, edentulous, higher dependence level based on the Barthel Index and poorer physical activity according to ability to walk 100 yards.

From a medication perspective, there was no significant change in either anticholinergic exposure or multiple antipsychotic use, at the two timepoints. However, there was a significant increase in the use of multiple laxatives and the polypharmacy (concurrent use of 5 or more medications) with exclusion of medications with anticholinergic activity.

3.4.2 Anticholinergic Cognitive Burden Exposure; Comparing Wave 1 and Wave 4

At both time points, around 30% of the participants had no anticholinergic exposure (total ACB = 0), as illustrated by *Table 3.4-1*. The anticholinergic exposure did not change significantly between Wave 1 and Wave 4, with 70% and 71.5% of the participants having had anticholinergic exposure (ACB score 1 or over), respectively. Participants with mild anticholinergic exposure (total ACB score 1 - 4) increased by 5%, from 40% in Wave 1 to 45% in Wave 4. There were 30% of participants who had a high exposure (total ACB score 5+) at Wave 1 and around 26% at Wave 4. There was a small increase in those reporting mild exposure and a small reduction in those reporting high anticholinergic exposure. Overall, anticholinergic exposure remained almost the same over the decade in this longitudinal cohort. By examining the ACB change in the longitudinal cohort, there were 102 participants who remained with no anticholinergic exposure over the studied period (total ACB = 0), as illustrated in *Figure 3.4-1*.

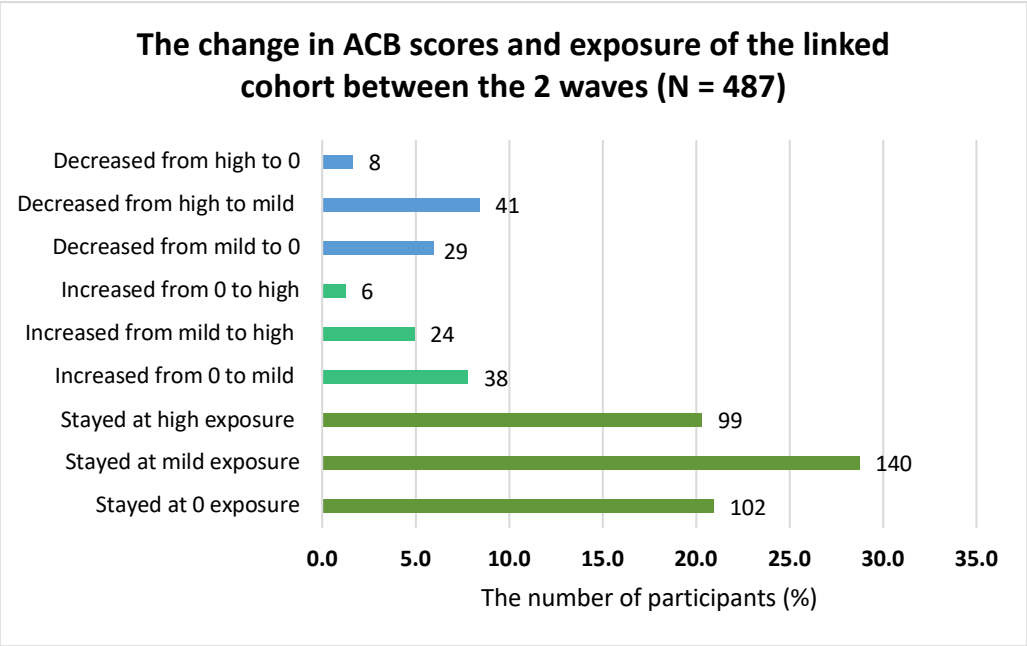

Figure 3.4-1 Changes in ACB exposure between Wave 1 and Wave 4 (N = 487)

Additionally, 140 and 99 participants stayed at mild (total ACB 1 – 4) and high ACB score (total ACB 5+), respectively. There were 70% (n = 341) of the participants reported the same ACB exposure at both Waves 1 and 4. On the other hand, there were 68 participants (14%) whose ACB exposure increased, compared to 78 of the participants (16%) whose exposure decreased. Most participants who had anticholinergic exposure continued to have the exposure until Wave 4, except for 37 participant who had anticholinergic exposure at Wave1 but reported zero exposure (ACB = 0) at Wave 4. *Table 3.4-2* illustrates descriptive analysis of the total ACB score at the two waves, including median, maximum, minimum, and percentiles. Overall, all of the frequencies reduced slightly for instance the median reduced from four in Wave 1 to three in Wave 4, and maximum reported ACB score was 16 in Wave 1 compared to 15 in Wave 4.

Table 3.4-2 Descriptive analysis of the total ACB scores at Wave 1 and Wave 4 for the linked cohort (N = 348)

	Wave 1 (N = 341)	Wave 4 (N = 348)
Median	4	3
Minimum, Maximum	1,16	1,15
Percentiles		
25	2	2
50	4	3
75	6.5	6

1.3.1.2 Cross Sectional Analysis

Comparison of the whole cohort at Wave 1 and Wave 4: The anticholinergic exposure did not change significantly between Wave 1 and Wave 4 when examined in the two cohorts, as illustrated in *Figure 3.4-2*. There was 523 (71.1%) and 499 (69.4%) participants who had anticholinergic exposure (ACB score 1 or over), in Wave 1 and Wave 4 respectively. In Wave 1, there was 305 (41.4%) participants with ACB 1 – 4 and 218 (29.6%) with total ACB of 5+, compared to 309 (43%) with ACB 1 – 4 and 190 (26.4%) participants with ACB of 5 or higher in Wave 4. Overall, the number of participants with mild anticholinergic exposure decreased by 3% while those with high exposure increased by 1.6%.

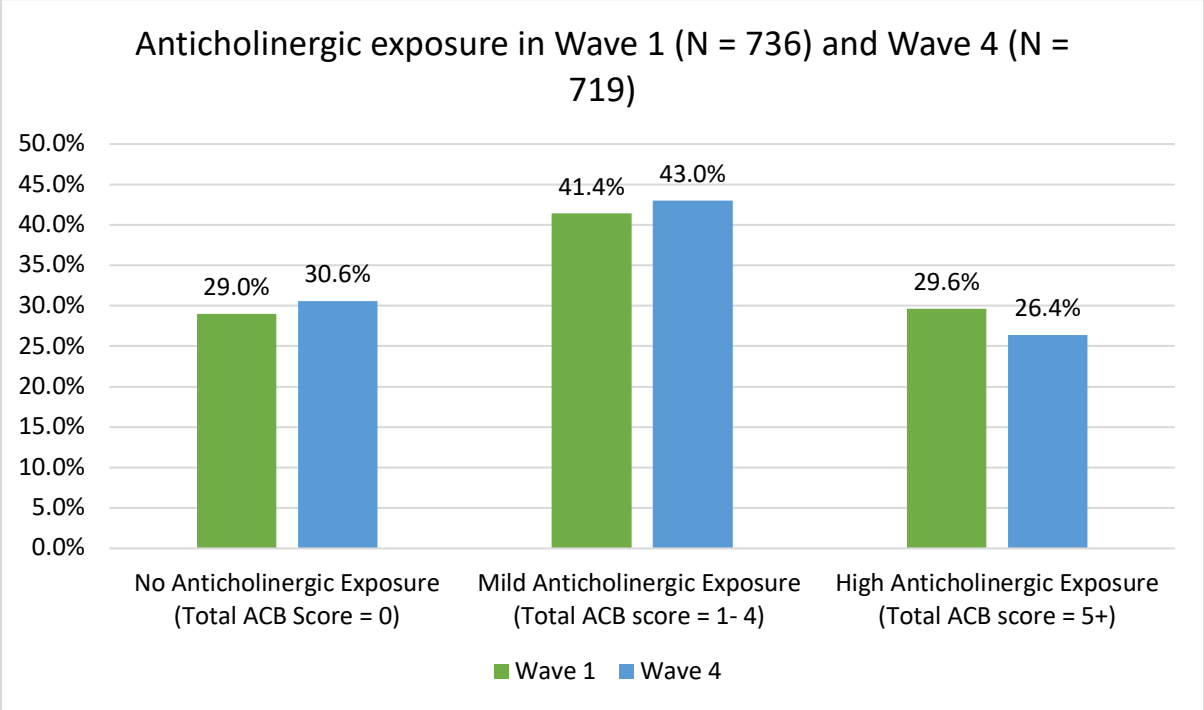

Figure 3.4-2 Anticholinergic exposure among all participants at Wave 1 and Wave 4

3.4.3 Comparison on Contribution of Medication Classes and Therapeutic Groups to the Total ACB score at Wave 1 and Wave 4

Analysis of the medication and therapeutic classes that contributed to the total ACB scores were conducted based on participants who had provided medication data and had anticholinergic exposure (ACB score = 1+) in Wave 1 (N = 522) and Wave 4 (N = 499). Antipsychotics medication made the greatest contribution to the total score at the two timepoints (Wave 1 = 35%, Wave 4 = 37%), with anticholinergic (Wave 1 = 16%, Wave 4 =

12%), antiepileptic and antidepressant medications contribute 10-12% each, see *Figure 3.4-3*. The prevalence of anticholinergic medication use fell from 16% to 12% between the two timepoints. Additionally, there was a slight reduction in the usage of anxiolytics by 1.3%. On the other hand, all other therapeutic classes increased slightly or remained the same at the two waves.

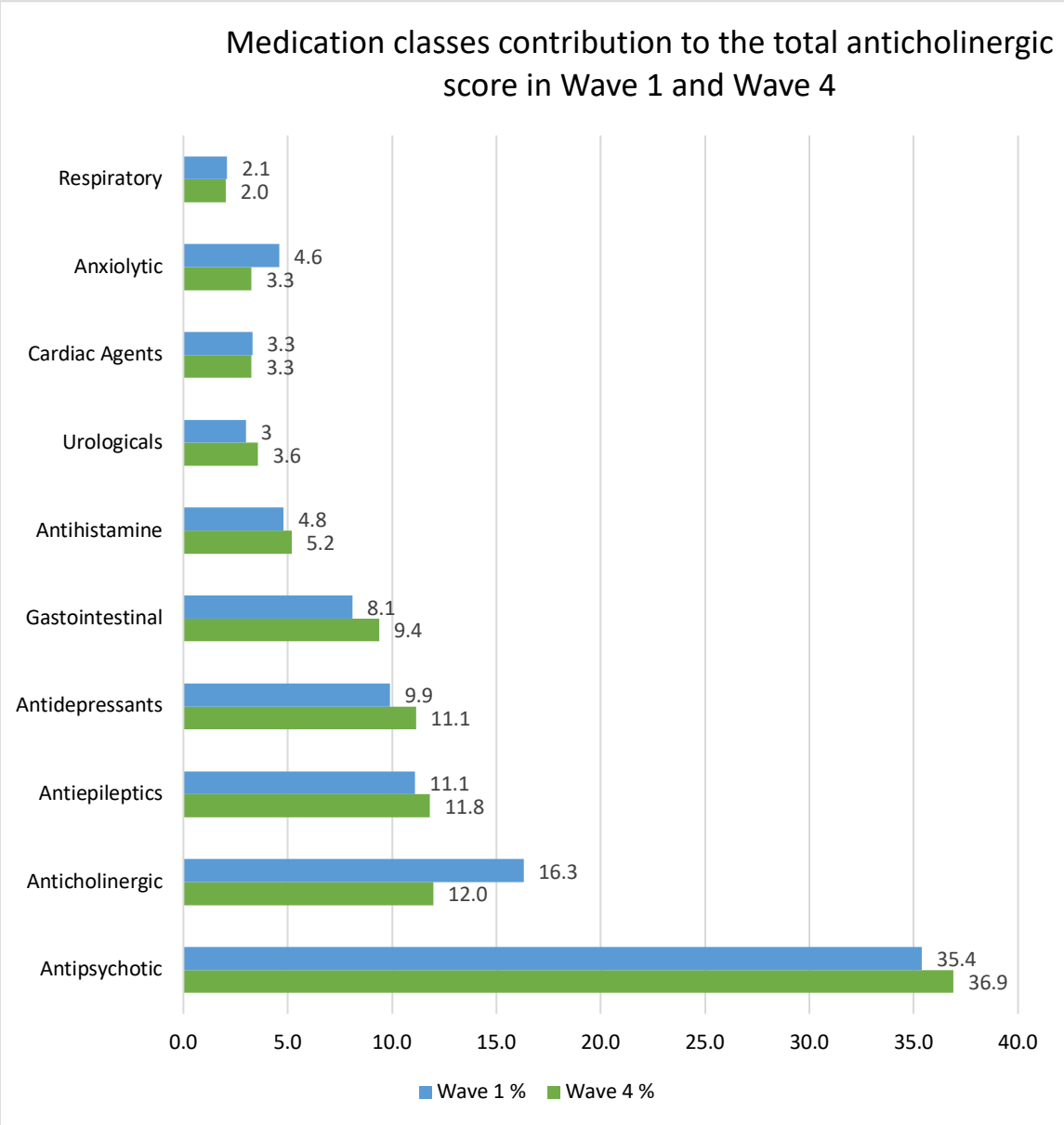

Figure 3.4-3 Medication classes and therapeutic groups contribution to the total anticholinergic score in Wave 1 (N = 522) and Wave 4 (N = 499) in percentage (%).

Additionally, the contribution of specific medication to the anticholinergic burden is presented in *Table 3.4-3.* The top four frequently reported medicines were in the same order at the two timepoints. Carbamazepine (ACB = 2) was the most frequently reported medicine with 22 - 24% reported by those with anticholinergic exposure at the two timepoints, followed by risperidone (21%), olanzapine (17 - 19%), and biperiden (11-16%). There are six highly anticholinergic drugs (ACB score = 3) in Wave 1 group but there are five in the Wave 4. Procyclidine, citalopram and paroxetine have been replaced by cetirizine, mirtazapine and scopolamine (hyoscine). The use of diazepam, chlorpromazine and haloperidol decreased by almost 7%, 6% and 2% respectively. The antipsychotics that contributed most to anticholinergic exposure included first-generation (typical) antipsychotics such as chlorpromazine and haloperidol, and second-generation (atypical) antipsychotics such as risperidone, olanzapine, and quetiapine.

Table 3.4-3 Top 15 most frequently reported medications with anticholinergic activity at Wave 1 (N = 522) and Wave 4 (N = 499)

No.	Wave 1 (N = 523)	ACB Score	n (%)	Wave 4 (N = 499)	ACB Score	n (%)
1	Carbamazepine	2	127 (24.3)	Carbamazepine	2	111 (22.2)
2	Risperidone	1	112 (21.4)	Risperidone	1	106(21.2)
3	Olanzapine	3	101(19.3)	Olanzapine	3	87 (17.4)
4	Biperiden	3	85 (16.2)	Biperiden	3	55 (11.0)
5	Diazepam	1	82 (15.7)	Escitalopram	1	48 (9.6)
6	Chlorpromazine	3	70 (13.4)	Loperamide	1	45 (9.0)
7	Loperamide	1	56 (10.7)	Diazepam	1	44 (8.8)
8	Haloperidol	1	44 (8.4)	Quetiapine	3	41 (8.2)
9	Procyclidine	3	37 (7.1)	Chlorpromazine	3	38 (7.6)
10	Escitalopram	1	35 (6.7)	Haloperidol	1	33 (6.6)
11	Ipratropium	1	31 (5.9)	Cetirizine	1	33 (6.6)
12	Quetiapine	3	27 (5.1)	Furosemide	1	33 (6.6)
13	Citalopram	1	25 (4.8)	Ipratropium	1	28 (5.6)
14	Paroxetine	3	25(4.8)	Mirtazapine	1	25 (5.0)
15	Furosemide	1	23 (4.3)	Scopolamine	3	24 (4.8)

3.4.4 Factors Associated with Mild and High ACB Score in Wave 4 (N = 719)

Multinomial logistic regression examined socio-demographic and health-related factors associated with mild anticholinergic exposure (total ACB score = 1 – 4) and high exposure (total ACB score = 5+), compared to participants with no anticholinergic exposure (ACB = 0, reference category) in Wave 4 (*Table 3.4-4)*. The regression model was adjusted for age, sex, level of intellectual disability, type of residence, multimorbidity (two or more chronic condition), neurological disease, mental health conditions and non-anticholinergic polypharmacy.

By testing the model fit, the multinomial logistic regression model had significant *P*-value (< 0.001) which indicates that the full model represented a significant improvement in the fitness over the null model. By testing Goodness-of-fit, both of Pearson Chi-Square and Deviance were shown to be non-significant (Pearson Chi-Square = 0.71, Deviance = 0.71) and that indicates that the model fits the data well.

Table 3.4-4 Factors associated with mild ACB score (1 - 4) and high ACB score (5+) among all participants in Wave 4 (N = 719)

	ACB = 0 (N = 220)	ACB 1 – 4 (N = 309)			ACB 5 + (N = 190)		
	n (%)	n (%)	OR (CI at 95%)	*P*-value	n (%)	OR (CI at 95%)	*P*-value
Sex							
Male	122 (17.0)	129 (17.9)	1 (reference)		81 (11.3)	1 (reference)	
Female	120 (16.7)	176 (24.5)	1.25 (0.84,1.86)	0.28	91 (12.7)	0.95 (0.58,1.55)	0.91
Age Category							
40-49 years	66 (9.2)	42 (5.8)	1 (reference)		20 (2.8)	1 (reference)	
50-64 years	131 (18.2)	175 (24.3)	1.66 (0.97,2.85)	0.06	90 (12.5)	1.28 (0.62,2.63)	0.50
65+ years	45 (6.3)	88 (12.2)	1.89 (1.00,3.57)	0.05	62 (8.6)	1.71 (0.76,3.84)	0.19
Level of Intellectual Disability							
Mild	82 (12.0)	82 (12.0)	1 (reference)		37 (5.4)	1 (reference)	
Moderate	107 (15.7)	114 (16.7)	0.76 (0.47,1.21)	0.24	69 (10.1)	0.71 (0.39,1.31)	0.27
Severe/Profound	35 (5.1)	95 (14.0)	1.58 (0.89,2.82)	0.12	60 (8.8)	1.34 (0.66,2.75)	0.42
Residence							
Independent/ family	78 (11.0)	38 (5.3)	1 (reference)		8 (1.1)	1 (reference)	
Community homes	108 (15.2)	157 (22.1)	1.74 (1.01,3.01)	0.17	79 (11.1)	**3.28 (1.28,8.39)**	**0.013**
Residential care	53 (7.5)	106 (14.9)	1.65 (0.85,3.19)	0.39	84 (11.8)	**4.67 (1.68,12.96**)	**0.003**
Multimorbidity							
No	76 (10.6)	24 (3.3)	1 (reference)		7 (1.0)	1 (reference)	
Yes	165 (23.0)	281 (39.1)	**2.13 (1.17,3.89)**	**0.013**	165 (23.0)	1.74 (0.66,4.55)	0.26
Mental Health condition							
No	199 (27.7)	147 (20.4)	1 (reference)		35 (4.9)	1 (reference)	
Yes	43 (6.0)	158 (22.0)	**3.72 (2.39,5.78)**	**<0.001**	137 (19.1)	**13.91 (8.00,24.18)**	**<0.001**
Neurological condition							
No	176 (24.5)	175 (24.3)	1 (reference)		98 (13.6)	1 (reference)	
Yes	66 (9.2)	130 (18.1)	1.16 (0.75,1.81)	0.50	74 (10.3)	1.01 (0.59,1.73)	0.97
Polypharmacy (excluding ACB medication)							
No	168 (23.4)	144 (20.0)	1 (reference)		53 (7.4)	**1 (reference)**	
Yes	74 (10.3)	161 (22.4)	1.51 (0.97,2.35)	0.067	119 (16.6)	**2.95 (1.71,5.08)**	**<0.001**

Reference category: ACB = 0 (n=220). Significant *P*-value is <0.05 and all significant values are in bold. Pseudo R-Square: Cox and Snell = 0.40, Nagelkerke = 0.45, McFadden = 0.24

Participants living in community group homes were three times more likely to be exposed to a high ACB score (OR 3.28, 95% CI 1.28 – 8.39). An even higher exposure rate was reported by participants living in residential care settings with a rate of four times higher compared to participants with no ACB exposure (OR 4.67, 95% CI 1.68 – 12.96).

Furthermore, those with multimorbidity were twice more likely to report a mild ACB exposure (OR 2.13, 95% CI 1.17 – 3.89).

Participants with mental health conditions were more likely to be exposed to mild and high ACB scores, with four times (OR 3.72, 95% CI 2.39 – 5.78) and almost 14 times higher rate (OR 13.91, 95% CI 8.00 – 24.18), respectively. These results indicate that most medications used for mental health conditions, have anticholinergic activity.

Polypharmacy (concurrent use of 5 or more medications with excluding medication with anticholinergic activity) was significantly associated with reporting high ACB scores with an OR of 2.95 (95% CI 1.71 – 5.08). Although medications with anticholinergic activity were excluded, polypharmacy remained a significant indicator for higher ACB exposure.

There was no evidence to illustrate a significant association between anticholinergic exposure and the other tested factors.

3.4.5 Longitudinal Association between Anticholinergic Cognitive Burden Score at Wave 1 with Outcomes Reported at Wave 4 (N = 487)

Multivariate logistic regression analysis was used to examine association between ACB score in Wave 1 and the reported adverse effects at Wave 4 (N = 487). The model was adjusted for socio-demographic factors including age, sex, type of residence, level of intellectual disability, epilepsy in Wave 4. Additionally, polypharmacy status was adjusted, and medication count excluded medication with anticholinergic activity because it was included in Anticholinergic Cognitive Burden quantification, to avoid over-adjustment given the high correlation between the ACB score and polypharmacy when included medications with anticholinergic activity (Spearman's rho 0.524). *Table 3.4-5* demonstrated results of the longitudinal logistic regression model. Detailed results are provided in *Appendix 3.4-1*.

Table 3.4-5 Multivariate logistic regression model of health-related outcomes reported at Wave 4, associated with ACB scores (1-4) (5+) at Wave 1 (N = 487).

Outcomes reported at the follow-up (Wave 4)	Anticholinergic Exposure at the baseline (Wave 1) (N = 487)	
	ACB = 1 – 4 (N = 193) OR (99% CI), *P*-value	ACB = 5+ (N = 148) OR (99% CI), *P*-value
Falls	1.51 (0.86 , 2.64), 0.15	**1.86 (1.03 , 3.38), 0.04**
Mental Health Conditions	**6.60 (3.69 , 11.77), <0.001**	**17.38 (8.97 , 33.61), <0.001**
Dementia/Alzheimer/or taking anti-dementia medicines (N06D)	**0.39 (0.15 , 0.97), 0.042**	**0.21 (0.07 , 0.64), 0.006**
Barthel Index	0.95 (0.48 , 1.86), 0.88	0.87 (0.37 , 2.01), 0.74
Constipation	1.09 (0.65 , 1.85), 0.73	1.05 (0.60 , 1.85), 0.86
Laxative Use	1.18 (0.68 , 2.02), 0.55	1.42 (0.79 , 2.53), 0.24
Edentulous	0.81 (0.44 , 1.48), 0.49	1.24 (0.67 , 2.30), 0.49
Reference category: ACB = 0 (N= 146). Significant *P*-value is < 0.05 and all significant values are in bold. The model was adjusted for Wave 4 age, sex, level of intellectual disability, residence, epilepsy and Wave 1 polypharmacy status excluding medications with anticholinergic activity.		

A significant association was found between ACB exposure at Wave 1 and the reporting of falls, mental health conditions, and dementia or Alzheimer's disease at Wave 4. However, there was not enough evidence to show a significant association between ACB scores at Wave 1 and reports of constipation, laxative use, Barthel Index scores, or edentulism at Wave 4.

Falls: Participants with an ACB score of 5 or higher at Wave 1 were nearly twice as likely to report falls at Wave 4 (OR = 1.86, 95% CI: 1.03 - 3.38, *P*-value 0.04) compared to those with an ACB score of 0.

Mental Health Conditions: Participants with mild and high ACB scores at Wave 1 were six times and 17 times more likely, respectively, to report a mental health condition at Wave 4 compared to those with an ACB score of 0 (ACB 1-4: OR = 6.60, 95% CI 3.69 - 11.77, *P*-value < 0.001; ACB 5+: OR = 17.38, 95% CI 8.97 - 33.61, *P*-value < 0.001). Those living in community homes were twice as likely, and those in residential care were three times as likely, to report a mental health condition compared to individuals living independently or

with family (community homes OR = 2.38, 95% CI 1.07 - 5.31; residential care OR = 3.21, 95% CI 1.35 - 7.60). Additionally, participants with epilepsy were less likely to report a mental health condition (OR = 0.57, 95% CI 0.35 - 0.93). Full results in *Appendix 3.4-1*.

Dementia, Alzheimer's Disease or taking Anti-dementia Medicines (N06D): Participants with mild and high ACB scores at baseline (Wave 1) were less likely to report dementia, Alzheimer's disease, or the use of anti-dementia medication at follow-up (Wave 4) compared to those with an ACB score of 0 (ACB 1-4: OR = 0.39, 95% CI 0.15 - 0.97, *P*-value 0.042; ACB 5+: OR = 0.21, 95% CI 0.07 - 0.64, *P*-value 0.006).

Barthel Index: Dependency, as measured by the level of assistance needed with daily activities, was twice as high in participants aged 65 and older (OR = 2.08, 95% CI 1.10 - 3.93) compared to those aged 55-64. Participants with severe or profound intellectual disability were six times more likely to be dependent (OR = 6.32, 95% CI 1.95 - 20.55) compared to those with mild intellectual disability. Dependency was also twice as high for individuals living in community homes (OR = 2.43, 95% CI 1.17 - 5.03) and over six times higher for those in residential care (OR = 6.88, 95% CI 2.48 - 19.07) compared to those living independently or with family. The BI was more than five times higher for participants with polypharmacy (OR = 5.66, 95% CI 2.06 - 15.57) compared to those without it.

Constipation and Laxative Use: Participants living in community group homes were more than twice as likely to report constipation (OR = 2.13, 95% CI 0.99 - 4.59), and those in residential care were even more likely (OR = 2.61, 95% CI 1.16 - 5.90), compared to those living independently or with family. Moderate and severe/profound intellectual disability also doubled the likelihood of constipation (moderate: OR = 1.73, 95% CI 1.01 - 2.94; severe/profound: OR = 2.48, 95% CI 1.33 - 4.65) compared to mild intellectual disability. Additionally, participants with polypharmacy were nearly twice as likely to experience constipation (OR = 1.93, 95% CI 1.21 - 3.07), as were those with epilepsy (OR = 1.67, 95% CI 1.079 - 2.56).

Laxative use was higher among those with moderate intellectual disability (OR = 2.60, 95% CI 1.48 - 4.58), severe/profound disability (OR = 2.78, 95% CI 1.45 - 5.32), individuals in community homes (OR = 6.65, 95% CI 2.25 - 19.68), residential care settings (OR = 10.79, 95% CI 3.52 - 33.06), and those with polypharmacy (OR = 2.04, 95% CI 1.26 - 3.29).

Edentulous: Participants aged 65 and older were more than four times as likely to report being edentulous compared to those aged 55 to 64 (OR = 4.24, 95% CI 2.65 - 6.77).

3.5 Discussion

This is the first longitudinal cohort study to assess anticholinergic exposure at two time points over a 10-year period. Although the study did not track ACB exposure continuously throughout the decade, it is likely that most participants remained exposed during this time. A large majority, 450 (92.4 %) out of 487 participants, were exposed to medications with anticholinergic activity at both time points, with only 37 participants ceasing exposure at some point between the two waves. There was a 3.5% decrease in the number of participants exposed to a high ACB score. This decline may be attributed to changes in the selection of alternative psychotropics, such as antipsychotics and antidepressants, over the past ten years.

3.5.1 Health Outcomes Associated with Anticholinergic Exposure

A previous cross-sectional study based on Wave 1 did not find a direct association between high ACB scores and falls, although it did reveal a significant link with daytime drowsiness (67). In contrast, this longitudinal analysis established a significant association between a high ACB score at Wave 1 and the occurrence of falls at Wave 4. These findings align with those of eight other studies that reported an association between ACB and the risk of falls in the general elderly population, as noted in a systematic review (155). This study also found a significant association between ACB scores in Wave 1 and reporting mental health condition in Wave 4. Medications with anticholinergic activity are well-known for their central adverse effects, such as delirium, drowsiness, confusion, and cognitive decline (156). Older individuals, in particular, are at a greater risk for these central anticholinergic side effects due to changes in pharmacokinetics and increased permeability of the blood-brain barrier (156). These findings are consistent with an Italian multicentre cross-sectional study, which also found a significant association between ACB scores and the reporting of mental health conditions in a similar population (95). Both anticholinergics and psychotropic medications can cause constipation as a side effect. A previous study highlighted that constipation can be painful and may lead to distress and aggressive behaviour in individuals with intellectual disability who are unable to communicate their symptoms, which may then be misinterpreted and treated as behaviour that challenges

(157, 158). However, another IDS-TILDA study did not find a direct link between constipation or pain and challenging behaviours, suggesting that further research is needed in this area (159).

3.5.2 Antipsychotic Medications

There are concerns about the inappropriate and long-term use of antipsychotics among individuals with intellectual disability (159). This study found that antipsychotic medications were the primary contributors to the total ACB scores in the cohort, with olanzapine, chlorpromazine, quetiapine, and risperidone being the most frequently reported antipsychotics. Although the overall use of antipsychotics remained high across both time points, there was a decrease in the reporting of haloperidol (1.8%) and chlorpromazine (5.3%). Both are first-generation antipsychotics, also known as typical antipsychotics. A longitudinal cohort study within IDS-TILDA, which examined psychotropic use patterns at each of the four waves (Wave 1-4), reported significant changes in medication use, including a decrease in the use of first-generation antipsychotics (chlorpromazine) and an increase in the use of antidepressants (sertraline) and atypical antipsychotics (quetiapine)(62).

Antipsychotics are prescribed to manage mental health conditions and, in some circumstances, to control behaviours that challenge such as physical or verbal aggression, self-injury, hyperactivity, and repetitive stereotypic behaviours (160). However, due to the limited evidence supporting the safety and efficacy of antipsychotics for managing these behaviours, the National Institute for Health and Care Excellence (NICE) guidelines recommend that antipsychotics should only be used to control behaviours that challenge if psychological and other interventions have proven ineffective within an agreed timeframe (3). Furthermore, NICE guidelines advise against the exclusive use of antipsychotics, emphasizing that they should always be combined with psychological or other interventions when treating behaviours that challenge in people with intellectual disability.

Research has shown a high prevalence of antipsychotic polypharmacy, where individuals with intellectual disability are prescribed more than one antipsychotic medication to manage behaviours that challenge (159, 161). The excessive use of antipsychotics among individuals with intellectual disability is a widely recognized issue. Antipsychotics are often

prescribed for extended periods without a clear diagnosis and with insufficient monitoring of their effectiveness, tolerability, and safety (162). A cohort study conducted in the United Kingdom found that the proportion of people with intellectual disability treated with psychotropic medications is significantly higher than those with documented mental diseases (163). Moreover, the study reported that antipsychotics are frequently prescribed to people with intellectual disability who have a record of behaviours that challenge even without a recorded of severe mental diseases.

Another study reported that discontinuing antipsychotics prescribed for behaviours that challenge in people with intellectual disability led to an improvement in their behaviours (164). The study also noted that tapering off the medication may not be necessary if it has been used for less than 14 weeks. Since there has been some debate about the appropriateness of using antipsychotics to manage behaviours that challenge, then perhaps the reported reduction in antipsychotics may reflect a slight shift from this practice or switching to alternatives such as antidepressants.

3.5.3 Anticholinergic Medications

This study found a 4.3% reduction in medications with anticholinergic activity, despite a 1.5% increase in antipsychotic use between the two waves. For instance, procyclidine, an anticholinergic that ranked 9th among the most frequently prescribed medications at 7% in Wave 1, did not appear in the list at Wave 4 (*Table 3.4-3*). Additionally, the recorded frequency of biperiden, another anticholinergic, decreased by 5.3%. A previous IDS-TILDA study using Wave 2 data found that one-third of participants taking antipsychotics for behaviours that challenge were also using anticholinergic medications like biperiden (159). These anticholinergics were likely prescribed to manage extrapyramidal side effects resulting from the long-term use of antipsychotics (67). Therefore, the change could be related to shifts in prescribing practices, particularly the combination of anticholinergics with antipsychotics to manage potential extrapyramidal side effects. In addition, the use of alternative or newer antipsychotics in Wave 4, which are less likely to be associated with extrapyramidal side effects, may explain the reduction in the use of procyclidine (165). Scopolamine (hyoscine) (4.8%) was also reported in Wave 4 but is indicated for travel sickness and could be used to manage excessive salivation (drooling) (166), not to control the extrapyramidal effects of antipsychotics (unlike biperiden and procyclidine). Since the

indication for each drug is not reported in the IDS-TILDA dataset the reason(s) for the use of scopolamine would have to be determined separately.

3.5.4 Other Covariates

A significant association was observed between polypharmacy (excluding medications with anticholinergic activity) in Wave 1 and the presence of constipation, laxative use, and increased dependency levels at Wave 4. As participants age, the prevalence of this polypharmacy significantly increased from 34.7% to 54.0%, likely due to age-related health conditions. The occurrence and onset of chronic health issues tend to rise as individuals with intellectual disability get older. Between Wave 1 and Wave 3 of IDS-TILDA, there was an increase in the incidence of conditions such as osteoporosis, constipation, obesity, falls, and dementia (167). This study further confirmed a significant rise in the prevalence of constipation, multiple laxative use, dependency in activities of daily living, edentulous, and Alzheimer's disease/ dementia/ taking anti-dementia medications. This could explain the increased use of non-anticholinergic medications, as these drugs are often prescribed to manage age-related health issues, including laxatives, anti-osteoporotic medications, and anti-dementia agents. Therefore, individuals with intellectual disability who are on multiple medications require regular medication reviews, including those for anticholinergic drugs, and a review tool tailored to the specific needs of this population should be developed. A draft tool for Optimizing Pharmaco-Therapy and Improving Medication for Aging with Intellectual Disability (OPTIMA-ID) was recently developed in IDS-TILDA as the first comprehensive tool aimed at optimizing prescribing for older adults with intellectual disability (168).

This study demonstrated that, after controlling for other confounding factors, participants living in residential care settings, those with mental health conditions, and those experiencing polypharmacy were more likely to have high ACB scores (total ACB = 5+). As a result, further investigation is needed to improve the management of prescribing medications with anticholinergic effects for individuals with intellectual disability living in residential care environments.

3.5.5 Dementia and Anticholinergic Exposure

Medications with anticholinergic activity have been suggested to disturb neural network involved in memory and learning ability (169), reduce the level of phosphatidylcholine in the brain, and raise B-amyloid formations (170), may cause neuroinflammation (171), and increase tau-driven neurodegeneration (172). These findings suggest that long-term anticholinergic exposure might increase the risk of dementia, particularly dementia of Alzheimer disease. However, this study reported lower odd ratio of dementia/ Alzheimer/ taking anti-dementia medication in Wave 4 associated with high ACB score in Wave 1. This finding contrasts with the results of a systematic review by Zheng *et al.,* which identified a dose-dependent relationship between ACB exposure and the risk of dementia in the general population. However, the sample size in this study was small (N = 29) for those reporting dementia/Alzheimer's disease or taking anti-dementia agents (N06D), and only half of these participants had ACB exposure. Additionally, the wide confidence intervals (95% CI: (0.15, 0.97), (0.07, 0.64)) suggest limited understanding of the effects, indicating the need for further investigation. Moreover, diagnosing dementia in people with intellectual disability is challenging due to pre-existing cognitive impairments related to their conditions and limited access to screening services.

The prevalence of dementia is higher among individuals with intellectual disability compared to the general elderly population, particularly for those with Down syndrome. Due to the triplication of chromosome 21, individuals with Down syndrome typically exhibit the neuropathology of Alzheimer's disease by the age of 40 (167). Moreover, the average age at which dementia is diagnosed in individuals with Down Syndrome is 52.3 years, while those with intellectual disability from other aetiologies are diagnosed with dementia at an average age of 65.5 years (167). Dementia causes around 70% of deaths in people with Down Syndrome which resulted in 20 year gap of life expectancy compared to the general population (173). People with down syndrome experiencing a decline in cognitive function had limited access to expert clinical service in dementia (174).

Based on the recent Wave 5 report in IDS-TILDA, 42.7% of individuals with Down syndrome, who did not have a dementia diagnosis, had never undergone a dementia assessment, which could lead to under-reporting of dementia cases (175). Since 2020, following Wave 4, dementia screening has increased with the establishment of the

National Intellectual Disability Memory Service, which offers memory screening and assessment for all individuals with intellectual disability in Ireland.

To investigate the relationship between anticholinergic exposure and incidence of dementia among older adults with intellectual disability, a larger sample size would be needed. Additional research should focus on examining the ACB exposure among individuals with Down Syndrome and those with intellectual disability from other aetiologies. A high anticholinergic exposure might account for the increased prevalence of dementia in individuals with Down Syndrome, indicating the need for further care for this vulnerable population.

3.5.6 Impact of Study Finding on Practice

The findings of this study highlight the necessity of reassessing prescribing guidelines for antipsychotics, especially those with an ACB score of 3 such as chlorpromazine, quetiapine and olanzapine, for older adults with intellectual disability living in residential setting area. The study raises questions about potential alternatives to these high-ACB medications and whether these alternatives would be effective, safer, and accessible for people with intellectual disability. Further research is needed to explore these alternatives, their efficacy, and their availability. The study also emphasizes the importance of regular medication reviews, particularly for individuals on polypharmacy, to assess the potential for reducing or discontinuing medications, both with and without anticholinergic activity.

3.5.7 Disseminating Accessible Study Findings

The PhD candidate prepared the findings of this study in accessible materials for the public. As part of this effort, she participated in the Three-Minute Thesis competition at Trinity College Dublin, where students present the concepts and findings of their PhD research in accessible language using only one slide and within three minutes. She was awarded the "People's Choice Award" and the "Runner-Up Award" in the competition. Following this, LA participated in the Faculty of Health Sciences Research Blitz, where she shared her key findings with other health researchers. Additionally, she presented her work at the Provost Council Meeting at Trinity College Dublin, offering an opportunity to communicate these findings to a diverse audience, including members of the public,

stakeholders, and policymakers. The PhD student also created a short video summarizing the study findings, which was shared on YouTube, LinkedIn, and Twitter through the author's and co-authors' personal accounts, as well as the official IDS-TILDA and School of Pharmacy and Pharmaceutical Sciences accounts. Furthermore, the findings and the video were presented at the International Association for the Scientific Study of Intellectual and Developmental Disabilities (IASSIDD) Congress in Chicago, USA (*Figure 3.5-1*). The video will also be used for educational purposes in the School of Pharmacy at Trinity College Dublin and the College of Health Sciences in Oman (QR code for the video provided below). Through these engagements, the accessible presentation of study findings significantly raised awareness about medication use among older adults with intellectual disability, with a particular focus on medications with anticholinergic activity.

Figure 3.5-1 Presenting accessible video in IASSIDD, Chicago, 2024. Picture taken by Maire O'Dwyer

QR Code for the Three Minute Thesis Video

3.5.8 Strength and Limitations

This is the first longitudinal study to explore the relationship between anticholinergic exposure and associated outcomes over a 10-year period among older adults with intellectual disability. It analysed a cohort with a substantial follow-up duration between two timepoints (Wave 1 and Wave 4), spanning 10 years, which allowed for the assessment of adverse effects related to ACB exposure a decade previously. The research was conducted using a large, randomly selected, population-representative sample at both timepoints, enhancing the generalizability of the findings to older adults with intellectual disability in Ireland. Additionally, highly trained field researchers in IDS-TILDA achieved a 97% rate of participants providing medication data at both timepoints, and the accuracy of this data was verified through reviews conducted by field researchers during the CAPI. Additionally, in Wave 4, participants were asked to verify or correct previously reported health conditions, which enhanced the accuracy of the data collected. Another strength of the study is the use of the ACB score to measure anticholinergic burden, which ensures that the findings are robust and relevant to clinical practice. The list of medications with anticholinergic activity was reviewed and updated before the study to maintain its accuracy. The study assessed ACB scores at both waves to evaluate exposure over the two timepoints. IDS-TILDA collected extensive datasets at each wave, allowing for thorough analysis of the associations between various factors, outcomes, and ACB scores. The observational nature of the study and absence of information linking medication use to a specific indication mean that it is only possible to consider potential associations with the changes in anticholinergics and other medicines between the two waves. A limitation of the study is that while it investigated the adverse effects reported at Wave 4, additional potential effects such as frailty, cognitive impairment, and daytime drowsiness should be explored in future research.

3.5.9 Recommendation for Future Work

Additional analysis is needed to investigate exposure by incorporating medications taken during Waves 2-3, which are three years apart. To capture a more comprehensive view of population trends over time, complex longitudinal modelling techniques could be applied. Generalized Estimating Equations (GEE) could be used to infer average population

responses over time, while Generalized Linear Mixed Models (GLMM) could model individual trajectories using random effects. The advantage of GLMM is that it does not require complete cases, allowing for the inclusion of all participants in the analysis, even if they did not respond in every wave. The GEE model was effectively used in previous research, to examine changes in psychotropic medication patterns over the four waves of data within IDS-TILDA (62).

3.6 Conclusion

In summary, older adults with intellectual disability are often exposed to a significant anticholinergic burden over extended periods. Antipsychotic medications are the primary contributors to this high burden, followed by anticholinergics and other medications with anticholinergic activity. Both mild and high ACB scores at Wave 1 were significantly associated with an increased risk of falls and mental health conditions in these individuals after 10 years. There is a persistent need for regular reviews of antipsychotic and anticholinergic medications for this group of population to minimize avoidable adverse effects and improve their quality of life.

Chapter 4

Prescriber's view on prescribing and deprescribing of medications with anticholinergic activity among older adults with intellectual disability: a qualitative study

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Prescriber's view on anticholinergic deprescribing among older adults with intellectual disability: A qualitative study protocol

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4.1 Introduction

As outlined in *Chapter 1*, anticholinergics are a class of medications used to treat various conditions such as urinary incontinence, gastrointestinal disorders, cardiovascular diseases, and neurological and mental health disorders (176, 177). Additionally, there are other medications that, while not classified as anticholinergics, exhibit anticholinergic activity. Ageing altered pharmacokinetics and pharmacodynamics could increase the risk of adverse drug reactions (ADR) (176, 177).

Older adults with intellectual disability experience a greater anticholinergic burden compared to the general elderly population (20, 67, 93). This burden is notably higher among those residing in nursing homes and community group homes (93), those of advanced age (67), and individuals with psychiatric or neurological diseases (67, 93). While some studies have examined the adverse effects of high anticholinergic exposure in this population, findings have been limited. Reported adverse effects include daytime drowsiness (67), constipation and use of multiple laxatives (67, 93). However, the published scoping review (131) indicates a lack of longitudinal studies investigating the possible adverse effects associated with long-term exposure to high anticholinergic burden. Nonetheless, longitudinal studies in the general elderly population have demonstrated that prolonged exposure to high anticholinergic burden is associated with cognitive decline (97, 114, 176), poorer physical function (97, 117), and an increased risk of developing dementia (101, 127) and Alzheimer disease (101). Anticholinergics and medications with anticholinergic activity are still being widely prescribed for older adults with intellectual disability, although research has reported high anticholinergic exposure among this population.

As illustrated in *Chapter 1*, multimorbidity drives medication prescribing and medications may be continued even when they are no longer required or when their risks outweigh their benefits (178). Such potentially inappropriate prescribing can lead to adverse drug reactions, negatively impact quality of life, consume healthcare resources and increase mortality. However, polypharmacy is not inherently harmful and may be necessary to address multimorbidity effectively.

Medication optimisation, defined as a “person-centred approach to safe and effective medicine use to ensure people obtain the best possible outcomes from their medicines”

(179), could improve the appropriateness of polypharmacy (180). A medication optimisation approach may involve initiating new medicines or stopping existing ones. Deprescribing, a key component of medication optimisation (181), is a planned process that involves reducing or discontinuing potentially inappropriate medications. The goal of deprescribing is to minimise harm and reduce medication burden while maintaining or improving patients' health and quality of life. Several studies in the general population of older people, have shown that deprescribing can effectively reduce the number of potentially inappropriate medications (PIMs) (182-186) and improve quality of life (186).

4.1.1 Theoretical Behavioural Frameworks

To enhance the effectiveness of interventions, it is essential to understand both behavior and behavior change, which requires a theoretical foundation (187). This involves understanding the mechanisms that drive change (mediators) and factors that influence the effectiveness of change (moderators), as well as having assumptions about human behavior and the factors that shape it. Using theory is strongly recommended as a crucial step in the design and evaluation of interventions, as well as in synthesising evidence, as emphasized by the UK Medical Research Council's guidelines for developing and assessing complex interventions (105). A variety of theoretical frameworks are used to explore determinants of behaviour and to understand the barriers and facilitators to the behaviour(s) under investigation. There are a large number of literature which supports the use of theoretical frameworks when developing behaviour change interventions (187, 188). These theoretical frameworks include COM-B (Capability, Opportunity and Motivation for behaviour) and the Theoretical Domains Framework (TDF), which are explained in more detail below.

COM-B Framework: The COM-B model helps researchers understand the determinants of behaviour by examining an individual's capability, which includes both physical and psychological aspects; opportunity, encompassing social and physical factors; and motivation, which involves both automatic and reflective processes (189).

Theoretical Domains Framework: Another common framework is the Theoretical Domains Framework (TDF) which is an integrative frameworks that combines 33 theories of behaviour change and 128 key theoretical constructs to synthesize a single framework with 12 theoretical domains (190). The TDF aims to simplify behaviour change theories,

making them more accessible and usable for researchers. There are two versions of the TDF: the first version comprises 12 domains, while the refined and validated updated version includes 14 domains and 84 component constructs (191). In version 2 of the TDF, some of the constructs have been placed under different domains to improve clarity and coherence.

The COM-B and TDF are both used as frameworks for understanding behaviour and to identify barriers and facilitators for behaviour change (191). However, the TDF unpacks the COM-B further and expand it into 14 domains instead of 3 main domain, so the TDF allows a further detailed investigation of behavioural determinants.

4.1.2 Intervention Development Framework

Behaviour Change Wheel (BCW) (189) is one of the most knowing frameworks and it consists of three stages or process to support behaviour change and these are:

1. Sources of behaviours; Capability, Opportunity and Motivation for behaviour, Knowing as COM-B.
2. Intervention function: illustrate interventions assigned to each targeted behaviour for instance education, training, enablement, persuasion, etc.
3. Policy categories: provide policies to support the intervention with a more structural level for example regulation, guidelines, service provision and legislation (189).

The BCW is useful to develop an intervention through mapping the relevant components of the identified behaviour to an intervention function and policy category, as illustrated in *Figure 4.1.-1*

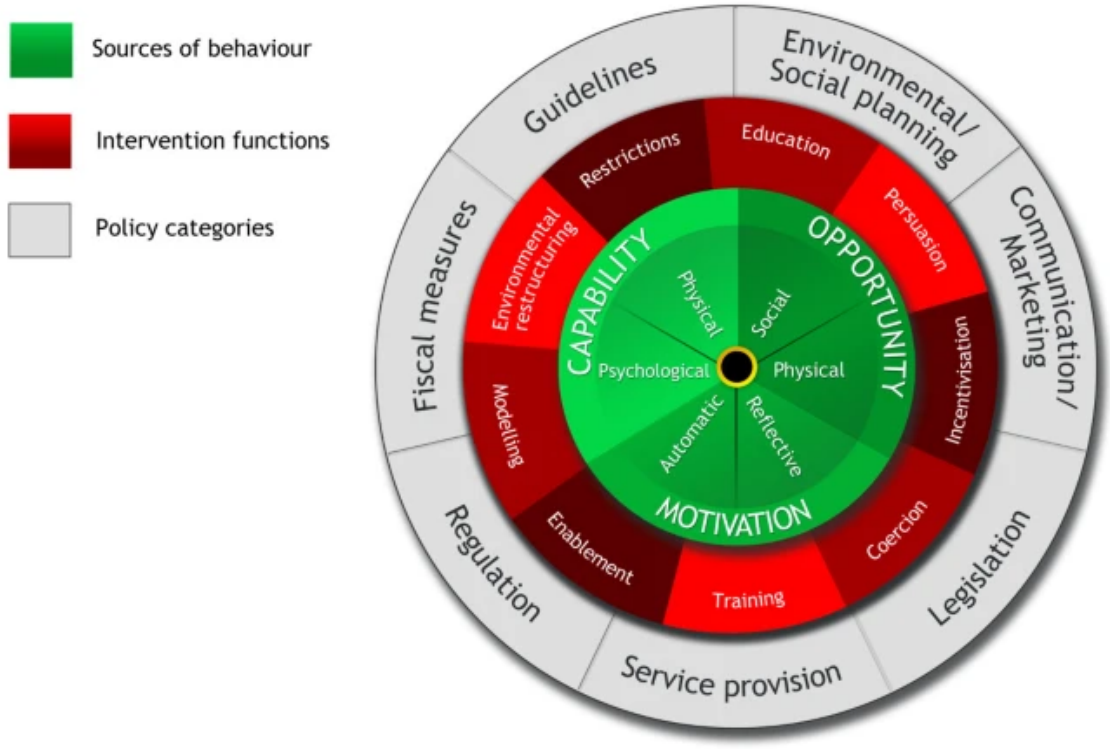

Figure 4.1-1 The Behavior Change Wheel developed by Michie *et al.*

When designing interventions, the TDF, like COM-B, aligns well with the BCW, helping to identify appropriate interventions based on the relevant components of the targeted behaviour. Furthermore, the domains of TDF has been mapped to COM-B (191), as illustrated in *Table 4.1-1*. Additionally, it has been used as an additional layer to the BCW after the COM-B in some health-related research (192).

Table 4.1-1 Mapping TDF domains to the COM-B components

COM-B component		TDF Domain
Capability	**Psychological**	Knowledge
		Skills
		Memory, Attention and Decision Process
		Behavioural Regulation
	Physical	Skills
Opportunity	**Social**	Social Influences
	Physical	Environmental Context and Resources

Table 4.1-1 Continued		
COM-B component		TDF Domain
Motivation	**Reflective**	Social/Professional Role and Identity
		Beliefs about Capabilities
		Optimism
		Beliefs about Consequences
		Intentions
		Goals
	Automatic	Social/Professional Role and Identity
		Optimism
		Reinforcement
		Emotion

The barriers and facilitators of deprescribing have been explored through the TDF (193-196) and BCW (197, 198). More recently, the TDF has been applied in systematic reviews to identify barriers and facilitators for deprescribing specific medications, such as benzodiazepines (199) and opioid analgesic (200), within particular populations. Based on this, the study will use the updated version of the TDF framework (Version 2, see *Appendix 4.1-1*), as it offers a more comprehensive approach compared to the COM-B model. This framework allows for a detailed investigation of the behavioural components associated with anticholinergic deprescribing among prescribers working with older adults with intellectual disability.

4.2 Aim and objectives

This qualitative study aimed to explore prescribers' views on deprescribing of medications with anticholinergic activity among older adults with intellectual disability.

The specific objectives of the study were to:

1- Recruit prescribers to older adults with intellectual disability, until data saturation is reached (8 – 10 participants)

2- Examine prescribers' knowledge of anticholinergic burden as it relates to people with intellectual disability, anticholinergic adverse effects, and the tools used to quantify anticholinergic burden

3- Identify barriers and facilitators of deprescribing of anticholinergics and optimising anticholinergic use, using the TDF

4- Investigate prescriber's opinion on the pharmacist role in deprescribing and optimising use of medications with anticholinergic activity.

4.3 Method

4.3.1 Study Design

This semi-structured qualitative study, grounded in the TDF, aims to identify the barriers and facilitators to anticholinergic deprescribing behaviours among older adults with intellectual disability. A study protocol was developed and published in the HRB Open Research journal (201). The study design comprised the following seven steps according to the TDF:

1. Selection and Specification of Targeted Behaviours
2. Selection of the Study Design
3. Development of Study Materials
4. Selection of the Sampling Strategy
5. Data Collection
6. Data Analysis
7. Reporting Findings from interviews

4.3.2 Selection and Specification of the Targeted Behaviours

This study aimed to target the behaviour of anticholinergic deprescribing to reduce anticholinergic burden exposure and to optimise medicine use among older adults with intellectual disability. *Table 4.3-1* illustrates the details of the main behaviour to be targeted and the context.

Table 4.3-1 Context and details of the targeted behaviour

Targeted behaviour	Details
Behaviour	Deprescribing of medications with anticholinergic activity to reduce high exposure or high anticholinergic burden
Who	Prescribers involved in prescribing for older adults with intellectual disability
What	Taking action/intervention to lower anticholinergic burden in case of identified high anticholinergic exposure/ optimise exposure
When	Identified high and inappropriate anticholinergic exposure
Where	All healthcare setting areas
How often	As required
With whom	All prescribers involved in prescribing for older adults with intellectual disability

4.3.3 Selection of the Study Design

This study involved semi-structured one-to-one qualitative interviews, which were conducted either online via Zoom or in person based on the interviewees' preferences. The study aimed to include prescribers from various specialties who prescribe medications for older adults with intellectual disability in Ireland. This included consultants, specialists, general practitioners, and nurse prescribers.

4.3.4 Development of the Study Materials

The interview topic guide was structured around the domains of TDF version 2 and developed to align with the study's aim and objectives (see *Appendix 4.3-1*). The topic guide was reviewed by the research team, LA, CR, and AG. CR and AG have extensive experience in qualitative research and application of the TDF. The topic guide was divided into five main sections. The first section collected demographic information, including the prescriber's role, length of employment, and workplace. The second section explored the prescribers' experiences and challenges in prescribing for older adults with intellectual disability. The third section examined their knowledge of the term "anticholinergic burden," relevant tools or scores, and associated adverse effects. The fourth section examined the barriers and facilitators to anticholinergic deprescribing behaviour, with questions informed by the TDF framework. The final section focused on the role of pharmacists in the prescribing and deprescribing process for this population.

Additionally, a supplementary document was provided and discussed with participants during the third section of the interview. This document included findings from a longitudinal cohort study (see *Chapter 3 and Appendix 4.3-1*) on anticholinergic exposure and the most prescribed medications with anticholinergic activity among the studied population.

The topic guide was piloted with three members (Professor and two Assistant Professors in Pharmacy Practice), from IDS-TILDA and the School of Pharmacy and Pharmaceutical Sciences in Trinity College Dublin. No amendments were made to the topic guide.

4.3.5 Selection of the Sampling Strategy

This study aimed to recruit 8-10 prescribers, or until data saturation was achieved. This sample size was selected based on previous deprescribing studies, which typically included 10-15 prescribers (202-207), and the expectation of a smaller number of prescribers who provide care for older adults with intellectual disability in Ireland.

The recruitment targeted prescribers from various specialties, such as neurologists, psychiatrists, general practitioners, nurse prescribers and others involved in the care of this population and likely to be involved in prescribing medications with anticholinergic activity. Participants were recruited by advertising the study through the IDS-TILDA Twitter account, which facilitated outreach to a diverse group of prescribers caring for older adults with intellectual disability. Additionally, an invitation letter was sent to stakeholders provided by a gatekeeper (MAH) from the IDS-TILDA team, and the snowballing method was also applied. The study was advertised in September 2023. The PhD candidate had sent an invitation email to the list of stakeholders provided by the gatekeeper. Intellectual disability services contacted included: Avista, Carriglea Cairde Service, Peamount Health Care, St Michael's House and Stewarts Care.

4.3.6 Data Collection

Individual interviews were conducted between 15-09-2023 and 27-06-2024 by the PhD candidate. All interviews took place online via Zoom at the preference of the participants. The PhD candidate ensured that each participant returned a signed consent form before the interview commenced. The interviews were recorded and securely stored in the PhD candidate folder within IDS-TILDA encrypted secure drive, following Trinity College Dublin's Data Protection guidelines and ethical approval guidelines. As recommended by TCD, recording will be kept until the end of the PhD candidate’s academic validation. Prior to starting each interview, the PhD candidate verified the eligibility and identity of the participants. Each participant was assigned a unique code, such as P1, P2, P3, etc. The interviews were transcribed *verbatim*, titled with participant codes, and no personal or identifiable information.

4.3.7 Data Analysis

The framework method (208) was utilised to conduct data analysis for this study. The framework method consists of seven data analysis stages, which include:

1. Transcription
2. Familiarisation with the interview
3. Coding
4. Development of a working analytical framework
5. Application of the analytical framework
6. Charting data into the framework matrix
7. Interpretation of the data

These are described in detail below.

Stage 1: Transcription

The interviews were recorded and transcribed using Zoom and the recoded interview and transcription saved directly in the PhD candidate's OneDrive. After each interview, the PhD candidate listened and re-listened to the recorded interviews and amended the saved transcription to ensure the accuracy of the transcription. The transcripts had a large line spacing and margins for coding notes and comments.

Stage 2: Familiarisation with the interview

The PhD candidate re-read and re-listened to the recorded interviews and their transcripts to be familiarized with them. The PhD candidate checked any important notes, thoughts, comments or analytical notes which were taken during the interviews and recorded by the margins and discussed them with the research team when needed.

Stage 3: Coding

A coding scheme and main themes were developed based on the TDF version 2 domains. A randomly selected sample of three transcripts (P-2, P-4, and P-5) was used for developing the coding scheme, which was performed independently by the PhD candidate and a second team member (AG). The codes were based on commonly occurring themes identified during the familiarisation stage. The coded transcripts were then compared, and a third team member was involved to resolve any disagreements. The agreed-upon codes were organized and grouped into overarching categories, which were subsequently used to develop the final coding scheme.

Stage 4: Development of a Working Analytical Framework

The coding scheme was developed using the three randomly selected transcripts at the coding stage. Each domain within the TDF served as a coding category, and subcategories were created based on the themes identified in the three transcripts. The coding scheme consisted of six main parts, covering codes for demographic information, general prescribing experiences among people with intellectual disability, comparisons to the general population, and the contribution of pharmacists. The final coding scheme was then reviewed and discussed by the research team (see *Appendix 4.3-2*). The coding scheme consisted of 20 codes within seven categories.

Stage 5: Application of the Analytical Framework

In this step, the developed coding scheme was applied to the remaining transcripts. Two members of the research team (the PhD candidate and AG) independently applied the coding scheme to all of the transcripts. The coded transcripts were then compared.

Stage 6: Charting Data into the Framework Matrix

Data from the coded transcripts were charted in Excel. The data were organized according to the seven main categories from the coding framework, with each category presented in a separate sheet and a row dedicated to each participant. During this stage, the data were summarised, and qualitative data analysis was performed using Excel software version 16.88.

Stage 7: Interpretation of Data

All notes, ideas, and early interpretations recorded by LA during data processing were reviewed and discussed with the research team. Any associations, differences, or causal relationships between categories were discussed and reported.

4.3.8 Reporting Findings from interviews

All of study findings are anonymized and reported based on the Consolidated criteria for reporting qualitative research (COREQ-32), the checklist provided in *Appendix 4.3-3*. The anonymized results were shared with research team, and any future publication will be shared with the participants.

4.3.9 Ethical Approval

Data Protection Risk Assessment (DPRA) was attained for this study on 03-12-2022 from Trinity College Data Protection Office, see *Appendix 4.3-4*. Ethical approval was obtained from the School of Pharmacy and Pharmaceutical Science in Trinity College Dublin on 12-05-2023, see *Appendix 4.3-5*.

The consents forms received prior to each interview and stored in password-protected file in the PhD candidate's folder within IDS-TILDA secured drive.

4.4 Results

4.4.1 Demographic Characteristics

Five intellectual disability services were approached for participant recruitment, alongside advertisements on social media. In total, ten prescribers who provide healthcare services and prescribe medication for older adults with intellectual disability in Ireland were recruited (five consultant psychiatrists, three general practitioners and two geriatricians). In total, > 50% were female prescribers. The interviews were conducted online between September 2023 and June 2024, and all interviews were conducted by the PhD candidate. The interviews ranged from 16 to 60 minutes in duration. *Table 4.4-1* illustrate the demographic information of all prescribers interviewed.

Table 4.4-1 Demographic of prescriber interviewed

Interview code	Role	Length in role
P-1	Consultant Psychiatrist	>20 years
P-2	Consultant Psychiatrist	>20 years
P-3	General Practitioner	5 - 20 years
P-4	Consultant Psychiatrist	5 – 20 years
P-5	Consultant Psychiatrist	< 5 years
P-6	General Practitioner	5 – 20 years
P-7	General Practitioner	5 – 20 years
P-8	Geriatrician	< 5 years
P-9	Geriatrician	5 – 20 years
P-10	Consultant Psychiatrist	>20 years

To ensure the participants remained unidentifiable, given the small group of prescribers working with people with intellectual disability, gender information was removed, and the length of time in their role was categorized into broader categories.

The results of this study are categorised based on the developed coding scheme discussed above.

4.4.2 Appropriate Prescribing for Older Adults with Intellectual Disability

Medication review, deprescribing, updating their knowledge, following guidelines and involving carer/family, were important processes the prescribers reported following to maintain appropriate prescribing for people with intellectual disability. They considered this as a big part of their role to ensure safety and efficacy of medicine use among this population.

> *"you want to be practicing safe medicine, so you want to make sure you're picking a medication that is efficacious and that it has the least amount of side effects…..everybody was getting a regular medical review at least every 12 months. Some people regularly could be monthly or whatever. But you're continually reviewing their medication... you want to reduce the burden of frequency of medication. So if you can.. prescribe.. long-acting drugs, or once a day, or even twice a day, it's much better than prescribing something four times a day."* [P-6]

> *"we do an annual medical review, and we tend to use that twice yearly, at least to look at medications that are long term medications. Can they be deprescribed?...That would be across the whole Kardex or medication list."*[P-3]

Additionally, there are special precaution while prescribing for people with intellectual disability diagnosed with dementia.

> *"for somebody with dementia… who develop seizures during their dementia. Usually we're not looking at the really fancy new anti-seizure medications. We're looking at those…old and gold…like lamotrigine and sodium valproate and … Keppra…"* [P-1]

Prescribers highlighted further concerns regarding prescribing practice related to challenging behaviour among people with intellectual disability.

> *" So 2 of the places I worked in, there was a psychiatrist … who thought that everybody who had challenging behaviour had epilepsy. So everyone got put on a combination of anti-epileptic medication. One of my jobs has been to peel that away. Because.. the doses were above the doses recommended for epilepsy...we have to admit that some forms of challenging behaviour are related to epilepsy, but not everyone. "* [P-2]

> *"People who are prescribed anti psychotics for challenging behaviour, and historically maybe would have been prescribed,...for many years medications for challenging behaviour and we're trying now to reduce them…it's a little more challenging in residential settings because I suppose people can get quite anxious in relation to the reductions in medications, and then can start to over attribute .. different adverse effects to the reductions that you might be trying to introduce in medications. So I think there's a cultural difficulty in addressing that in residential settings when there's a high level of staff anxiety in the culture."* [P-5]

Another factor considered by prescribers to achieve an appropriate prescribing for people with intellectual disability was the differences in pharmacological responses to medication in comparison to general population. Prescribers noted higher sensitivity to medication and their adverse effects. Therefore, prescribers are following the rule “start low and go slow” using much lower doses and longer interval between the doses compared to general population.

> *"kind of starting slow and really expecting adverse effects to occur, and probably taking adverse effects more seriously because people with ID can't describe them to you. So, .. you're being more careful and looking more closely at them "* [P-5]

"You just need to be a bit more aware of people being more sensitive to the medication, the side effect of the medication...they are on polypharmacy.. because of their multiple medical conditions. So you really need to be aware to whether this medication is going to make any difference as opposed to cause any harm which is the constant debate"[P-4]

Guidelines used by prescribers to maintain appropriate prescribing for people with intellectual disability included: Maudsley guidelines for intellectual disability (209), the Frith Guidelines (55), consensus statements on prescribing for people with dementia and down syndrome, Health Service Executive (HSE) guidelines on antibiotic prescribing (210), ICGP deprescribing tool (211), the National guideline (212), the NICE guidelines(213), and College Psychiatry guidelines (214).

4.4.3 Challenges in Prescribing for Older Adults with Intellectual Disability

The prescribers were asked to discuss their experience in general prescribing and conducting medication review for older adults with intellectual disability challenging. Based on their responses, here are the factors that had an impact on prescribing/medication review for older adults with intellectual disability. There is a summary table at the end of the section illustrating factors contribute to challenge in prescribing for older adults with intellectual disability.

4.4.3.1 Patient-Related Factors

Patient-related factors that had an impact on prescribing practice for older adults with intellectual disability reported by prescribers includes the complexity of morbidities as well as the communication barriers. These presented below.

The complexity of morbidities associated with intellectual disability: this population have brain abnormality, brain dysfunction, neurological diseases. This is a complex process as the majority of the population have multiple comorbidities, and are prescribed polypharmacy, often since childhood.

"we're dealing and supporting people that have kind of…a brain dysfunction, a brain abnormality, … neurological issues, at the basis of their intellectual disability, due to chromosomal or trauma, or whatever … cause of disability.. " [P-1]

" you have to be very mindful of the multiple co-morbidities... you really need to look at the medical comorbidities... people would have down syndrome, multiple medical conditions, mitochondria disorders and things like that or epilepsy. So you need to look at that profile..., much more medical conditions, such as maybe kidney, liver failure… because of genetics syndrome." [P-4]

Communication barriers: Another factor impacting appropriate prescribing was the patient's difficulty in communicating symptoms and adverse effects, along with challenges in understanding medical information. As a result, healthcare providers often rely on family members or caregivers as key sources of information.

"... you're facing a population who.. might not express their symptoms in the same way as you would outside of this community. So you have to be very careful and consider .. your choice of prescribing ... you need to be really carful." [P-7]

"Certainly, communication, a lot of our service users would be non-verbal, and the consultation would include their carers or family. So it wouldn't be your typical consultation." [P-3]

4.4.3.2 Environment-Related Factors

The residence and institutional settings were another factor that had an impact on prescribing practices for this patient population. Influencing factors includes change of staff, availability of medical records, the impact of long-term institutional and of de-institutional, and access to medication.

"*most people who come to our clinic….we inherit them...on a very long list of antipsychotic medications that they've been on for a long number of years, it hasn't been readdressed, and often they come where the service won't know their past medical history or their psych history, won't have notes from a psychiatrist*" [P-8]

"there's a high turnover of care staff in the residential services in particular. So people who are in residential care, it would tend to be a little bit more difficult than when people are with families…families have a greater degree of understanding when people are living at home, so it tends to be a bit easier in those places to pick up .. side effects medication. You kind of get very used to listening to families concerns because they pick them up very quickly, whereas in residential services it is definitely more difficult because you're speaking to different staff members on different days who may not know the person all that well" [P-5]

Additionally, the environment and type of setting where people with intellectual disability live, has an impact on the diagnosis of diseases.

"... lot of people who have been institutionalized since childhood and now are in their sixties, seventies, and eighties, and have been on major tranquilizers since before the age of 10, for some of them...and when they're moving from a long-term institutionalisation to community houses… we are realising that they have autism rather than schizophrenia, they would have been thought of schizophrenia or bipolar disorder. But actually, if you look closely at their behaviour, which is the basis on which the diagnosis was made. It's most likely to be due to them having to some variety of autistic spectrum disorder combined with an intellectual disability" [P-2]

"I think one of the key things is as we've got to understand conditions such as autism spectrum disorder more… how important the environment and sensory inputs are, and that medication, if people were challenging for this nebulous term of challenging behaviour, which means absolutely nothing…and we're actually looking at something very different."[P-1]

Moreover, prescribers noted that the involvement of different prescribers also influences prescribing practices.

> *"it's a huge area of issue… the involvement of other prescribers or the I suppose the result of having so many prescribers involved in people with intellectual disabilities...because the problem with people for people with intellectual disabilities is that because they tend to have so many kind of disparate medical complaints and attend lots of different clinics, specialist clinics in hospitals for various things, including...the neurologist,.. the endocrinologist,.. the cardiologist, and then the psychiatrist...there's no overarching prescriber. There's no one looking at the overarching tally of medications... the rest of us can advocate a little bit more for ourselves, and be kind of more on the on top of coordination between all different specialists we might be attending. People with Id are not going to be able to do that... the GPs just don't have time to be doing full medication reviews for people"* [P-5]

In summary, there were various factors reported that contribute to challenges to maintain good practice among this population, as illustrated in *Table 4.4-2.*

Table 4.4-2 Factors contribute to challenges in prescribing for older adults with intellectual disability

Factor	Description
Patient-related factors	Presence of brain dysfunction and abnormalities due to the aetiology of intellectual disability
	Comorbidities and frailty
	Difficult to diagnose condition
	Greater sensitivity to medication and related adverse effects, an unexpected side effects
	A higher degree of polypharmacy leads to a cascade of medication prescribing.
	Being on medication for a very long time and some people have been institutionalized since childhood and being on tranquillizer since then.
	Communication barriers in expressing medication side effects and limited understanding of drug interactions and instructions. When patients have limited verbal skills, they rely on caregivers, family members, or staff to communicate adverse effects of medications.
	Shorter life-expectancy

Table 4.4-2 Continued	
Environment-related factors:	Involvement of so many prescribers and lack of overarching prescribers
	A high workload and limited General Practitioners (GP) time often result in an inability to thoroughly review medications prescribed by various specialties.
	Outdated legacy prescribing practices, such as the adjunctive use of anticholinergics with antipsychotics to avoid adverse effects, are no longer considered good practice.
	Limited documentation of patient medication history and diagnosis.
	A lack of specific guidance for prescribing medication to individuals with intellectual disability.
	A lack of consistent staffing, challenges in recruiting staff, and many incoming staff with poor English proficiency present ongoing difficulties.
	High level of staff anxiety in relation to deprescribing and reduction of doses/medications
	Culture in residential setting which results in high psychotropic prescriptions rate as there is access to 'as required' psychotropics, in comparison to those living in community and family.
	Drug availability
	High pressure from carer to prescribe for behaviours that challenge

4.4.4 Prescriber's Definition of Anticholinergic Burden and Tools Used to Quantify it in Practice

Some prescribers describe the term 'anticholinergic burden' as the cumulative or total score of medications that have anticholinergic adverse effects.

> *"..I suppose my understanding would be the total sum of the anticholinergic effect of the medication on the various systems throughout the body… the dry mouth effect, the sedation effect, blurred vision, constipation, cognitive effects, so the overarching effect of the anti-cholinergic effect of that medication..."* [P-5]

> *"My understanding of that is that when people are prescribed multiple drugs with a possible side effect of anticholinergic drugs, they then add up and give you a bigger side effect profile for that drug or those drugs together "* [P-4]

Prescribers were asked if they used any tools to quantify anticholinergic burden, and only two reported using the 'ACB Calculator' in practice. Additionally, two other prescribers mentioned that they conduct audits using the ACB scale in their services, which may lead to the scale being adopted as a standard practice in those settings. The Drug Burden Index was also mentioned by a prescriber [P-10], but this tool is not currently used in practice by that prescriber.

> *"I usually use the.. ACB calculator, and I find that really helpful when working with Staff, because I'll put it into my and I'll hold it up and say, look, red, 5... It starts at yellow, but very quickly to red. Unfortunately, most a lot of the people I deal with, it's quickly to red. So I find that very helpful."* [P-2]

> *" we don't use a scale and part of … the audit that we're doing, maybe we will start using a scale"* [P-1]

4.4.5 Potential Facilitators for Deprescribing and Optimising the Use of Medication with Anticholinergic Activity Among Older Adults with Intellectual Disability

Deprescribing of medications with anticholinergic activity was not always reported as a priority if the benefits outweigh the adverse effects, especially when used in palliative care or when the indication for the anticholinergic is considered valid, as described by some prescribers. In this part of the interview, a document was presented to the prescribers that highlighted findings from *Chapter 3* of this thesis on anticholinergic exposure among older adults with intellectual disability. The document illustrated data on high anticholinergic exposure and indicated the most medications with anticholinergic activity have been reported in use with individuals with intellectual disability in Ireland.

"I try to reduce it as much as possible, but I can't take people off their olanzapine and I can't take somebody of .. other medication that they really need… and this is the problem with polypharmacy in this group of people."[P-6]

" palliative care.. where somebody has a very short life expectancy. They are dying and of an illness, and this medication has suited them. It might be very cruel to change them just because of a theoretical side effect." [P-10]

"the other thing is, if there is a clear benefit from the medication... if somebody is on an anticholinergic medication, but it is treating their urinary incontinence and they would feel that not being incontinent is a greater quality of life than cognitive decline, and they're reluctant to go back to the incontinence phase. Then, again... my focus on cognition may be trumped by their desire to remain continents to those sorts of things " [P-9]

Prescribers were asked about facilitators to deprescribe medications with anticholinergic activity among older adults with intellectual disability, and the results were grouped according to the TDF domains and the related themes as illustrated in *Table 4.4.-3.*

Table 4.4-3 Facilitators to deprescribe and optimise the use of medication with anticholinergic activity among older adults as reported by prescribers in the study (N = 10) using the TDF framework

TDF Domain	Themes	Sample Quotes
Environmental context and resources	**Availability of medical records**	*"people are living in the residential centre. We have their full medical history, we would have their full list of medications. So you can sort of look and figure out what would you do, and what would you not do? And should you do anything?"* [P-4]
	Medication Review	*"… just add regular medication review as its own entity… and to do so with somebody who's familiar with the service user as well. And I had to consider each medication for its current need, within current guidelines... if we observe a physical and cognitive decline... we would always look towards medication as a possible cause within that and do medication review, and we would look towards more recently prescribed medications first, but also in the context of already established medications... then we would consider if… a possibility we'd consider deprescribing or prescribing something in alternative."* [P-7]
		"and then just ensuring that somebody undergoes a regular medication review, either on the 6 monthly or annual basis, so that something isn't prescribed and left on the script for years without anybody ever reviewing it again" [P-9]
	Awareness and education on the anticholinergic burden	*"I suppose having an awareness is the first thing.... an awareness that anticholinergic side effects can be significant and additive basically is absolutely key cause... when you don't know about it, you don't think about it...."* [P-1]
		" the education… It's the key one. if you did nothing else, that'll be the main one." [P-2]

Table 4.4.5-5 Continued

TDF Domain	Themes	Sample Quotes
Environmental context and resources	**Awareness and education on the anticholinergic burden**	*"I'm geriatric medicine trainee, so ... part of our training ... we're informed about anticholinergic burden and the risk of anticholinergic burden … I find that very useful ... So I think having structured education on anticholinergic burden would be helpful across specialties, so that people know that when they're in introducing those medications, that there should be a strong indication, that there should be follow up, and that the risks of medication should be communicated to the person and their carer as well, so this potential side effects are recognized as side effects of that medication, and not of some other process."* [P-9]
	Working within a multidisciplinary team	*"..they are so good they're constantly reviewing the patients and saying, let's give them a chance off medication. Of course, things go pear shape, but if anything, they're always trying to cut and stop medication. I have been blessed ... I'm sure my practice wouldn't be as good if I had been working single handedly without psychiatrists "*[P-6]
		"a full MDT, like clinical psychology, OT, Speech and social work, with psychiatry and clinical specialists to tackle the deprescribing as a team rather than trying to do it just as psychiatrists, without being able to put the behavioural support plans in place without being able to have a social worker to support the staff or to support the family and managing it without having... an SLT to help the communication needs of that person without having a nurse to go out there every week and monitor how that deprescribing is going, and support staff with any questions and all that would make deprescribing a lot easier." [P-5]

Table 4.4.5-5 Continued

TDF Domain	Themes	Sample Quotes
Environmental context and resources	**Working within a multidisciplinary team**	*"...People like me particularly who are working in well-functioning multidisciplinary teams.. I got access to psychologists who are doing really nice behavioural plans...people don't come to me with behaviour alone. They come after all, those things have been tried and failed... we work together" [P-10]*
		"...I work with a consultant geriatrician and a consultant ID psychiatrist who both obviously are well versed in use of these medications. " [P-9]
		"the facilitators of the deprescribing within nursing home... It's really great support... you have skilled staff who will and potentially identify any problems early ... so this is a great facilitator of that... and ...we have an evidence-based medicine system here...and everybody's on board with evidence-based medicine, so I think they're maybe great facilitators."... "our population group is, I would guess of an average age of maybe 75...we also have to be wary of a cognitive decline or cognitive decline dementia, so we also have the benefit of a dementia specialist Support Service and we utilize them too"... [P-7]

Table 4.4.5-5 Continued

TDF Domain	Themes	Sample Quotes
Environmental context and resources	**Tools and guidelines to identify and deprescribe anticholinergic medication**	*" I think the DBI is useful because... it includes the management of the dose which the other scales don't… So I think that would be really useful, because… there's a lot of people who'd be on like tiny little Quetiapine 25, and it's not going to have the same anticholinergic burden as someone who's on Quetiapine 300."* [P-5]
		"Since I've learnt this tool (ACB online calculator), I find that very helpful, whereas before … I've realized that I wasn't including certain medications that I now do, because I use this tool... the calculator is the easiest thing. I have it on my, on your phone. It's everywhere you go. So you don't even have to depend on having computer." [P-2]
		"maybe not specific to Anticholinergics. But there is an Irish College of General Practitioners (ICGP) deprescribing tool which I've used " [P-3] ... Stoppfrail Deprescribing tool.
Knowledge and Skills	**Knowledge and application of appropriate prescribing**	*"I try to avoid Anticholinergic activity because I work with people with dementia and down syndrome. So I would be trying my very best to avoid medication for that reason, but also say, I've got somebody on an antipsychotic. I would never, ever use an anticholinergic medication as a side effect tablet. I would try to reduce my antipsychotic down, if at all possible."* [P-10]

Table 4.4.5-5 Continued

TDF Domain	Themes	Sample Quotes
Knowledge and Skills	**Knowledge and application of appropriate prescribing**	*"The older kind of … atypical antipsychotics, such as chlorpromazine, haloperidol, are almost not used within the service. I mean, we have a small number of people who are on them for 30, 40 years that we haven't taken all for have been unable to completely deprescribed. So we do have people on some of the on atypical antipsychotics also, but that's quite small…. I'm very conscious that next month the month that also I'm dropping some, if I prescribe antipsychotic, I'm dropping some seizure threshold. So… they're increased risk of having a seizure, so their seizure threshold is dropping every day with their dementia, and I give them an antipsychotic, I'm dropping it further… and it's not anticholinergic thing but it's actually it does affect prescribing habits very much in dementia. "* [P-1]
		"In terms,... of selection of stuff…I would be very conscious about trying not to select medications with the greater anticholinergic burden because I have kind of in my mind always, or particularly for people with down syndrome, the higher risk of dementia in people with down syndrome. So I'm kind of always thinking around, if this person is getting into their fifties with down syndrome, then you really don't want to add to their anticholinergic burden, but across the board for people with ID because there's such a degree of polypharmacy you don't want to be adding to their anticholinergic burden… I do absolutely consider it and try to minimize it…, probably using like if it was an antipsychotic using Risperidone rather than using Quetiapine or Olanzapine as a first line. And then, if it's antidepressant…, we don't tend to prescribe those like tricyclics. Or Paroxetine, I would tend to go for Sertraline as first line antidepressant." [P-5]

Table 4.4.5-5 Continued

TDF Domain	Themes	Sample Quotes
Knowledge and Skills	**Knowledge and application of appropriate prescribing**	*"if we start a medication like that, we would see somebody back between 1 and 3 months to assess the response to it. So if we see that there's a clinical benefit from it, and those behaviours are managed, we'll continue it. If we see that the behaviours are persisting, we may increase the dose. If we see that there's been any side effect, we would stop it and potentially try an alternative medication in that instance. "* [P-9]
		"I have a cohort of people who are on multiple medications, many of them have comorbid mental health problems. They could be on atypical antipsychotics, and they may be on antiepileptic, on rescue medication...therefore, anything I introduce I need to be very careful. I'm trying to go for a clean drug …. if we prescribe a drug, we would review it and working in a situation where we'd have a lot of nurses and care staff who would advocate. It would be very quick to point out the side effects. So if we put somebody on a medication and is not suiting them, you will know fairly quickly, and then we, on introducing a medication something like Baclofen or Tizanidine you're checking their LFTs, anyway, very regularly. Baclofen before every increase., I'd be reviewing them and my practice with people in this cohort I would always prescribe low and slow, so I prescribe a very small dose, and then review them sort of every 2 weeks or every 4 weeks," [P-6]

Table 4.4.5-5 Continued

TDF Domain	Themes	Sample Quotes
Knowledge and Skills	**Knowledge and application of appropriate prescribing**	*"There are certain times of year I won't reduce medication. So, coming into Christmas, certain times of the summer. Because of staff. It's more likely to be staff changes at Christmas. That can be quite difficult for a lot of the people I deal with because of their history of family trauma and things. But otherwise, I would go for it."… ".. a few weeks ago I was reviewing somebody but they were having increased seizures, and I had been reducing their antipsychotic medication. But there was a chance that the neurologist was going to change the antiepileptic. So I think it's very important that we only change one medication at a time, because otherwise we don't know. So I put off the reduction in the medication to see if ..the neurologist did change the medication. So I said, I'll wait… that was a delay rather than a decision not to do it anymore..." " doing things slowly... unless there's an emergency, unless there's a long QRS on the ECG, or someone is very slowed down or ataxic, or having lots of problems of constipation to do it slowly. even to the extent of changing people from one formulation of medication to another, so I can take them down in smaller decrements. So moving them from a tablet to a liquid form for instance"* [P-2]
	Appropriate deprescribing skills	*" I'm fortunate that I'm in a job where I am able to offer short interval follow up to give the reassurance that these changes aren't going to be made without appropriate follow up."* [P-9]

Table 4.4.5-5 Continued

TDF Domain	Themes	Sample Quotes
Knowledge and Skills	**Appropriate deprescribing skills**	*"I would have a discussion with the person and their carer around the medication. We have very much a preventative focus. So not only are we trying to treat dementia, but we're also trying to prevent cognitive decline, so we would discuss the potential benefit of removing medications which may in time, as the person gets older and they become more vulnerable, impact cognition. So I would generally discuss the potential of trying to ween or cessation of one of these medications, and if the person is agreeable to, then proceed with that with appropriate kind of interval follow up to see how they're managing with those change… the other thing is, if there is a clear benefit from the medication... So, if somebody is on an anti-cholinergic medication, but it is treating their urinary incontinence and they would feel that not being incontinent is a greater quality of life than cognitive decline, and they're reluctant to go back to the incontinence phase. Then, again... my focus on cognition may be trumped by their desire to remain continents to those sorts of things "* [P-9]
Social Influences	**Involving carer/family in the decision of anticholinergic deprescribing**	*"I have many people who have Parkinsonian side effects from the medication but would hate to come off them because of the psychic trauma they would have. So what I would do is I would talk to the person. I would explain their side effects to them. and I would sort of say, Well, you know, like, if I do this, X will happen. If I do this, y will happen. Which of the 2 would you prefer? I think it's a trade-off in medication by explaining it and having people in partnership with you."* [P-10]
		"the main facilitator is engaging the carers and getting their support... and the education… It's the key one. if you did nothing else, that'll be the main one." [P-2]

Table 4.4.5-5 Continued

TDF Domain	Themes	Sample Quotes
Social Influences	**Involving carer/family in the decision of anticholinergic deprescribing**	*" I think it's a good idea to reduce it (anticholinergic exposure) .... you're supporting people that have kind of brain dysfunction. Essentially, and that can be ... due to kind of a neurological disorder... trauma... too many different reasons. So ... the less centrally acting medication in general... part of them anticholinergic effects. I'm looking at other things as well, but it's a but certainly sort of reducing sedation, reducing the risk of... constipation, blurred vision, falls... is very positive for somebody who's already maybe has limited mobility, limited cognitive reserve.... have cataracts ... people with down syndrome get cataract, so you don't want to make their eyesight worse. And get in peace for falls for anybody of advancing years, particularly for people with intellectual disability can be quite devastating because the rehabilitation is so much more difficult if they have a broken hip, facture hip. By decreasing your anticholinergic burden you're hopefully reducing all those things all those negative experiences of the person can have, and that they have a better quality of life and a better kind of kind of physical health as well…. we're focused so much on deprescribing because we're trying to ensure that people's medications are rationalized, and if things could be stopped that they're stopped"* [P-1]
		"the main facilitator is engaging the carers and getting their support... and the education… It's the key one. if you did nothing else, that'll be the main one." [P-2]
Beliefs about consequences	**Beliefs of non-pharmacological treatment**	*"Do this group of people need as much medications to manage their symptoms? .. Could we change their diet very drastically. Should we making them exercise more? "*[P-4]

Table 4.4.5-5 Continued

TDF Domain	Themes	Sample Quotes
Beliefs about consequences	**Beliefs about consequences and impact of anticholinergic deprescribing**	*"I think the primary one, is quality of life in general. .. if we're talking about things like constipation and cognition, and possibly urinary retention … in people who are probably more prone to these anyway. But then there is definitely a positive cognitive issue and over the last few years, where I've been working more on a team. It's been very reassuring to see that people are reporting back that people have reduced their medications are engaging much more with peers and with staff and in activities. So it doesn't always work, obviously, but for but they're the major quality of life and medical health and cognitive health."* [P-2]
		"…you'd have the benefits of knowing that you're not adding to the cognitive effects of where they already have a high propensity to have cognitive impairment as they age, particularly in those with down syndrome. At least you're removing one variable from their already high propensity to cognitive decline in older age, but also you would be reducing ... their overall propensity to things like constipation, falls, sedation, all of that which can only be beneficial for their overall physical health… you're just in general going to reduce the level of polypharmacy across the board." [P-5]
		"Well, I think they're particularly vulnerable group, and I think anything that can reduce the serious side effects of anticholinergics is a good thing. To minimize harm, patient discomfort, falls, the typical anticholinergic effects, blurred vision, dry mouth, constipation, drowsiness, urinary retention and even skin flushing…" [P-3]

Table 4.4.5-5 Continued

TDF Domain	Themes	Sample Quotes
Beliefs about consequences	**Beliefs about consequences and impact of anticholinergic deprescribing**	*"...but very often it's a case of looking at other solutions, so ... can they be brought out for walk in the morning ... So they sleep properly. Don't ask for sleeping tablet but take them for a walk....in special of dementia, of somebody is having experience where they're very distressed in the evening. Then you look at other kind of non-pharmacological responses, such as having the correct lights on ... having the person orientated.... kind of not having anything too busy around.... There's a whole kind of wrap around support the person needs, and it's not a tablet, and my fear is that in cases where there isn't that understanding, it's very easy to reach and give somebody medication. "* [P-1]
		"you're going to reduce falls... to improve quality of life... to prevent confusion, have an overall benefit…improve constipation … gastric motility. The amount of people that are on laxatives… you're really gonna benefit everybody by reducing it. And you're going to have greater clarity of brain.... I probably still try to reduce as much as the person was able to tolerate. I don't think having a high anticholinergic burden is good for your body and I believe in a very wellness orientated…I'm always ..trying to make people as well as they can be physically and mentally. So I've been trying to make them as well as I could without jeopardize them..." [P-10]

4.4.6 Recommendations for Tools/Guidelines that Would Help for Optimising the Use of Medication with Anticholinergic Activity

Participants described what tools would help them in practice to identify medications with anticholinergic activity, and scores or alternatives which would assist their deprescribing decision and process. Their recommendations are described below.

> *" I think what's really helpful if you have a list, these are the anti-cholinergic burden, and these are the alternatives .. a simple tool would be very handy "* [P-6]

> *"short summaries and short guidance... 1 page, 2 page where I can get straight to the heart of.., and something that can improve my practice and is really enjoyable cause most of us.. love the job that we do, and love caring for people within intellectual disability, and want to do it to the best of our ability. And so anything that contributes that is very welcome."* [P-7]

> *"I think maybe looking at.. the higher frequency medications with the highest level of ACB... making people aware that they should be aware when they start prescribing these drugs…So just as we'll classifying the top 10 or 15…I think that might be useful from guidelines point."* [P-4]

> *"So certainly having a tool that can be used, is very useful, having a list of potential side effects or things to look out for, can be very useful, and having that kind of almost on one sheet that can be easily dispersed could be helpful"* [P-1]

4.4.7 Potential Barriers to Deprescribe and Optimise the Use of Medications with Anticholinergic Activity Among Older Adults with Intellectual Disability

Participants were asked about barriers to deprescribing anticholinergic exposure to reduce inappropriate high anticholinergic burden among older adults with intellectual disability, and *Table 4.4-4* groups under TDF domains and related themes the barriers described by the participants.

Table 4.4-4 Barriers to deprescribe and optimise the use of medications with anticholinergic activity among older adults with Intellectual disability

TDF Domain	Themes	Sample Quotes
Environmental context and resources	**Involvement of other prescribers**	*"..I can be responsible for prescribing habits of my end but I don't control what the GP Prescribes... GPs can vary in their experience of working in intellectual disability services. They can vary in their understanding of the kind of some sort of effects of medications."* [P-1]
		"..it's everyone's responsibility as a prescriber to be looking at the overall picture. But the problem is not the like the responsibility. The problem is being able to make changes when other prescribers are involved, and when we don't have… network of communication with other prescribers and other specialists, that's the issue…" [P-5]
		"... people having multiple physicians and attending multiple clinics, and on the difficulty of modifying other people's prescription… *what I feel would be beyond my responsibility, would be dealing with other people's prescriptions. That's the problem that a lot of people go to ID psychiatry, and they're on all these medications. And often we don't feel comfortable stopping them, because we're not always aware of the indications that they were started for, or it's difficult to manage medications when there's multiple prescribers..."* [P-8]
		"however my barrier... in the care setting where I work ... if the area that I identify is within a psychiatric medications, I won't deprescribed because I'm not the responsible prescriber for that. But I think today have good working relationship with my colleagues there, that I could highlight my concerns within that area." [P-7]

Table 4.4-4 Continued

TDF Domain	Themes	Sample Quotes
Environmental context and resources	**Involvement of other prescribers**	*"there's all those other people out there prescribing, so I can make suggestions but I can't tell them what to do…then there's the other issue, too, of resistance to rationalization of medication"* [P-2]
		"what is beyond me is convincing the other doctors… to take away their medication...it's not that I'm saying that mine is the most important, but it can be quite difficult to do that … the other thing, if you take away one set of drugs, then people will move to another. So, for example, we took away the Benzodiazepines from the GPS, and they moved to the atypical antipsychotics. Now. if I had anxiety in the general population. I would much prefer to be on benzodiazepines for a very short period of time, than to be put on an antipsychotic for a short period of time, but sometimes the changes you can make might have deleterious side effects that you might not realize. So I think it's just proceeding very slowly, very carefully." [P-10]
	Lack of awareness	*"a lot of the people I see come with a mythology, I would call it, of how dangerous they were in the past before the medication. so often the staff who are working with the person don't never saw them like that. But there is that myth there that this person was really dangerous before they went on all this medication, so I need to work with them... It's about psychopharmacological education for staff and carers is the first step."* [P-2]

Table 4.4-4 Continued

TDF Domain	Themes	Sample Quotes
Environmental context and resources	**Lack of awareness**	*"is the lack of awareness that people have around the issues and I find certainly, when I'm doing clinics ... that a chunk of my work is educating.... like .. around sort of hypnotic use and that there's ways of getting around hypnotics and sleep hygiene and doing all these things. Likewise for when it comes to deprescribing, people just think you're just doing it for fun ... so there's that education piece about explaining.. actually this person is now older, they're now getting more and more physical comorbidities. So as their mental health issues have stabilized for the last 20 years, their physical needs are increasing. So we're kind of I can't keep the mental health meds there, but their physical meds are catching up in the background. Can we ..., bring this down as this is going up? and hopefully their medication for the medical stuff would be work really well, and they won't have this adverse effect of all these kind of centrally acting medications that may be of absolutely no use to them at this stage of questionable use to them. So there is an education piece."* [P-1]
	Lack of Medical Records	*"... what other medications these people are on ... usually you ask for that, but you might not get the information.... it's very hard to know what other medication they're on... some people, you do know, you know their medical history. But you might not know their medications, they might change or may not be on them. They might see a neurologist who also adds another medication that you have no idea that they've done. So that's the problem with prescribing with people who are not within our residential service. Because you don't have all the medication list"* [P-4]

Table 4.4-4 Continued

TDF Domain	Themes	Sample Quotes
Environmental context and resources	**Lack of Medical Records**	*" So you may have a real gap in institutional knowledge there. As... this person.. maybe 30 years ago, when they first were prescribed this medication, and would have needed it at that time for whatever, however, they were presenting but would be very different in their presentation now 30 years later. But that knowledge isn't there... particularly if there's not family members to give that history."* [P-5]
		"part of my role is to review the medications and deprescribed where possible but because of the types of some of the medications that are coming through, like for those people that have been on antipsychotic .. for 6 or 7 years, and I don't know who started it, or... why it was started… and I don't know when those changes were made in those cases. I am more reluctant to adjust them….if I have somebody who's got what appears to be a stable mood, who's on multiple antipsychotics and no one can tell me .. the time the medication was started? Where they have a good clinical response to this medication? I don't know if I'm interrupting a medication regime that is introduced stability or if I'm gonna be causing problems by deprescribing a medication where the indication for its introduction isn't clear." [P-9]
		"we don't have a full, comprehensive, like history of these patients, and it's very difficult to know why they're ever on these medications in the first place, and that makes very difficult to stop them, particularly if they're kind of half being seen by a flag service somewhere, There was a big reluctance to tamper with their medications." [P-8]

Table 4.4-4 Continued

TDF Domain	Themes	Sample Quotes
Environmental context and resources	**Lack of integrated health system between the different specialities involved in providing care for older adults with intellectual disability**	*" if we were working in a more integrated system, where maybe if you're working in a general hospital, you'd have an integrated system where you would have an overarching pharmacist looking at the all the medications, and you would be able to liaise more effectively between specialties. Then I think it would be a lot easier… to coordinate and ask questions about whether or not this medication can be reduced.... we're working in a silo here... It's a question of being able to communicate effectively between specialties to make... because you can't make changes to other people's specialist medication where they're needed for neurological indications where they're needed for gastrointestinal, or… prostatic."* [P-5]
		" in prescribing between primarily psychiatry and non-psychiatry could be a barrier, and within this too, but that's true within all spaces within Ireland is.. there will be a division within prescribers... so the barrier might be where you mightn't have regular communication with the other team members responsible for their care..." [P-7]
		"we have some people that live at home and they have their own GP. So .. you have to go back to the GP and say, Can you please? may we do blood tests or ECG before I put them on an anti-psychotic or an SSRIs?" [P-4]

Table 4.4-4 Continued

TDF Domain	Themes	Sample Quotes
Environmental context and resources	**Lack of integrated health system between the different specialities involved in providing care for older adults with intellectual disability**	*" the barrier for it would be to have… more integrated clinical teams even within our service. The provision of the services is split between a mental health service and a disability service and I think that's across the country, that the disability services are separate even though they're in the same organization, they're separate to the mental health services. So... if you're trying to deprescribe for someone with an ID, You're .. working in a silo, and that is a huge barrier to trying to deprescribe. So even though you might be trying to involve the clinical psychologist in in supporting a behavioural support plan... to go alongside your deprescribing of an antipsychotic medication, for example. It can be really difficult to coordinate that and... that's a huge barrier to deprescribing. I think in other countries they have different setups… where things are much more cohesive and ...if you think about the patient as the centre of the system, We don't generally have it set up so that the patient gets kind of the services that they need... from a centralised position... "* [P-5]
		" in prescribing between primarily psychiatry and non-psychiatry could be a barrier, and within this too, but that's true within all spaces within Ireland is.. there will be a division within prescribers... so the barrier might be where you mightn't have regular communication with the other team members responsible for their care..." [P-7]
		"we have some people that live at home and they have their own GP. So... you have to go back to the GP and say, Can you please? may we do blood tests or ECG before I put them on an anti-psychotic or an SSRIs?" [P-4]

Table 4.4-4 Continued

TDF Domain	Themes	Sample Quotes
Environmental context and resources	**Lack or limited access to medical tests, other facilities and health services**	*"people in this age group, on these medications should be having regular ECGs and other tests. But as regards the anticholinergic, the ECG is important, it's often hard to get an ECG, because maybe the person won't cooperate, maybe there isn't a facility to get ECGs. Most of the places I go to work, people haven't been having ECGs and I'm trying to get them to have them now. So anyone without an Id, who's in the age group.., should be having ECGs if they're on these medications anyway. So definitely, people with intellectual disabilities should be. But it can be harder to get them."* [P-2]
		"we don't have access to ECGs within the service, and it's difficult...waiting lists for ECGs in general hospitals. So that's been a particular barrier… if you're starting someone on a psychotic medication particularly, you want to do a measurement of their QT interval prior, just as a baseline, because we know that people with ID can have .. a higher propensity to cardiac deficits…, and sometimes it delays prescribing and sometimes it means you can't because you don't feel comfortable going ahead and prescribing."… "I think … there's a push towards... really slowing down the decrements to psychotropic reductions in general. And this push to tapering strips... and those kinds of interventions... we're … looking at even for Risperidone if you go from 0.5 to maybe point 0.25 at a push and then to 0.05 and so, if we did have such kind of tapering strip approach I think that would probably go a lot better." [P-5]
		" Obviously we'd use a little bit of clonazepam in epilepsy, and I know it has an anticholinergic burden… we had to use it a lot lately as a substitution for other medication because they weren't available and we had to use unfortunately clonazepam which I hate because it's so sedating " [P-6]

Table 4.4-4 Continued

TDF Domain	Themes	Sample Quotes
Environmental context and resources	**Lack or limited access to medical tests, other facilities and health services**	*"one of the barriers to me recently... would have a high anticholinergic burden, and we'd all know that it's clozapine… It might be a brilliant drug for the schizophrenia, but I can't get them on... we can't get people admitted into hospital. So if they become very unwell. they stay in their residential house, which isn't fair for the other residents in the house. So if I became schizophrenic tomorrow... I'd be in St. Patrick's or St. John's. That's very good. I might want to be there... if that happened to one of my clients, they would not be able to go in. They are discriminated in terms of their mental health... they don't get it .. and what's worse, is the other clients and the other family have to live with them at that period of time. "… "...there are places in the country where you don't have an ID psychiatrist. You don't have an MHIT team. Your access to them is really quite difficult, and some of the prescribing has not been done by a psychiatrist..."* [P-10]
	Limited financial support	*"the other barrier, is problems we have now with getting money for appropriate environments, appropriate activities, appropriate staffing "* [P-2]
Knowledge	**Pharmacological response due to the long-term occupation of receptors**	*"there are medications that just the big barrier to stopping them is the tolerance of even really small incremental reductions, you can get down to a point, and then you get to a stage where you're actually just exposing too many receptors. I think I have to assume that's what's happening, because you're just seeing somebody who's coming back and they're kind of … irritable… anxious, and it's very much of a withdrawal picture that you're seeing. So that is a barrier to fully deprescribing things."* [P-1]

Table 4.4-4 Continued

TDF Domain	Themes	Sample Quotes
Knowledge	**Pharmacological response due to the long-term occupation of receptors**	*"... with the benzos in particular, it's just that kind of up regulation of receptors and your fighting nature...someone is addicted to medication and you're taking them off medication that had been addicted to for 20,30, 40 years and that is a big barrier."* [P-1]
		"if you're thinking particularly about reducing or stopping anti-psychotic medication, it has to be done really, really, gradually and we have quite a lot of experience here with deprescribing particularly for people .. with challenging behaviour who may be on antipsychotics for a long time. But the problem with that is that you have dopamine receptors that have been occupied for could be 20, 30 years and you're trying then to slowly reduce, and in my experience you can reduce to a point and usually successfully, if it's done slowly enough and ... with the support of the rest of the clinical team in supporting the staff through it as well. But generally, I find that the at the very end, where you're trying to reduce fully and stop is where you really run into difficulties, and I think that seems to be due to the I suppose the long occupancy of those dopamine receptors for so many years. At the very last... few reductions to medication, you do tend to start to see deteriorations in mental state and challenging behaviour." [P-5]
Social Influences	**Workload and relationship with the prescribers**	*".. for me as a GP, my time is always my most limited commodity, and that's true of everybody in healthcare is true to say."* [P-7]

Table 4.4-4 Continued

TDF Domain	Themes	Sample Quotes
Social Influences	**Workload and relationship with the prescribers**	*"the other barrier is the if that medication was started by a GP or another physician with whom the person has a trusted relationship, me coming in as an external person on one review and suggesting a change, can be challenging as well, because there needs to be that level of trust" [P-9]*
		"I suppose barriers would …. Sometimes a workload " [P-3]
	Staff, carer or family resistance	*"it's often hard to get people off them because Staff are afraid that people will be worse if you stop them… the first thing is getting the confidence of the carers because if you don't have that, it's going to be very hard to reduce the medication, because... something will always happen when you reduce medication, because it was going to happen anyway. But if you've reduced the medication, they'll say it's because of you... I presume you're dealing with a population most of whom need care and support and so that... my main target audience for decreasing the medication isn't the individual. It's the carers"* [P-2]
		"..Lot of the staff don't want them to come off.." [P-4]
		"... I suppose another barrier is that sometimes Staff feel that their lives are easier, if people are on these medications and they might be a little bit more sleepy during the day, but that helps staff... So sometimes there's a reluctance from some carers to deprescribe." [P-8]
		"I suppose barriers would be the patient themselves, their carer, family…" [P-3]

Table 4.4-4 Continued

TDF Domain	Themes	Sample Quotes
Social Influences	**Staff, carer or family resistance**	*"I've encountered patient or carer reluctance to change their medications. Especially if somebody feels well and they're on a range of medications. Sometimes any sort of change can be seen as potentially risky. I will always say that I only can offer guidance and advice, so whether or not that advice is accepted. It's not up for me to enforce a change like that. "* [P-9]
		"Sometimes the barrier is staff and not because .. of any badness, they just don't want to see the client as they see suffering from side effects. Families can be very resistant to change... " [P-10]
		"The barriers ...it's very much more often the people that are supporting them... their family, or it's their carer. ".. " resistance from the individual themselves or from their family and in that case you kind of do maybe give some education and come back again in a couple of months and discuss again and so just takes longer" [P-1]

4.4.8 Prescribing practice and deprescribing experience of specific medications with anticholinergic activity

This section covered participants' practices regarding the prescribing of certain medications with anticholinergic activity and their experiences with deprescribing specific anticholinergic drugs. The medications discussed were classified into therapeutic classes and statements were divided into experiences related to prescribing and deprescribing among older adults with intellectual disability, as described by the prescribers. The results are illustrated in *Table 4.4-5*.

Table 4.4-5 Prescribing practice and deprescribing experience of specific medications with anticholinergic activity (N = 10)

Medication Class	Prescribing practice	Experience of deprescribing
Antipsychotics	*"Olanzapine .. would be widely used.. Quetiapine occasionally. Risperidone .. would be quite frequently used in terms of antipsychotics … The older kind of .. atypical antipsychotics such as chlorpromazine, haloperidol, are almost not used within the service… we have a small number of people who are on them for 30, 40 years that we haven't taken all for have been unable to completely deprescribed. So we do have people on some of the atypical antipsychotics, but that's quite small…. I'm very conscious that next month .. if I prescribe antipsychotic, I'm dropping some seizure threshold. So .. they're increased risk of having a seizure, so their seizure threshold is dropping every day with their dementia, and I give them an antipsychotic, I'm dropping it further.. and it's not anticholinergic thing but it's actually it does affect prescribing habits very much in dementia"* [P-1]	*" if I have somebody who's got what appears to be a stable mood, who's on multiple antipsychotics and no one can tell me .. the time the medication was started? Where they have a good clinical response to this medication? I don't know if I'm interrupting a medication regime that is introduced stability or if I'm gonna be causing problems by deprescribing a medication where the indication for its introduction isn't clear."* [P-9]
	"antipsychotic is probably going to be the biggest burden.. for anticholinergic burden, so risperidone, olanzapine, quetiapine and those kind of drugs… they do have a benefit. But .. sometimes the overriding side effect, which is the weight gain and the type 2 diabetes and all that on a population that really doesn't move as much, probably doesn't have the most healthiest lifestyle, but also can't physically be as active, and they don't sometimes choose their own meals... people are preparing all of this for them. So they're very complicated." [P-4]	*" Olanzapine can be really sticky, really hard to get people off "* [P-1]

Table 4.4-5 Continued

Medication Class	Prescribing practice	Experience of deprescribing
Antipsychotics	*".. Quetiapine would be up there as one of the main antipsychotics with the high anticholinergic burden. Olanzapine would be probably the next to that, and then .. Risperidone .. would be .. the next, and Risperidone is probably the most commonly prescribed antipsychotic, but obviously not the highest anticholinergic burden, although it's still there."* [P-5]	*" if you take away one set of drugs, then people will move to another. So, for example, we took away the Benzodiazepines from the GPS, and they moved to the atypical antipsychotics."* [P-10]
	"most commonly would be some antipsychotics which we would use for behavioural or reactive behaviours in dementia. So Quetiapine, risperidone and trazodone would probably be the main three that we would use." [P-9]	
	"I would only be treating if I felt there was a reasonable indication. So if I saw somebody with a psychosis.. I am not in general going to be treating somebody who comes in with a behaviour with a medication. I'm going to be treating somebody who's got autism and irritability with an evidence. There is an evidence base for drugs like Aripiprazole and Risperidone in that, and that's where I might treat somebody for it…I would be avoiding the chlorpromazine " [P-10]	
Anticholinergic	*"I don't commonly prescribe Biperiden for people with intellectual disabilities…. Because I think if you're at the point where you're inducing Parkinsonism and people because of their antipsychotic use, then you've gone past the point of therapeutic kind of value for the antipsychotic you're prescribing, so I don't generally prescribe it…because of its obvious Anticholinergic effects."* [P-5]	*"I had an episode recently where someone was on an anticholinergic and I could see no reason for it, and I stopped it and they deteriorated hugely, which I couldn't work out. But then one of my colleagues told me they'd seen a withdrawal reaction to I think, was procyclidine, and I had to put them back on it."* [P-2]

Table 4.4-5 Continue

Medication Class	Prescribing practice	Experience of deprescribing
Anticholinergic	*"We have very few people attending this service on actual anticholinergic medication, because like, when I was training initially, once somebody went on to an antipsychotic...they automatically almost went on to sort of like some kind of some anticholinergic medication to kind of to protect against side effects. So that's kind of like we have some a very small number of people that, for historical reasons, are still on anticholinergic to counter the side effects of their antipsychotic. But again, it would be very, very, very small numbers at this stage. And it's practicing that we're just over time. We're trying to deprescribe and move away from that."* [P-1]	
	"..if I've got somebody on an antipsychotic, I would never ever use an anticholinergic medication as a side effect tablet. I would try to reduce my antipsychotic down, if at all possible… I would obviously .. be avoiding the chlorpromazine… people using risperidone... very commonly used drug, but probably would be under the impression that it had little or no, and that's why they were using it. We'd know that... olanzapine and chlorpromazine .. are high... I'd be surprised at risperidone having the 1." [P-10]	
Antidepressants	*"antidepressants, they would be mostly be kind of SSRIs, So we would look at kind of the main ones we would use would be sort of Citalopram, Escitalopram, fluoxetine, think that would be the main to the main medications that we would use."* [P-1]	*"I had a patient who .. was postherpetic neuralgia and she was on historically amitriptyline, a very tiny dose…an awful drug, but we finally got her off it."*[P-6]

Table 4.4-5 Continued

Medication Class	Prescribing practice	Experience of deprescribing
Antidepressants	*"Tricyclic antidepressants wouldn't generally be prescribed frequently in our service, so it would be the SSRIs which do obviously have their anticholinergic burden less, so it would be so Citalopram and Escitalopram, and Sertraline would be the main… we don't tend to prescribe paroxetine."* [P-5]	*"... some of the SSRIs are very difficult to come off (paroxetine), not because of the anticholinergic, it's the way the chemical works in the brain, and people may have a sort of a rebound effect when they come off... it can cause other effects when you come off.... That doesn't stop me but that can make it very difficult for carers and family members because they think all this person is now having a depressive habit of anxiety when actually it's though withdrawal effect of medication."* [P-4]
	"I prescribe probably sertraline, Cipramil (Citalopram) things like that...Mirtazapine.." [P-4]	"Paroxetine, one of the SSRIs, can be really hard to get people off." [P-1]
	" There are times in which people have to use tricyclics because you've got very resistant depression. But, to be honest, I wouldn't be using them in my population. I've tried to give you things as clean as possible." [P-10]	
	" I suppose, SSRIs, like escitalopram. We would try and stay away from prescribing the risperidone and the olanzapine, but, like I said, we inherit patients on these medications all the time." [P-8]	
Anti-epileptics	*" I inherited a lot of people on carbamazepine...I absolutely hate carbamazepine.. It interacts with everything I know...there is no reason why carbamazepine should be prescribed so much in an ID population, so that's a legacy history thing. I do have people with that I'm trying desperately to get off. But they are probably still a lot of people on that drug."* [P-4]	

Table 4.4-5 Continued

Medication Class	Prescribing practice	Experience of deprescribing
Anti-epileptics	"we certainly historically would have used kind of carbamazepine. You would have used and Epilim .. sodium valproate. The lamotrigine would be sort of the main medications that we would use. But certainly in more recent years. What's happening is that there are sort of more and more ones coming into the market and say, for example, one of the main ones like Levetiracetam, Keppra, is a medication that we would use kind of quite a bit now. But, I don't think that has any major anti-cholinergic effects, as far as I know. but so that would be anti-epileptics so like within psychiatry like they'd be the main ones we use now we would." [P-1]	
	"it's also quite surprising what's high, so carbamazepine, for instance, people think of as a harmless medication probably and yet people with ID get thrown on it for all sorts of reasons. As I said, that the person I'm talking about would put everyone on it for challenging behaviour." [P-2]	
	"We would tend to prescribe quite a bit of sodium valproate for the management of bipolar disorder so that's the main anti-epileptic medication I would prescribe. I don't prescribe carbamazepine for people. So the carbamazepine that you probably had there is prescribed as antiepileptic. It would be very rare that we would prescribe it for.. mood stabilizing effects. we don't prescribe here the rest of the anti-epileptic medications other than the Lamotrigine and I'm not sure the anti-cholinergic effects of Lamotrigine, but I don't think they're significant. " [P-5]	

Table 4.4-5 Continued

Medication Class	Prescribing practice	Experience of deprescribing
Benzodiazepines	*"if you have someone who's very agitated, disturbed, and at risk of falls and won't interact, they probably do need some medication. But at the same time we know the medication may make things worse, and especially some of the traditional medications used, the benzodiazepines which are going to increase impulsivity, decrease cognitive functioning and effect bell functioning, which will also affect cognitive functioning and ability."* [P-2]	*"with benzodiazepines ... I have a lot of experiences of deprescribing those, and you can go from 15 milligrams of days upon a day down to 4 a day, and next thing , you can't go any further, because the person really starts decompensating. But at least you've gone from 15 down to 4. That's good….I'm much more anxious.. if somebody ... coming off diazepam. They're going down every couple of months and milligram and milligram, and they get down to the low doses. And then I'm kind of going, okay I'm gonna get a phone call next week.. next month about this, probably saying the person isn't doing so well, but we'll give it a try, and I don't know whether it's a 5 milligrams or 4 milligrams or 3 milligrams .. they're going to experience that. So there's always a certain anxiety around that absolutely... with the benzos in particular, it's just that kind of up regulation of receptors and your fighting nature...someone is addicted to medication and you're taking them off medication that had been addicted to for 20,30, 40 years and that is a big barrier "* [P-1]
	"Then I suppose the benzodiazepines would be the next widely prescribed and they have obviously their anticholinergic effects. Alprazolam would probably be the one I prescribed most." [P-5]	*"the biggest challenge of my life is actually the benzodiazepines, to try and take, when so people perceive them with their lovely, short acting effect as to be the thing that's keeping the person well. It can be...the biggest challenge in my life, it's not the antipsychotics, it's not the antidepressants, it is for sure, it has been the benzodiazepines. They are a nightmare… they are so …*

Table 4.4-5 Continued

Medication Class	Prescribing practice	Experience of deprescribing
Benzodiazepines	*"I would never use .. benztropine or anything like that ... particularly because of the side effect profile of them. "* [P-10]	*difficult to remove from a Kardex that is my biggest issue, not even the client stuff."* [P-10]
	"We have some people on them historically, but.. we would kind of try not to prescribe it. Things like alprazolam, or diazepam.... and we haven't been able to deprescribe them, and that can have a slight additive effect." [P-1]	
Antihistamines	*"Now I feel very pressurized to prescribe antihistamines over the years because people would be saying, Oh, people have hay fever, they're coughing,.. I tend to go for non-sedating either loratadine or occasionally cetirizine. but I hate prescribing it and I also think one of the reasons I'm asked to prescribe it, is because it makes people sleepy…I tried to avoid.. these cough bottles which .. sedating antihistamine in them... Hate those and they're loved by some of the staff" "* [P-6]	*"one lady was on a massive dose of.. Chlorpheniramine. But She had still had.. dreadful dermatitis. This was pushed on by the hospital but .. I successfully got her off that. I have her on .. Telfast (fexofenadine, ACB =1)..regular Telfast, and that is actually improved things much better."* [P-6]
	" .. then you've got the antihistamines as well, which I would not be prescribing. But people might be on them for various reasons and nowadays most people are trying to avoid the more sedating ones which are usually the ones with the anti-cholinergic properties, and trying to be applicable on lower ones. But unfortunately, people will be on at this time of the year… but it's not as much as it used to be." [P-10]	*" a lot of people are on antihistamines, 12 months a year when maybe they only need them in the summer or PRN. And I've managed to work with the GPs.. to stop those regular medications."* [P-2]

Table 4.4-5 Continued

Medication Class	Prescribing practice	Experience of deprescribing
Muscle Relaxants	*"I would have some people on Baclofen because they have a spastic cerebral palsy, and they need it... it has a low.. anticholinergic burden…I would have 1 or 2 people to Tizanidine .. for spasticity which is the standard treatment. I know it would have probably slightly higher Anticholinergic burden… people with... Tizanidine, or the Baclofen,.. I would look at it and say, What are the risk benefits here?.. Do we continue it on, or do we not? And I would have certainly had to discontinue it if clinically indicated that the patient was not tolerating it."* [P-6]	*"I had a patient who had .. very severe cerebral palsy, but the staff felt that she really had deteriorated with her spasticity, and we put her on baclofen .. She stopped eating, drinking and became very constipated. So we stopped it. We started then to Tizanidine, and we have the same thing. So she really was extremely sensitive to this medication, she could not tolerate it, and I put that down to the anticholinergic burden of those drugs. .. another patient .. an older woman with spasticity. We put her on Baclofen and again she stopped eating and I think it was due to dry mouth and became constipated. We investigated her high up and low down, and I think she developed an anorexia from the anticholinergic effect of the medication, and we stopped it"* [P-6]
Gastrointestinal agents	*"lansoprazole .. I think it has an anticholinergic burden of about one… reflux is so high in these patients and if you stop their PPI's.. they get reflux, and they're back in with hematemesis and all that sort of thing ... Glycopyrronium.. to decrease salivary production and we would use some of that topical.. scopolamine which is sort of standard treatment for drooling... so I would use that .... We would have some people on Domperidone. It would have an anticholinergic burden of about one.. but they really need this to empty their stomachs, to stop them refluxing. "* [P-6]	*"A lot of people.. producing too much saliva, so there is a new tendency to be putting people on Hyoscine which obviously has anticholinergic properties... and..It will depend on how bad their side effects are. But if they do have side effects. I am avoiding those ones. I suppose working as much as I can within good clinical practice and trying to avoid polypharmacy. Sometimes it's inevitable."* [P-10]

Table 4.4-5 Continued

Medication Class	Prescribing practice	Experience of deprescribing
Urinary agents		*"If they are on drugs for their bladder. I try to get off those drugs from a bladder.. You can't do anything about the bladder medication. They're on it from the urologist and you try your best. And what I found is GPS are very reluctant, quite reasonably, to stop one consultant for another consultancy, You have to go directly consultant to consultant, to get and to sort of rationalize the medications."* [P-10]

4.4.9 Pharmacist Contributions to the Process of Prescribing and Deprescribing of Medications with Anticholinergic Activity for Older Adults with Intellectual Disability

4.4.9.1 Pharmacist Contributions

In this section, prescribers were asked about their views on the role of pharmacists in the prescribing and deprescribing of medications with anticholinergic activity for older adults with intellectual disability. All prescribers agreed that pharmacist input is essential for this population due to the complexity and high burden of medications, and emphasized the need for involvement of a clinical pharmacist specialized in this population.

> *" it's a brilliant resource to have to have a pharmacist ... who knows the individuals really well, who knows every medication they're on for the last 30 years. and you can have a conversation, and she is able to go to her computer, if … I want to deprescribe this, or I want to prescribe this … but I really want the smallest possible dose … she can just go online and come back to me in 5 min and sort of say, Okay, this is what's available, this is the formulation that comes in for this person, maybe liquid might be better… that can be incredibly useful. She also .. sort of flagged issues that might occur because of prescribing something."* [P-1]

> *"we would regularly communicate, interact with around all aspects of … medication prescribing and very often they would serve as an assistance or reminder regards to medication interactions, medication particulars of concern and occasionally that would include anti-cholinergic load"* [P-3]

> *“we had a senior clinical pharmacist, and she used to do rounds with me , drug review rounds, which was really good, and she was excellent because she was always challenging you, saying, You know, could we do this, or could we do that?... Then she left. She wasn't replaced. "* [P-6]

"… She (the pharmacist) mostly sends me letters about off license medication, things that causes falls for older group…and anti-psychotics plus non anti-psychotic drugs that can increased falls ... So if somebody starts falling, they'll send me a review all the medication that's caused that, so that's very useful, and.. very helpful, and she's usually quite good … she doesn't do the ACB, obviously but she does kind of flag up that they can cause.. falls, .. confusion, things like that and what might be an alternative. So she's really good … she has actually now started to talk to families and to some of the staff, and the persons individually … She go in and say, these are the medications, these are for what … and that's kind of nice from an education piece.." [P-4]

4.4.9.2 Availability of Pharmacists in Workplaces

This part of the interview focused on the availability of pharmacists in the prescribers' workplaces, as well as the barriers and facilitators to having a pharmacist on-site. Four out of the ten prescribers had an on-site pharmacist in their workplace [P-1, P-4, P-7, P-6]. The majority of prescribers expressed that having access to a pharmacist would provide significant benefits in caring for older adults with intellectual disability. Most prescribers identified the lack of financial resources as the primary barrier to having a pharmacist on-site.

"I think access to a pharmacist would lighten my burden because they would be able to explain the risks, … alternative medications, … rates of reduction, and it would make it much easier. But I don't have that access. " [P-2]

"The challenges is probably access to funding for the post and having to like a business case to justify its existence, and which takes a lot of time.." [P-8]

" it would be .. very useful to have somebody ... that we could ask for advice … on medication interactions or … interaction " [P-10]

"the fact that this population is generally experiencing polypharmacy, if not excessive polypharmacy… I have .. to try and figure out how long somebody's been on a medication, or why they were started on a medication, and I know it's not easy. So if you've got somebody that's trying to do that for everyone that's referred into the clinic, .. that is a big undertaking. " [P-9]

Community pharmacist roles were described by some prescribers, for example:

"the few community pharmacists are great and I've had many conversations with them. It's a different conversation to having your own in-house pharmacists to know somebody...really, really well for decades...so we having talking to community pharmacists, it could be in doing in locum. It could be somebody who's there one day a week.... I mean, it could be the pharmacist who's been there for the last 20 years, who owns the business and knows everybody, and that's again you get a different sort of as a support from that person, but certainly ... I'd be much slower to phone a community pharmacist and sort of say … let's talk about side effects… the dose.. formulation, because I know ... They're just really really busy ... But .. it's nice to have somebody that I can phone so the community pharmacists, yeah, any conversations. They've been very, very supportive…" [P-1]

"I am able to phone community pharmacists and ask about alternatives and ask about alternative formulations. But it's not the same as having somebody in the team meeting the carers. That will be much better." [P-2]

"I don't think that we would get the same working relationship with a community pharmacy. we definitely won't and don't get the same continuity, and continuity of care within Pharmacy is good, like continuity of care is good in GP and in nursing." [P-7]

4.4.9.3 Enhancement and Expanding of Pharmacist Role

This section includes suggestions and recommendations on the role of pharmacists for this population, as described by some participants

"I think it'd be really helpful if there was a pharmacist going around community houses looking at the medication." [P-2]

" It would be useful if .. the pharmacist tests the ACB score for us... kind said, 'Okay, this the ACB score. These are the 3 drugs… that would help focus the mind before you prescribe, or if you wanted to decrease. it also helps when it's not always coming from the doctor to decrease the drugs that it's coming from another professional. " [P-4].

"I suppose they could screen medication lists and calculator anticholinergic burden score, maybe look for indications of these medicines, and side effects" [P-8]

"if we had clinical pharmacists.. on the teams to kind of create more of a ... knowledge base and heighten awareness of the issues around polypharmacy. Then that would be hugely beneficial." … "I think the other resource that would be invaluable for people with an ID would be to have a clinical pharmacist who is.. attached and would be a person who would be an overarching, someone who could do medication reviews to try to bridge that gap between all the different specialities involved. So I think that would be an amazing resource to have for medication reviews.., potential inappropriate prescriber prescribing, and any potential reductions that could possibly be made could be looked at by that one person, and then communication to all the different prescribers. " [P-5]

" I would be advocating the role of a specialist clinical pharmacist particularly… supervising ... the prescribing in that group who are exposed to polypharmacy, and you're talking about those low, moderate, severe, and profound, because these are the group of people who have a lot of medication." [P-6]

4.5 Discussion

The TDF proved to be an effective tool for analysing the data, successfully identifying key barriers and facilitators to deprescribing anticholinergics in older adults with intellectual disability from the perspective of prescribers. Participant responses were rich and comprehensive, enabling the conclusion that data saturation was reached, as no new themes emerged during the later stages. This strengthens the reliability of the study's conclusions.

There were several key findings that contributed to the evidence base for improving prescribing practices for older adults with intellectual disability. Firstly, prescribing for older adults with intellectual disability is particularly challenging due to the complexity of co-morbidities and the higher prevalence of mental and neurological disorders in this population. The increased burden of polypharmacy, prolonged medication use, and greater sensitivity to medications and their adverse effects make the process of medication review and prescribing more complex for prescribers. Additionally, communication barriers, such as the inability of patients to effectively convey their symptoms and adverse effects, and the reliance on a family member for information, further complicate appropriate prescribing.

Similarly, the Maudsley Prescribing Guidelines in Psychiatry highlight these factors as significant issues in medication management for older adults with intellectual disability, including difficulties in diagnosis, comorbidities, and challenges in involving patients in decision-making (209). Other studies have confirmed that altered pharmacokinetics and pharmacodynamics result in a higher sensitivity to medication and their adverse effects in comparison to the general population (55, 215). Furthermore, additional research has established a higher rate of polypharmacy among people with intellectual disability (23-25). Another study found that prescription of potentially inappropriate medications is more common among older adults with intellectual disability compared to the general elderly population (52).

Several environmental factors impact on prescribing practices for older adults with intellectual disability. These factors include the availability of medical records, high workload for general practitioners, staff turnover in residential settings, easy access to medication, involvement of multiple prescribers, staff influence, and the lack of a unique

prescribing guidance for people with intellectual disability. Similar to the findings by Scheifes *et al*., the exclusion of people with intellectual disability from randomized clinical trials on psychotropics has led to a lack of evidence-based guidance (216).

4.5.1 Facilitators to Deprescribe Anticholinergics Among Older Adults with Intellectual Disability

Five key TDF domains were identified as facilitators for deprescribing medications with anticholinergic activity among older adults with intellectual disability. These domains are Environmental Context and Resources, Knowledge, Skills, Beliefs about Consequences and Social Influences.

4.5.1.1 The Environmental Context and Resources

The Environmental Context and Resources domain was the most important facilitator and includes five main themes.

Multidisciplinary team: The most frequently described factor to influence prescribing is working within a multidisciplinary team. Prescribers emphasized that having a comprehensive multidisciplinary team and support network around the patient greatly facilitates the decision-making and process of deprescribing for this population. Given the complexity of the cases, input from various healthcare specialties - including psychiatrists, general practitioner, nurses, pharmacists, dementia specialists, psychologists, speech therapists and social worker – was deemed essential.

Awareness and education on the anticholinergic burden: The second factor is awareness of the cumulative effects of medications that have anticholinergic activity. Prescribers noted that understating these effects is crucial, as it helps to consider the need for deprescribing anticholinergics when appropriate. Being aware of these medications enables prescribers to initiate deprescribing of anticholinergic whenever appropriate.

Tools and guidelines for identifying and deprescribing anticholinergics: The availability of tools and guidelines also influences the deprescribing process. A wide range of medications with anticholinergic effects are spread across various therapeutic classes, including antipsychotics, antiepileptics, anticholinergics, gastrointestinal agents, cardiovascular agents, and urinary agents. Because prescribers are typically more familiar within medication within their specialty, they may not readily identify medications with anticholinergic activity outside their area of expertise. Two prescribers reported using the

ACB online calculator (217), finding it to be a very helpful and an easy accessible tool. They also used it as an educational resource to explain the rationale behind deprescribing decisions to patients, carers, family, and staff.

Regular medication review: Conducting regular medication reviews ensures that patients are not on inappropriate long-term medication regimens and plays a crucial role in identifying the need for anticholinergic deprescribing.

Availability of medical records: Prescribers find it easier to access and review the medication lists for patients living in residential settings, which facilitates the decision-making process for deprescribing medications with anticholinergic activity.

4.5.1.2 Knowledge and Skills

The second TDF domain that acts as a facilitator is the prescriber's knowledge and skills on deprescribing of anticholinergics among older adults with intellectual disability.

Knowledge and application of appropriate prescribing: prescriber's knowledge of appropriate medication use plays a key role in optimising prescribing practices and avoiding medications with anticholinergic activity whenever possible. They consider factors such as polypharmacy, prescribing cascades, comorbidities, and cognitive impairment before adding medications that could increase the anticholinergic burden in this population. There is a clear intention to avoid medications with high anticholinergic activity and centrally acting medications to prevent adverse effects and then subsequent prescribing cascades to manage those effects.

Appropriate deprescribing skills: Prescribers demonstrated strong adherence to appropriate deprescribing practices, such as gradually reducing doses ("low and slow"), making one change at a time, avoiding certain periods (e.g., during staff turnover or around Christmas), and ensuring close follow-up to provide support during the process and prevent any deterioration.

4.5.1.3 Social Influences

Involving carers/family in anticholinergic deprescribing decisions Prescribers noted that involving carers and family in the decision-making process for anticholinergic deprescribing plays a significant role. Their understanding of the concepts and benefits of deprescribing is crucial, as their support is essential throughout the process.

4.5.1.4 Beliefs About Consequences

Prescribers' beliefs about the positive impact of anticholinergic deprescribing: An important facilitator is the prescribers' belief in the benefits of anticholinergic deprescribing for those patients. All interviewed prescribers agreed that reducing the anticholinergic burden positively impacts patient quality of life by lowering the risk of side effects such as constipation, sedation, drowsiness, blurred vision, falls, urinary retention, and dry mouth. They are also aware that people with intellectual disability are probably more prone to these symptoms due to factors such as limited cognitive function, cataracts, constipation, reduced physical function, and a higher risk of developing dementia, even before being exposed to anticholinergics.

Prescribers' beliefs about the role of non-pharmacological interventions: Some medication could be avoided or replaced by non-pharmacological interventions, such as dietary changes, increasing physical activity, encouraging walking, and adjusting environmental factors like lighting, room colour and noise level. Prescribers recognize the protentional of these approaches to reduce the need for certain medications.

4.5.2 Barriers to Deprescribing of Medications with Anticholinergic Activity Among Older Adults with Intellectual Disability

The study identifies three key TDF domains that play crucial role as barriers to the process of deprescribing of medications with anticholinergic activity for older adults with intellectual disability: Environmental Context and Resources, Knowledge, and Social Influences.

4.5.2.1 Environmental Context and Resources

Involvement of other prescribers: Prescribers find it easier to deprescribe medications they have initiated themselves, but it is challenging to deprescribe anticholinergics prescribed by others. Some prescribers believe it is each prescriber's responsibility to review their own medication. While they can suggest deprescribing to others, there is often a lack of communication and a sense it's not their responsibility to convince other prescribers to deprescribe.

Lack of awareness: There is a general lack of awareness regarding appropriate medication use, the cumulative risk of certain medications, the role of non-pharmacological interventions, and education about mental disorders among people who support the

patient. This lack of awareness act as a barrier to gaining the support from surrounding staff, carer, and family members.

Lack of medical records: Another important barrier is the lack of comprehensive medical records, including patient diagnoses, medication indication, treatment duration, and previous deprescribing experience. Prescribers may lack confidence in deprescribing without access to this crucial information, especially since many patients have been on medications for long periods, sometimes since childhood, posing a high risk.

Lack of integrated health system: Prescribers working with older adults with intellectual disability often find themselves working in isolation from other health services and specialities. There is a noticeable separation between mental health services and disability services, as well as between psychiatry and non-psychiatry services in Ireland. This lack of integration limits communication among healthcare providers, hindering comprehensive care and appropriate medication use. An overarching, central service is needed to provide a holistic care, bridge the gap between various services, and ensure appropriate medication management. Currently, the general practitioners are expected to fill this role, but their heavy workload often prevents them from effectively coordinating with other prescribers.

Limited access to medical tests and services: Access to essential medical tests, such as Electrocardiogram (ECGs), is limited for people with intellectual disability due to unavailability within certain services and long waiting lists at general hospitals. ECGs are crucial for monitoring QT intervals during the psychotropics treatment. Additionally, people with intellectual disability may face challenges in obtaining necessary blood tests and other evaluations needed before initiating treatment or monitoring medication effectiveness. Moreover, mental health services may not admit people with intellectual disability who developed schizophrenia or similar symptoms. As results, prescribers may hesitate to initiate deprescribing due to concerns about withdrawal symptoms and the burden it may be place on families or residential care staff. Furthermore, some areas lack specialized intellectual disability psychiatrists, leading to non-psychiatrists handling prescriptions.

4.5.2.2 Knowledge

Pharmacological response due to the long-term receptor occupation: Prescribers face challenges in completely discontinuing certain medications, such as benzodiazepines and

antipsychotics. While gradual dose reductions often work well initially, withdrawal symptoms and deterioration can occur at the final stages, leading to the patient being maintained on the previous dose. As a result, prescribers may reduce the dose to the minimum possible dose but find it difficult to fully deprescribe the medications, even when reductions are made slowly and with appropriate intervals. Prescribers believes this difficulty arises from the long-term occupation of receptors by these medications.

4.5.2.3 Social Influences

Workload and relationship with prescribers: Another barrier is the workload faced by GPs, which limits their ability to conduct proper medication reviews and act as an overarching coordinator between different prescribers. A further concern was that patients often have a strong trust in their GPs due to long-standing relationships, making it more difficult for other prescribers to initiate or recommend deprescribing.

Staff, carer, or family resistance: Many prescribers encounter resistance from the patient's support network, including staff, family, and carer, who are reluctant to deprescribe medications out of fear that the patient may deteriorate or suffer as a result. Despite efforts to educate and reassure them, this resistance can be difficult to overcome. Prescribers may find it challenging to initiate deprescribing without the support of these key individuals.

A recent qualitative systematic review by Stewart *et al*., explored and analysed qualitative studies that examined the barriers and facilitators to deprescribing anticholinergics (218). The review included only two studies, both of which focused on the perspectives of healthcare professionals. These studies were conducted in Australia and involved 48 healthcare professionals, comprising 23 general practitioners, 13 specialist clinicians, and 12 pharmacists. The data from these studies were analysed using Normalization Process Theory (NPT).

Consistent with the findings of this study, the systematic review identified lack of time and workload as barriers to deprescribing anticholinergics. Additionally, the review highlighted the importance of making anticholinergic reduction more meaningful and engaging the patient. Participants suggested that using a numerical scoring system could help engage patients and provide measurable scale to evaluate the progress of the process. Other facilitators identified in the review included good communication, strong relationships with the patients and their carer, and good collaboration among healthcare professionals.

On the other hand, the systematic review reported a low confidence in personal skills, which was not observed in our findings. This discrepancy could be attributed to the different professions of the participants; our study mainly included psychiatrists who are experts in psychotropics, anticholinergics, antidepressants and related medications. In contrast, the systematic review included a higher number of GPs and also involved pharmacists, who may not receive specific training in anticholinergic reduction. Additionally, the review found that participants varied in their beliefs about the importance of reducing anticholinergic burden compared to other clinical issues. However, in our study, all of the participants (n = 10) agreed on the importance of reducing the anticholinergic burden whenever possible. The review highlighted the importance of assigning prescribing responsibility to a specific individual. These findings align with our study, which found that the involvement of different prescribers complicates the process of reducing anticholinergic exposure.

Another systematic review, conducted by Anderson *et al*., which was a broader examination of general deprescribing (219). This review also identified findings similar to those of our study, where participants noted that poor communication among healthcare professionals, workload, and reluctance from patients, carers, or other healthcare professionals are key factors that reduce motivation to initiate or successfully carry out the deprescribing process. Additionally, the review emphasized that prescribers' beliefs in the benefits of deprescribing, along with their training and confidence in deprescribing, are crucial facilitators of the deprescribing decision and process.

The general review also included findings from the patient perspective, revealing that patients are generally supportive of deprescribing when they understand it is appropriate for them. This finding aligns with our study and the review by Stewart *et al*., where participants emphasized the importance of educating and involving patients and their carers in the decision-making process to ensure the success of deprescribing. Both of these systematic reviews were not specifically focused on anticholinergic deprescribing among older adults with intellectual disability. Therefore, the findings should be interpreted with caution, as the different population may present unique challenges and considerations. A study conducted at a Dutch mental health care centre reported that individuals with intellectual disability and their carers expressed a desire for greater involvement in decision-making related to deprescribing antipsychotics and medication

reviews (220). This highlights the importance of patient and carer involvement in the deprescribing process. Another review study focused on stakeholder experiences in deprescribing psychotropic medications for challenging behaviour in individuals with intellectual disability (221). It emphasized the importance of involving carers and individuals in the process, offering ongoing support, and improving access to non-pharmacological interventions, such as positive behaviour support. These strategies were found to contribute to successful outcomes, such as reducing or stopping psychotropic medication and improving quality of life.

This study confirmed that pharmacists contribute positively and play a key role in anticholinergic reduction. However, only few services have in-house pharmacists attending rounds, with most service relying on community pharmacists who may frequently change.

Future research should include the patient, carer, family, and other healthcare providers, including nurses and pharmacists. Although these barriers and facilitators have been identified, the limited evidence available leaves many uncertainties regarding crucial aspects of implementing ACB reduction in practice. In terms of intervention design, the identified TDF domains can be effectively integrated with the Behaviour Change Wheel (BCW) to identify appropriate interventions based on the targeted behaviour. This approach can guide the development of tailored strategies to address the specific challenges and facilitators identified in this study.

For future work, the findings of this study will be prepared in an easy-to-read format and shared with the PPI Panel within IDS-TILDA for consultation. Additionally, a deprescribing network for older adults with intellectual disability could be proposed, as suggested by McDonald *et al.,* and her team (222) and tools could be developed to support clinicians (168).

4.5.3 Strength and Limitations

This is the first qualitative study conducted within the intellectual disability population. The study was carried out in Ireland, and since most intellectual disability services are located in Dublin, it is somewhat geographically limited. Another limitation is that no nurse prescribers participated in the study. Additionally, as it was outside the scope of the research, the study did not explore other aspects of medicine administration and

adherence in older adults with intellectual disability. Further study should explore perspectives and views of other stakeholders including nurses, pharmacists, carers, family members and the patients regarding medicine optimisation and deprescribing of medications with anticholinergic activity.

4.6 Conclusion

This study provides valuable insights into the complexities of prescribing and deprescribing of medications with anticholinergic activity among older adults with intellectual disability. The findings underscore the unique challenges posed by this population, including the high prevalence of comorbidities, communication barriers, the careful balance required to manage polypharmacy and long-term medication use, as well as resistance to medication deprescribing from families, carers, and staff.

Key facilitators identified for such a careful balance include a multidisciplinary approach, enhanced awareness of the anticholinergic burden, and the availability of tools and guidelines that support prescribers in making informed decisions. Moreover, the involvement of carers and family members, along with prescribers' beliefs in the positive outcomes of deprescribing, play a significant role in facilitating this process.

Conversely, the study highlights several barriers, such as the lack of integrated health systems, limited access to essential medical tests, and the challenges posed by the long-term occupation of receptors by certain medications. The workload on general practitioners and resistance from patients' support networks further complicate efforts to reduce anticholinergic use.

The study points out the need for further research tailored specifically to older adults with intellectual disability. Future studies should focus on a more comprehensive approach that includes the perspectives of patients, carers, and a broader range of healthcare providers. Additionally, the role of pharmacists in this process should be further explored and integrated into standard practice to ensure the successful implementation of anticholinergic burden reduction strategies in this vulnerable population.

Chapter 5

Discussion and Recommendations

5.1 Discussion of Findings

This is the first study, to the PhD candidate's knowledge, to investigate the long-term impact of anticholinergic exposure on outcomes in older adults with Intellectual Disability. Additionally, the MRC framework used is in this research is, to the PhD candidate's knowledge, the first time it has been applied to examine medication use in people with intellectual disability. The qualitative study is also the first of its kind to explore prescribers' views and perspectives on the prescribing and deprescribing of medications with anticholinergic activity for older adults with intellectual disability.

Older adults with intellectual disability are known to experience a high burden of anticholinergic exposure, and this thesis suggests that they are likely exposed for prolonged periods. There could be many factors contributing to the prolonged exposure to a high anticholinergic burden. This research explored the barriers and facilitators that encounter by prescribers when attempting to reduce anticholinergic burden exposure among older adults with intellectual disability. Enhancing prescribing practices requires an intervention to support prescribers and healthcare professionals during the prescribing, deprescribing, and medication review processes of medications with anticholinergic activity. The findings of this thesis provide some of the evidence-base and theoretical foundation necessary for developing the intervention, as recommended by the MRC framework.

Chapter 1 of this thesis provided background on intellectual disability, focusing on the morbidity characteristics and medication use among people with intellectual disability as they age. A key finding from this chapter is that the onset and pattern of diseases differ from the general elderly population (14, 16), leading to differences in medication use (23-25). Additionally, older adults with intellectual disability exhibit greater sensitivity to medications and their adverse effects (57). Similar to the general population, their pharmacodynamics and pharmacokinetics change with age. As highlighted in *Chapter 1*, older adults with intellectual disability are exposed to a higher burden of anticholinergic activity due to the greater prevalence of mental and neurological disorders compared to the general ageing population (67, 93). This chapter also introduced the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA), the first study of its kind that allows for comparison between individuals with intellectual disability and

the general ageing population, where the research of *Chapter 3* was nested (1). The discussion is organised according to the aims and objectives of the thesis.

5.2 Aim 1

The first aim of this thesis was to map and examine the existing research literature on adverse effects associated with long-term exposure to medications with anticholinergic activity among older adults with intellectual disability. This was addressed in *Chapter 2.* Preliminary research conducted in order to refine the research question, indicated a lack of longitudinal studies that examine the adverse effects associated with long-term anticholinergic exposure in older adults with intellectual disability. Therefore, a scoping review was conducted as opposed to a systematic review. Both the study protocol and the main scoping review were published in the HRB Open Research Journal (130, 131). An empty review was reported, which was not surprising given the limited research involving people with intellectual disability. As noted by Yaffe *et al*., 15 out of 81 systematic reviews conducted on people with intellectual disability resulted in zero studies being included, highlighting the frequent exclusion of this population from clinical research (132). One key barrier to including people with intellectual disability in research is their dependence on family members or caregivers. A lack of support from caregivers can limit the recruitment of a sufficient sample size for studies involving this population. The scoping review presented in *Chapter 2* highlighted the urgent need for more inclusion of people with intellectual disability in research studies on medication use and to conduct further longitudinal studies to understand and examined long-term exposures of certain medication and outcomes associated with it.

5.3 Aim 2

The second aim of this thesis was to examine outcomes associated with long-term exposure to medications with anticholinergic activity amongst older adults with intellectual disability. This was addressed in *Chapter 3.*

Objectives of this chapter were to:

a. Examine the anticholinergic burden of people who participated in Wave 1 and remained in the study at Wave 4 (longitudinal cohort sample).
b. Compare the anticholinergic burden of the whole cohort at Wave 1 and Wave 4 (cross sectional analysis).
c. Identify and compare the most frequently reported medication and classes of medication contributing to anticholinergic burden in whole cohort of Wave 1 and Wave 4.
d. Examine socio-demographic and health-related factors associated with anticholinergic burden at whole cohort in Wave 4.

Following on from the empty review presented in *Chapter 2*, *Chapter 3* explored the anticholinergic exposure among older adults with intellectual disability at two time points, 10 years apart, using IDS-TILDA data. In addition to this, it examined the outcomes reported 10 years after the initial exposure to medications with anticholinergic activity. The key findings of the longitudinal analysis revealed that approximately seven out of 10 participants were exposed to anticholinergics, with 70% of them reporting the same exposure at both time points thus meeting Objective *a*. Similarly, there was no significant change in anticholinergic exposure among the whole cohort at Wave 1 and Wave 4 showing Objective *b* was met. This suggests that older adults with intellectual disability experience a high anticholinergic burden, often sustained over long periods.

Furthermore, the study identified antipsychotics as the class of medication contributing most significantly to this high anticholinergic burden, followed by anticholinergics, antiepileptics, and antidepressants at both time points. This finding shows that Objective *c* was met. These findings reflect the high prevalence of mental and neurological disorders within the studied population. The study also examined specific medications contributing to anticholinergic exposure and found that the top four medications remained the same at both time points. Carbamazepine ranked highest, followed by risperidone, olanzapine,

and biperiden. Objective *d* was met by examining factors associated with mild and high ACB scores. Thesis showed that anticholinergic exposure was more commonly reported by participants living in community homes and residential settings, as well as those with multimorbidity, mental health conditions, and polypharmacy (excluding medications with anticholinergic activity). A study investigating anticholinergic and sedative burden among people with intellectual disability and cognitive complaints, focusing on individuals attending memory clinic services in Ireland, concluded that the majority of participants were exposed to a high medication burden. Notably, this burden was found to significantly exceed that observed in the general population, raising concerns about the impact on this population (223).

This study established a significant association between a high and/or a mild ACB scores at Wave 1 and the occurrence of falls and reporting mental health conditions at Wave 4, Aim *2* was met.

Despite the consistently high antipsychotic use at both time points, there was a noticeable reduction in the use of older antipsychotics, such as chlorpromazine and haloperidol, as well as anticholinergics like procyclidine and certain antidepressants, including citalopram and paroxetine. A comparison between the findings from the prescribers interviews presented in *Chapter 4* and the longitudinal analysis of anticholinergic exposure presented in *Chapter 3*, was made for the key medication classes that contribute to anticholinergic exposure in the studied population.

Antipsychotics and anticholinergics: The qualitative study, presented in *Chapter 4,* highlighted increasing awareness among prescribers regarding the adjuvant use of antipsychotics and anticholinergics to prevent extrapyramidal side effects caused by antipsychotics. Most psychiatrists interviewed acknowledged this as an outdated and inappropriate practice, and many are actively working to deprescribe anticholinergics that were originally prescribed for this reason. This growing awareness is consistent with the findings from *Chapter 3*. However, there has been an increase in the use of quetiapine, which is anticholinergic. Further investigation is required to better understand its indication in this population.

Benzodiazepines: The longitudinal study, presented in *Chapter 3*, reported a 7% reduction in diazepam use. In *Chapter 4,* prescribers identified benzodiazepines as one of the most difficult medication classes to fully deprescribe. The majority of prescribers are avoiding

prescribing benzodiazepines to older adults with intellectual disability due to their adverse effects, including cognitive decline, anticholinergic side effects, and the challenges associated with discontinuing their use completely.

Antidepressants: The majority of prescribers are prescribing Selective Serotonin-Reuptake Inhibitors (SSRIs) rather than Tricyclic Antidepressants (TCAs). There has been an increase in the use of certain medications, including escitalopram (SSRI, ACB = 1) and mirtazapine (tetracyclic antidepressant, ACB = 1). Conversely, there has been a reduction in the use of paroxetine (SSRI, ACB = 3) and citalopram (SSRI, ACB = 1).

Another key finding of *Chapter 3* was that participants exposed to medications with anticholinergic activity at the first time point were significantly associated with a higher risk of falls and reporting of a mental health conditions, including hallucinations, anxiety, depression, emotional problems, schizophrenia, psychosis, mood swings, manic depression, post-traumatic stress disorder, and other conditions. Additionally, there was a significant increase in reporting constipation, despite the rise in the use of multiple laxatives, highlighting an important area for further investigation. While there was not enough evidence to directly link ACB exposure to constipation, other factors likely contribute to this issue. Non-pharmacological factors, such as diet, exercise, and overall lifestyle—especially for those living in residential settings—should be further explored. Non-pharmacological interventions, such as walking, are also needed to improve sleep quality, reduce anxiety, and manage insomnia, potentially avoiding the need for hypnotics.

5.4 Aim 3

The third aim of this thesis was to explore prescribers' views and perspectives on prescribing and deprescribing of medications with anticholinergic activity for older adults with intellectual disability. This was addressed in *Chapter 4.*

Objectives of this chapter were to :

a. Recruit 8 – 10 participants involved in prescribing for older adults with intellectual disability.
b. Examine prescriber's knowledge on anticholinergic burden, anticholinergic adverse effects, and tools used to quantify it.
c. Identify barriers and facilitators of deprescribing of anticholinergics using the TDF.
d. Investigate prescriber's opinion on the pharmacist's role in the process of prescribing/ deprescribing of medications with anticholinergic activity among older adults with intellectual disability.

The findings of *Chapter 3* were shared with participants in the qualitative interview study (*Chapter 4*), and many prescribers, particularly psychiatrists, were surprised to see carbamazepine at the top of the list. The majority agreed that it is not considered a first-line treatment for epilepsy, and they generally avoid it due to the high profile of adverse effects and significant drug interaction risks associated with carbamazepine. Some prescribers noted that very few patients are still on carbamazepine, likely because they have been taking it for a long time. However, another prescriber mentioned that some clinicians still view carbamazepine as a relatively harmless medication, prescribing it to people with intellectual disability not only as an antiepileptic but also for managing behaviours that challenge in both epileptic and non-epileptic patients, as quoted below. For epilepsy treatment, prescribers are now using medications such as lamotrigine, levetiracetam, and, in some cases, sodium valproate, all of which do not have anticholinergic adverse effects.

A review study highlighted that multiple factors influence behaviours that challenge and may be directly or indirectly associated with antiepileptic medications in people with intellectual disability (224). Antiepileptics are associated with behavioural and psychiatric adverse effects. The review emphasized the importance of conducting medication

reviews, annually at minimum, particularly for individuals aged 40 or older with intellectual disability and epilepsy, with a focus on high anticholinergic burden and/or polypharmacy (224). Another study found that people with intellectual disability who have epilepsy and are on antiepileptic medications are at a higher risk of hospital admission due to severe constipation (225). These admissions could potentially be prevented by reducing antiepileptic medication use when appropriate and initiating laxative treatment earlier.

The study explored barriers and facilitators to deprescribing medications with anticholinergic activity among older adults with intellectual disability using the TDF. This study identified barriers and facilitators to deprescribing from the perspectives of prescribers, including psychiatrists, general practitioners, and geriatricians in Ireland, with the results summarised in *Table 5.4-1*.

Table 5.4-1 Facilitators and barriers to deprescribe medications with anticholinergic activity among older adults with intellectual disability from prescribers' perspectives

	TDF Domains	Themes
Facilitators	Environmental Context and Resources	Multidisciplinary team
		Awareness and education on the anticholinergic burden
		Tools and guidelines for identifying and deprescribing anticholinergics
		Regular medication review
		Availability of medical records
	Knowledge and Skills	Knowledge and application of appropriate prescribing
		Appropriate deprescribing skills
	Social Influences	Involving carers/family in anticholinergic deprescribing decisions
	Beliefs About Consequences	Prescribers' beliefs about the positive impact of anticholinergic deprescribing
		Prescribers' beliefs about the role of non-pharmacological treatment/interventions
Barriers	Environmental Context and Resources	Involvement of other prescribers
		Lack of awareness among people who support the patient
		Lack of appropriate medical records
		Lack of integrated health system
		Limited access to medical tests and services
	Knowledge	Pharmacological response due to long-term receptor occupation
	Social Influences	Workload and relationship with prescribers
		Staff, carer, or family resistance

5.5 Aim 4

The fourth aim of this thesis was to synthesise data in order to assess the development of an intervention aimed at enhancing the prescribing and deprescribing of medications with anticholinergic activity among older adults with intellectual disability. This was addressed this section .

As discussed previously in section 3 of the *Chapter 1*, this thesis was designed based on the MRC Framework to provide the theoretical foundation and some of the evidence-base to assess intervention development for optimising prescribing of medications with anticholinergic activity among older adults with intellectual disability (105, 226). The MRC framework provides researchers with guidance on developing, implementing and evaluating complex interventions and it consist of four main stages as illustrated in *Figure 5.5-1*.

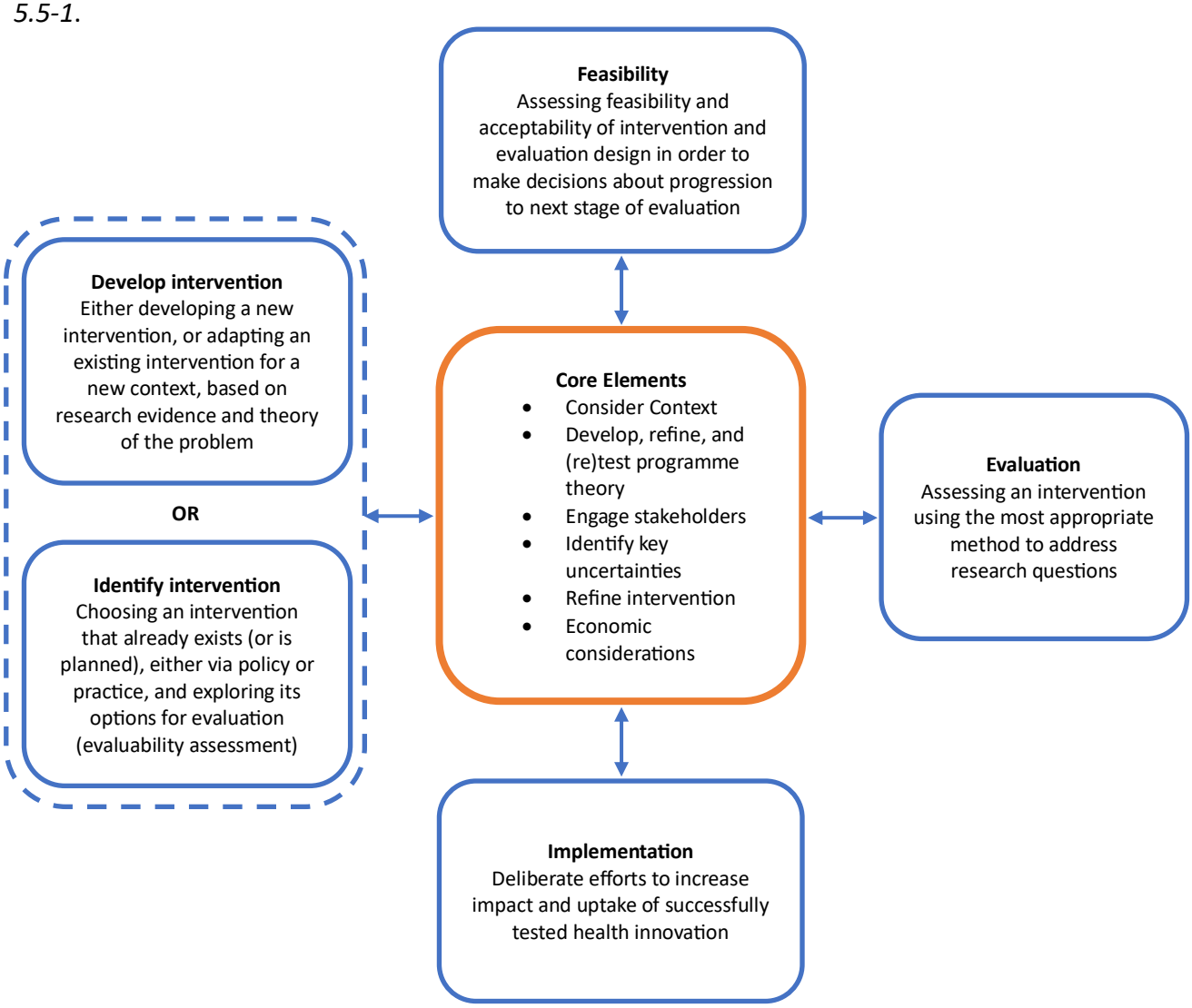

Figure 5.5-1 Components of MRC Framework adapted from Skivington, *et al.*

As noted in *Chapter 1,* and reiterated above, the first stage of MRC framework is the development of the intervention. This thesis had provided some of the research evidence and the theory of the problem, as recommended by the MRC framework. Based on the updated MRC framework, the development phase encompasses the entire process of designing and planning an intervention, from the initial idea through to feasibility, pilot, or evaluation stages (226). It does not always originate from a new or researcher-initiated intervention; it can involve adapting an existing intervention to a new context. This adaptation might include tailoring the intervention to a different population, setting, or targeting different outcomes.

This phase was only briefly outlined in the original MRC guidance, but O'Cathain and co-authors developed additional guidance to provide more support for researchers aiming to develop complex interventions (227). The guidance summarised the key actions recommended by O'Cathain *et al*., to complete when developing a complex intervention. However, developers may find it unnecessary or impractical to address all these actions during the development process, as some may not be applicable to every situation or context. The recommendation is for developers to assess the relevance and significance of these actions at the outset and continuously throughout the development process. Key actions recommended by O'Cathain *et al.,* are presented in *Table 5.5-1*.

Table 5.5-1 Key actions for developing interventions developed by O'Cathain *et al*.

Action	Consider the relevance and importance of the following
Plan the development process	Identify the problem to be targeted and refine understanding of it throughout the process. Assess whether the problem is a priority. Consider which aspects of the problem are amenable to change. Ask whether a new intervention is really needed and if the potential benefit of the new intervention justifies the cost of development. Determine the time needed to undertake intervention development. Obtain sufficient resources/funding for the intervention development study. Draw on one or more of the many published intervention development approaches, recognising that there is no evidence about which approach is best and apply flexibly depending on the problem and context. Involve stakeholders during the planning process (see next Action). Produce a protocol detailing the processes to be undertaken to develop the intervention.
Involve stakeholders, including those who will deliver, use and benefit from the intervention	Work closely with relevant stakeholders throughout the development process: patients, the public, the target population, service providers, those who pay for health and social services or interventions, policymakers and intervention design specialists. Develop a plan at the start of the process to integrate public and patient involvement into the intervention development process. Identify the best ways of working with each type of stakeholder, from consultation through to coproduction, acknowledging that different ways may be relevant for different stakeholders at different times. Use creative activities within team meetings to work with stakeholders to understand the problem and generate ideas for the intervention.
Bring together a team and establish decision-making processes	Include within the development team individuals with relevant expertise: in the problem to be addressed by the intervention including those with personal experience of the problem, in behaviour change when the intervention aims to change behaviour, in maximising engagement of stakeholders and with a strong track record in designing complex interventions. It may be hard to make final decisions about the content, format and delivery of the intervention, so only some team members may do this. There is no consensus about the size or constituency of the team that makes these final decisions, but it is important early on to agree a process for making decisions within the team.

Table 5.5-1 Continued

Action	Consider the relevance and importance of the following
Review published research evidence	Review published research evidence before starting to develop the intervention and throughout the development process for example, to identify existing interventions, to understand the evidence base for each proposed substantive intervention component. Look for, and take into account, evidence that the proposed intervention may not work in the way intended.
Draw on existing theories	Identify an existing theory or framework of theories to inform the intervention at the start of the process, for example, behaviour change or implementation theory. Where relevant, draw on more than one existing theory or framework of theories for example, both psychological and organisational theories.
Articulate programme theory	Develop a programme theory. The programme theory may draw on existing theories. Aspects of the programme theory can be represented by a logic model or set of models. Test and refine the programme theory throughout the development process.
Undertake primary data collection	Use a wide range of research methods throughout, for example, qualitative research to understand the context in which the intervention will operate, quantitative methods to measure change in intermediate outcomes.
Understand context	Understand the context in which the intervention will be implemented. Context may include population and individuals; physical location or geographical setting; social, economic, cultural and political influences and factors affecting implementation, for example, organisation, funding and policy.
Pay attention to future implementation of the intervention in the real world	From the start, understand facilitators and barriers to reaching the relevant population, future use of the intervention, 'scale up' and sustainability in real world contexts.
Design and refine the intervention	Generate ideas about content, format and delivery with stakeholders. Once an early version or prototype of the intervention is available, refine or optimise it using a series of iterations. Each iteration includes an assessment of how acceptable, feasible and engaging the intervention is, including potential harms and unintended consequences, resulting in refinements to the intervention. Repeat the process until uncertainties are resolved. Check that the proposed mechanisms of action are supported by early testing.

The findings of this thesis can be synthesised to plan the development process, engage stakeholders who will deliver the intervention, assemble a team, and design the intervention. The results from *Chapters 2, 3*, and *4* can all serve as evidence-based foundations and contribute to the theoretical foundation necessary for the intervention's development.

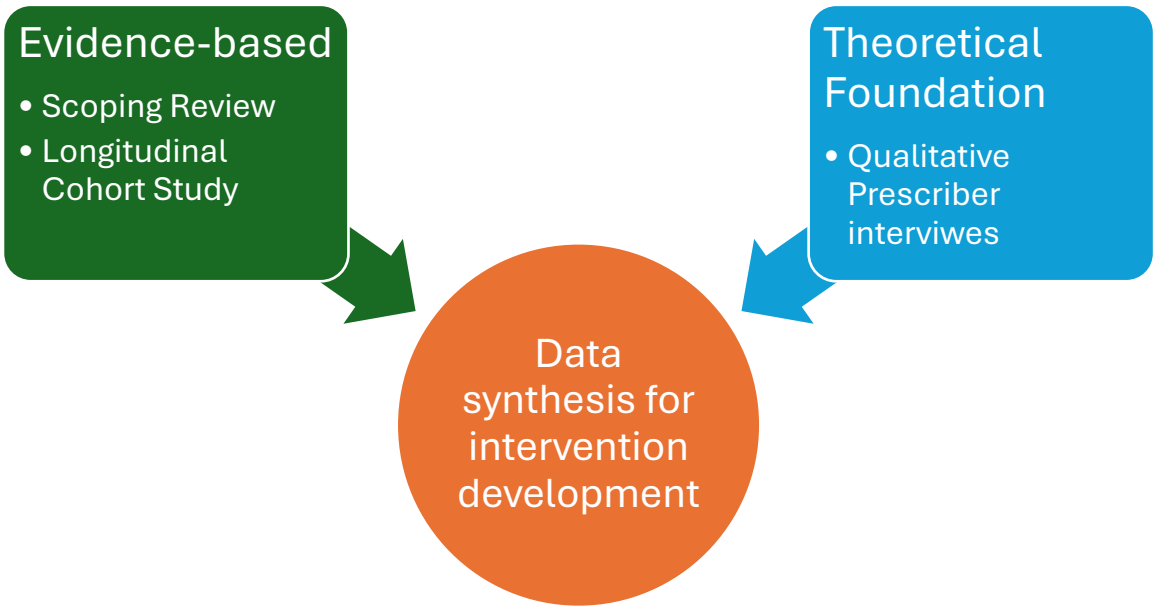

Figure 5.5-2 Data synthesis from thesis findings

The Scoping Review: *Chapter 2* presented an empty scoping review which showing that no studies have examined the adverse effects associated with long-term use of medications with anticholinergic activity among older adults with intellectual disability (131). This is despite extensive use of medications with anticholinergic activity in people with intellectual disability.

The Longitudinal Cohort Study Findings:

1. In total, seven in ten participants were exposed to medications with anticholinergic activity at both time points, which are 10 years apart.
2. The medication classes contributing most to high anticholinergic burden were antipsychotics, followed by anticholinergics, antiepileptics, and antidepressants at both time points.

3. The four most frequently prescribed medications with anticholinergic activity were carbamazepine, risperidone, olanzapine, and biperiden at both time points.
4. There was an increase in the prescribing of escitalopram and quetiapine at time point 2 (2019/2020), by 2.9% and 3.1% respectively.
5. There was a reduction in the prescription rates of diazepam, chlorpromazine, haloperidol, and procyclidine.
6. Exposure to a mild or high anticholinergic score at time point 1 was significantly associated with a higher risk of falls and mental health conditions at time point 2.
7. Higher anticholinergic exposure was observed among participants living in community homes and residential care settings compared to those living with family or independently, those with multimorbidity, reported mental health conditions, and those on polypharmacy.

The Prescriber's Interview Study Findings

1. **Challenges in Prescribing and Deprescribing**: Prescribing and deprescribing for older adults with intellectual disability is more challenging than for the general elderly population. These challenges arise from patient characteristics, including the complexity of disorders, comorbidities, polypharmacy, non-verbal or limited communication skills, and dependence on carers or family members. Additional difficulties are posed by environmental factors like limited medical history and the involvement of multiple prescribers.
2. **Facilitators for Deprescribing Anticholinergics**: Key facilitators identified by prescribers include the availability of comprehensive medical history, knowledge of appropriate medication use, beliefs about the consequences of prescribing anticholinergics to this population, involvement of the patient's support network in deprescribing decisions, working within a multidisciplinary team, and conducting regular medication reviews.
3. **Barriers to Deprescribing Anticholinergics**: Barriers include a lack of detailed medical history, resistance from family, carers, or staff, involvement of multiple prescribers, a lack of an integrated health system, high workloads for GPs, limited access to medical tests and services, and a general lack of awareness.

4. **Difficulty in Deprescribing Benzodiazepines and Antipsychotics**: Benzodiazepines and antipsychotics were identified as the most difficult medications to fully deprescribe in this population, with prescribers attributing this to the long-term occupation of receptors.
5. **Limited Knowledge of Anticholinergic Measuring Tools**: Many prescribers have limited knowledge of anticholinergic measuring tools, and most do not use any tool to identify or calculate the total anticholinergic burden. A few prescribers who use the ACB online calculator report a significant positive impact on their prescribing practices.
6. **Role of Pharmacists in Multidisciplinary Teams**: Having a pharmacist as part of the multidisciplinary team contributes positively to the appropriate use of medications in this population.
7. **Need for Accessible Tools and Guidance**: All interviewed prescribers agreed that easy access to a simple tool would enhance their prescribing practices. They expressed the need for a tool or guidance that helps identify medications with anticholinergic activity, suggests alternatives with lower or no anticholinergic activity, and provides descriptions of potential outcomes or adverse effects associated with both long-term and short-term use.

Firstly, the empty scoping review highlighted an urgent need for longitudinal studies among older adults with intellectual disability (131). Following this, the longitudinal study confirmed that this population are highly exposed to medications with anticholinergic activity at the two time points ten years apart, suggesting prolonged exposure to these medications. This exposure was significantly associated with a higher risk of falls and mental health conditions after ten years. Subsequently, the qualitative interview study revealed that prescribers had limited knowledge of tools used to quantify and identify medications with anticholinergic activity. During the interviews, the PhD candidate presented a document on the ACB Scale and a list of medications included in the scale along with their ACB scores. Prescribers expressed strong interest in the document, with many requesting access to the medication list. Additionally, prescribers provided input on the type of tool needed in practice, emphasizing the need for a simple, easily accessible tool that offers alternatives where possible and could be used to raise awareness and

educate patients, families, and carers, facilitating their involvement in the deprescribing process.

Generally, deprescribing long-term medications is a complex process that raises concerns and anxiety for both patients and healthcare professionals (228, 229). Healthcare professionals may worry about safety, the uncertain impact of deprescribing (229, 230), and potential challenges in managing withdrawal symptoms (231). Patients, on the other hand, may be concerned about losing the perceived benefits of the medications they rely on and uncertainties around managing their symptoms without medication (232-234). These concerns and challenges are heightened in individuals with intellectual disability due to the complexity of comorbidities, communication barriers, their reliance on family members or carers in most situations and other environmental factors.

Several prescribers highlighted the ACB online calculator as an effective tool for improving their practice due to its simplicity and accessibility (217). Developed by Rebecca King and Steve Rabino, this tool not only facilitates easy calculation of ACB scores but also serves an educational purpose, particularly with its color-coded system: yellow for an ACB score of 1, orange for a score of 2, and green for a score of 3. The calculator automatically calculates the total ACB score and issues a red alert if the score is 3 or above, signalling an elevated risk of confusion, falls, and death for the patient. Additionally, the website provides a comprehensive list of medications with their corresponding ACB scores and offers alternative suggestions to help reduce the anticholinergic burden. Furthermore, a more comprehensive list and additional alternatives could be added to the tool to broaden the options available for prescribers. The medication list included in this tool could also be updated to align with the drugs approved for use in Ireland. The author of this thesis could provide an online education piece around the use of this tool through the IDS-TILDA network.

A tool known as Medichec has been developed in the United Kingdom (235). It is designed to help healthcare professionals assess the anticholinergic burden of medications and support decision-making in clinical practice. It provides access to comprehensive information on the side effects of multiple medications simultaneously, assisting clinical decision-making, optimising treatment, and enhancing patient safety, particularly in vulnerable adult populations. The tool is based on the Anticholinergic Effect on Cognition (AEC) Scale, which was developed by the South London and Maudsley NHS Foundation

Trust (SLaM) team (236). The AEC scale has been validated in individuals with dementia/delirium and has demonstrated greatest predictive accuracy for dementia compared to other anticholinergic burden measurement tools (237). Medichec is available as both a website and a mobile application, providing healthcare professionals with convenient access to assess anticholinergic burden and support clinical decision-making (235).

In Ireland, a tool had been developed recently aiming to improve prescribing in people with intellectual disability - Optimising Pharmaco-Therapy and Improving Medication for Ageing with Intellectual Disability (A) (168). It is the first tool that designed for optimising medication use older adults with intellectual disability. The process involved in developing OPTIMA-ID included evaluating existing evidence, reviewing prescribing tools and guidelines used for other populations to identify relevant criteria, considering logical clinical approaches to medication management, consulting with expert focus groups (including prescribers and those who manage medication in people with intellectual disability), and validating the tool through a Delphi consensus process. The tool incorporates guidelines for optimising the use of medication with anticholinergic activity, such as avoiding medications with high anticholinergic activity and not using anticholinergics to manage extrapyramidal side effects. This tool should be tested to determine its effectiveness in reducing anticholinergic exposure.

Creating a network focused on addressing polypharmacy can help to overcome challenges by connecting individuals with expertise and interest in deprescribing, serving as a valuable source of support and resources (222). In the past decade, various deprescribing networks have been established to tackle polypharmacy, with evidence of both individual and collective success. Examples include the Australian Deprescribing Network (ADeN) (238), the Canadian Medication Appropriateness and Deprescribing Network (239)(CADeN), the United States Deprescribing Research Network (USDeN) (240), and the Network of European Researchers in Deprescribing (NERD)(241). Such networks offer numerous benefits, including sparking interest, generating ideas, and fostering enthusiasm through the exchange of information, public engagement, and collaboration with healthcare providers and other key stakeholders. As people with intellectual disability are exposed to high burden of medication and anticholinergics, there should also be a dedicated network for deprescribing among older adults with intellectual disability to

provide essential support for prescribers, individuals with intellectual disability, policymakers, and other relevant parties.

5.6 Recommendations for Future Work

Further analysis is required to assess medication exposure by including data from Waves 2-3, which are spaced three years apart. To gain a more thorough understanding of population trends over time, advanced longitudinal modelling techniques could be employed. Generalized estimating equations (GEE) can be used to estimate average population responses over time, while generalized linear mixed models (GLMM) can track individual trajectories by accounting for random effects. One benefit of GLMM is that it allows for the inclusion of participants who may have incomplete data, as it does not require responses from every wave.

A larger sample size is necessary to explore the link between anticholinergic exposure and the development of dementia in older adults with intellectual disability. Since 2020, following Wave 4, dementia screening has increased with the establishment of the National Intellectual Disability Memory Service, which provides memory screening and assessment for all individuals with intellectual disability in Ireland. Future research should specifically examine ACB exposure in individuals with Down Syndrome, as well as those with intellectual disability from other causes. The high anticholinergic exposure may contribute to the higher rates of dementia seen in individuals with Down Syndrome, highlighting the need for increased attention and care for this vulnerable group.

From the perspective of the qualitative study, future research should involve patients, caregivers, families, and other healthcare professionals, including nurses and pharmacists. Then next step, the identified barriers and facilitators should be prioritized, and the relevant components should be applied, using the Behaviour Change Wheel, to develop interventions that support the deprescribing process. This method can help in creating tailored strategies to address the specific challenges and facilitators highlighted in the study. While this study has identified key barriers and facilitators, there are still significant uncertainties due to the limited available evidence on how to implement ACB reduction effectively in practice. A literature review should be undertaken to investigate existing interventions or effective approaches for deprescribing medications with anticholinergic activity that could be adapted for older adults with intellectual disability.

As illustrated in *Chapter 2*, the findings from the scoping review chapter were presented and discussed with a member of the PPI panel within IDS-TILDA. However, due to time limitations, the PhD student was unable to conduct a full PPI meeting with the entire panel. Therefore, the results from both the longitudinal and qualitative studies should be prepared in accessible formats, presented to the PPI panel, and discussed to gather feedback and suggestions for future work.

5.7 Impact of Study Finding on Practice

The results of this thesis emphasize the need to re-evaluate prescribing guidelines for antipsychotics, anticholinergic, and antidepressants, particularly those with an ACB score of 3, such as chlorpromazine, quetiapine, and olanzapine, for older adults with intellectual disability living in residential settings. Regular medication reviews are also essential for these individuals, especially those on polypharmacy, to assess the possibility of reducing or discontinuing medications, both with and without anticholinergic activity.

The presentation of a complex area via the PhD candidate's award-winning Three Minute Thesis is a novel approach. This three minute video has received over 159 views so far on YouTube. It has been used as a presentation at the IASSIDD World Congress. The innovative and novel method of making a complex topic accessible and engaging is being used as a teaching tool in a Trinity Year 4 pharmacy workshop on polypharmacy for vulnerable patients. Additionally, this video is being incorporated into the 2024 National Health System in Ireland's Health Service Executive (HSE) National Clinical Frailty Programme, adapted for intellectual disability, where it will be part of the medicines module.

As described in *Section 3.5.7* of *Chapter 3,* the PhD candidate participated in several events to raise awareness of the anticholinergic burden and its cumulative effects on people with intellectual disability. Furthermore, the video has been shared via social media to reach a broader audience, including the public and healthcare professionals. The PhD candidate completed a Post-Graduate Certificate in Statistics and another in Innovation and Entrepreneurship for researcher during her PhD. Both courses have inspired and helped the author of the thesis to achieve these novel findings and creativity sharing them with the public. The following section outlines the key and novel findings from this research, which will have significant implications for practice.

The developed and updated list of ACB medication, along with the paper (submitted for publication) and the video, are being used in teaching a polypharmacy workshop for complex case studies for 4th year pharmacy students at Trinity College Dublin. These resources are also being used by Intellectual Disability Services in the south of Ireland to influence the prescribing/deprescribing of these medication for older adults with intellectual disability. Additionally, they are being used by colleagues in neuropsychiatry at the University of Plymouth to inform work on anticholinergic burden and will be

included as part of the HSE National Frailty Programme, adapted for people with intellectual disability, to guide practitioners.

The findings of the qualitative study will be published, shared and used by the College of Psychiatrists of Intellectual Disability and other Intellectual Disability Services. The PhD candidate plans to conduct a webinar through IDS-TILDA, with a key stakeholders panel from HSE and the College of Psychiatrists, to update practitioners and services on the key findings of this research.

From an intervention perspective, several prescribers noted that the Anticholinergic Cognitive Burden (ACB) online calculator is an effective tool for enhancing their practice due to its ease of use and accessibility. This tool not only simplifies the calculation of ACB scores but also serves an educational role with its color-coded system: yellow for an ACB score of 1, orange for a score of 2, and green for a score of 3. It automatically computes the total ACB score and issues a red alert if the score is 3 or higher, indicating a heightened risk of confusion, falls, and mortality for the patient. Additionally, the website offers a detailed list of medications with their ACB scores and suggests alternatives to help reduce the anticholinergic burden. To further enhance its usefulness, the tool could benefit from an expanded list of medications and updated options to reflect the drugs approved for use in Ireland.

5.8 Impact of COVID-19

This PhD project began in September 2020, but due to COVID-19 travel restrictions, the PhD student was in her home country, the Sultanate of Oman. As a result, she completed the first nine months of the program online and was unable to access data due to data protection laws, as she was located outside the European Union. During this period, she conducted a literature review, developed the study protocol for the scoping review, and published the protocol in the *HRB Open Research Journal*.

As a result, there was nearly a year-long delay in accessing the data. Once she arrived in Ireland, she began inputting the Wave 4 medication data, manually transferring it from the PIQs into SPSS for each participant. This was followed by data checking and cleaning.

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Appendices

Appendix 1.3-1: Individual Contribution to each study/chapter in the thesis

Chapter/Study	Contributors
Chapter 2 **Al Shuhaimi L, Henman M, McCallion P, McCarron M, O'Dwyer M.** **The impact of long-term exposure to anticholinergics among people with intellectual disabilities: a scoping review protocol** **Al Shuhaimi L, Henman M, McCallion P, McCarron M, O'Dwyer M.** **The adverse effects of long-term exposure to anticholinergics among people with intellectual disabilities: a scoping review**	**Al Shuhaimi L:** Overall study design, conceptualization, prepared study materials (data collection documents), conducted the database search, scanned and reviewed the database search results, contacted stakeholders for consultation stage, contacted librarian for search strategy. wrote first manuscripts of the study protocol, scoping review paper and Chapter 2. Submitted the manuscripts the *HRB Open Research Journal* for publication. Amended comments from co-authors and editorial team from the journal. Management of revisions from the peer reviewer. **Henman M:** Contributed to overall study design and concept, scanned the results of the search, suggested stakeholders for consultations, reviewed the study protocol, the scoping review paper and the chapter, contributed to journal selection, suggestion of peer reviewers. **McCallion P:** Contributed to overall study design and concept, reviewed all of the study protocol and scoping review manuscripts, suggested stakeholders for consultations, contributed to journal selection. **McCarron M:** Contributed to overall study design and concept, reviewed all of the study protocol and scoping review manuscripts, suggested stakeholders for consultations, contributed to journal selection. **O'Dwyer M:** Contributed to overall study design and concept, scanned the results of the search, suggested stakeholders for consultations, reviewed the study protocol, the scoping review paper and the chapter, contributed to journal selection, suggestion of peer reviewers.

Chapter 3 **Outcomes associated with long-term exposure to anticholinergics amongst adults aged 40 or over with intellectual disability: a longitudinal cohort study** **Al Shuhaimi L, Henman M, McCallion P, McCarron M, O'Dwyer M** **<u>Al Shuhaimi L</u>, Maidment I, Henman M, Myint P, O'Connell J, Ryan C, McCallion P, McCarron M, O'Dwyer M.** **10-Year Outcomes of Anticholinergic Use Among Older Adults with Intellectual Disability: Findings from the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA)**	**Al Shuhaimi L:** Overall study design, conceptualization, had inputted Wave 4 medication data from the PIQs into the SPSS, double checked and cleaned the data. Reviewed and updated the list of medication included in ACB scale, Calculated the ACB score of Wave 4, recalculated the ACB score for Wave 1, prepared medication variables (polypharmacy and number of laxatives) for Wave 4, recreated polypharmacy variable for Wave 1, requested other variables needed for the study, conducted statistical tests, interpreted the results. Wrote first manuscripts of the paper, submitted the manuscripts to the *Intellectual Disability Research Journal* for publication, amended comments from co-authors and editorial team from the journal. **Henman M:** Contributed to overall study design and concept, involved in statistical tests selection, model development, results interpretation, contributed to updating the list of medication in ACB scale, reviewed manuscripts of the paper and the chapter, contributed to journal selection and management of co-authors and journal team revisions. **Maidment I:** Contributed to overall study design and concept, reviewed manuscripts of the paper, contributed to updating the list of medication in ACB scale, results interpretation. **Myint P:** Contributed to overall study design and concept, reviewed manuscripts of the paper, contribute to results interpretation. **O'Connell J:** Contributed to ACB calculation, reviewed manuscripts of the paper. **Ryan C:** Contributed to overall study design, involved in statistical tests selection, model development, results interpretation and reviewed manuscripts of the paper.

	McCallion P: Contributed to overall study design and concept, reviewed manuscripts of the paper, contributed to journal selection and involve in management of co-authors comments. **McCarron M:** Contributed to overall study design and concept, reviewed manuscripts of the paper, contributed to journal selection and involve in management of co-authors comments. **O'Dwyer M:** Contributed to overall study design and concept, involved in statistical tests selection, model development, calculated Wave 1 ACB score, provided polypharmacy variable for Wave 1, contributed to results interpretation, contributed to updating the list of medication in ACB scale, reviewed manuscripts of the paper and the chapter, contributed to journal selection and management of co-authors and journal team revisions.
Chapter 4: **Prescriber's view on anticholinergic deprescribing among older adults with intellectual disability: A qualitative study** **Al Shuhaimi L, Henman M, Ryan C, Gorman A, McCallion P, McCarron M, O'Dwyer M.** **Al Shuhaimi L, Henman M, McCallion P, McCarron M, O'Dwyer M.** **Prescriber's view on anticholinergic deprescribing among older adults with intellectual disability: A qualitative study protocol** **HRB Open Research 2021, 4:62**	**Al Shuhaimi L:** Overall study design, conceptualization, developed study protocol, Wrote first manuscripts of the study protocol and Chapter 4. Submitted the manuscripts of the study protocol to the *HRB Open Research Journal* for publication. Amended comments from co-authors and editorial team from the journal. Management of revisions from the peer reviewer. Wrote application for ethical approval and manage all comments. Advertise the study and sent invitation for stakeholders for recruitment of participants. Conducted and transcribed all interviews, developed data collection documents, cleaned the data, developed analytical framework, anonymised data, coded all transcripts, analysed data. **Henman M:** Contributed to overall study design and concept, reviewed the study protocol and the chapter, review application for ethical approval and contribute to management of comments, contributed to journal selection for the study protocol and involve in management of co-authors comments. Reviewed the analytical framework and chapter 4.

	Ryan C: Contributed to overall study design and concept, reviewed the topic guide and the chapter. **Gorman A:** Involved in the development of the analytical framework, coded all transcripts, contributed to data analysis, reviewed first draft of the chapter. **McCallion P:** Contributed to overall study design and concept, reviewed manuscripts of the study protocol and chapter 4, contributed to journal selection and involve in management of co-authors comments. **McCarron M:** Contributed to overall study design and concept, reviewed manuscripts of the study protocol and chapter 4, contributed to journal selection and involve in management of co-authors comments. **O'Dwyer M:** Contributed to overall study design and concept, reviewed the study protocol and the chapter, review application for ethical approval and contribute to management of comments, contributed to journal selection for the study protocol and involve in management of co-authors comments. Reviewed the analytical framework and chapter 4.

Appendix 2.2-1: Databases Search Methodology

PubMed Search Strategy:

Concept 1:

1. Mesh search : Anticholinergic :
    a. Cholinergic antagonists
    b. Cholinergic antagonists [pharmacological action]
2. Add to search builder with OR : "Cholinergic Antagonists" [Pharmacological Action] OR "Cholinergic Antagonists"[Mesh]
3. Search PubMed
4. Advance search
5. Search Keywords of anticholinergic: 'anticholinergic Burden' OR 'anticholinergic exposure' OR 'anticholinergic' OR 'cholinergic antagonist' OR 'antimuscarinic drugs' OR ' muscarinic antagonist' OR ' anticholinergic' OR ' anticholinergic agent' OR ' antimuscarinic' OR ' antimuscarinic agent' OR 'cholinergic blocking agent' OR 'acetylcholine antagonist' OR 'cholinergic receptor antagonist' OR 'cholinergic antagonists' OR 'cholinolytics'. Add with OR
6. Search

Concept 2:

1. Long-term exposure:
    a. Toxicity tests, chronic
    b. Clinical Trial, Phase III [Publication type]
2. Add to search builder with OR : "Toxicity Tests, Chronic"[Mesh] OR "Clinical Trial, Phase III" [Publication Type]
3. Search PubMed
4. Advance
5. Search Keywords: 'chronic use' OR 'long-term use' OR ' ≥ 3 months'. Add with OR
6. Search

Concept 3:

1. Intellectual Disability:
    a. Intellectual Disability
    b. Persons with Mental Disability
2. Add to search builder with OR: "Intellectual Disability"[Mesh] OR "Persons with Mental Disabilities"[Mesh]
3. Search PubMed
4. Advance
5. Search Keywords: 'cognitive impairment' OR 'intellectual disabilities' OR 'learning disabilities' OR 'developmental disabilities' OR 'mentally disabled persons' OR 'handicap' OR 'Down Syndrome' OR 'mental retardation' OR ' intellectual development disorders' OR 'psychosocial mental retardation' OR 'mental deficiency' OR 'mentally disabled' OR 'mentally handicapped' OR 'persons with intellectual disability' OR 'mentally retarded'

6. Add to query box with OR
7. Search

Concept 4:

1. Adverse drug reaction Mesh search:
    a. Drug-Related Side effect and adverse reactions
    b. Anticholinergic: anticholinergic syndrome
2. Add to search builder with OR: ("Drug-Related Side Effects and Adverse Reactions"[Mesh]) OR "Anticholinergic Syndrome"[Mesh]
3. Search PubMed
4. Search keywords: 'adverse effect' OR 'drug toxicity' OR 'adverse outcomes' OR 'side effects' OR 'drug related side effects' and 'adverse reactions' OR 'side effects of drugs' OR 'drug side effects' OR 'adverse drug reactions' OR 'adverse drug event' OR 'anticholinergic toxicity' OR 'anticholinergic effect' OR 'anticholinergic syndrome' OR 'peripheral anticholinergic syndrome' OR 'central anticholinergic syndrome' OR 'anticholinergic toxicity' OR 'anticholinergic effect' OR 'cognitive function' OR 'cognitive disorder' OR 'cognitive impairment' OR ' dementia' OR 'delirium' OR 'physical function' OR ' physical activity' OR 'frailty' OR 'falls' OR 'accidental falls' OR 'hip fracture' OR 'mortality' OR 'death' OR 'constipation' OR 'urinary incontinence'
5. Add to query box with OR
6. Search

Then:

- Combine Mesh search and Keywords search for each concept with 'OR'
- Combine all concept search together with 'AND'
- Refine the results with limitation : English, age

CINAHL and APA PsycINFO Search strategy:

1. Searching: CINAHL Ultimate, MEDLINE, APA PsycINFO
2. Advance search

S1 : DE "Cholinergic Blocking Drugs" OR DE "Atropine" OR DE "Benactyzine" OR DE "Levodopa" OR DE "Nicotine" OR DE "Orphenadrine" OR DE "Scopolamine" OR DE "Trihexyphenidyl"

S2 : 'Anticholinergic Burden' OR 'anticholinergic exposure' OR 'Anticholinergic ' OR 'Cholinergic antagonist' OR 'antimuscarinic drugs' OR ' muscarinic antagonist' OR ' anticholinergic' OR ' anticholinergic agent' OR ' antimuscarinic' OR ' antimuscarinic agent'

S3 : DE "Cognitive Impairment"

S4: Cognitive impairment' OR ' intellectual disabilities' OR ' learning disabilities' OR ' developmental disabilities' OR 'mentally disabled persons' OR 'handicap' OR ' Down Syndrome'

S5: DE "Side Effects (Drug)"

S6: ‘adverse effect’ OR ‘drug toxicity’ OR ‘adverse outcomes’ OR ‘ side effects’ OR ‘anticholinergic toxicity’ OR ‘anticholinergic effect’ ‘Cognitive function’ OR ‘ cognitive disorder’ OR ‘ cognitive impairment’ OR ‘ dementia’ OR ‘delirium’ OR ‘physical function’ OR ‘ physical activity’ OR ‘frailty’ OR ‘falls’ OR ‘accidental falls’ OR ‘hip fracture’ OR ‘mortality’ OR ‘death’ OR ‘constipation’ OR ‘ urinary incontinence’
S7: S1 OR S2
S8: S3 OR S4
S9: S5 OR S6
S10: S7 AND S8 AND S9
Limiters: Publication Year: 1970-2021; English language; Age Groups: Thirties (30-39 yrs), Middle Age (40-64 yrs), Aged (65 yrs & older), Very Old (85 yrs & older)

Cochrane Library Search Strategy:

#1. MeSH descriptor: anticholinergic: explode all trees
#2. ‘anticholinergic Burden’ OR ‘anticholinergic exposure’ OR ‘anticholinergic’ OR ‘cholinergic antagonist’ OR ‘antimuscarinic drugs’ OR ‘ muscarinic antagonist’ OR ‘ anticholinergic’ OR ‘ anticholinergic agent’ OR ‘ antimuscarinic’ OR ‘ antimuscarinic agent’ OR ‘cholinergic blocking agent’ OR ‘acetylcholine antagonist’ OR ‘cholinergic receptor antagonist’ OR ‘cholinergic antagonists’ OR ‘cholinolytics’.
#3. #1 OR #2
#4. MeSH descriptor: Long-term exposure: explode all trees
#5. ‘chronic use’ OR ‘long-term use’ OR ‘ ≥ 3 months’.
#6. #3 OR #4
#7. MeSH descriptor: Cognitive Impairment: explode all trees
#8. Cognitive impairment’ OR ‘ intellectual disabilities’ OR ‘ learning disabilities’ OR ‘ developmental disabilities’ OR ‘mentally disabled persons’ OR ‘handicap’ OR ‘ Down Syndrome’
#9. #7 OR #8
#10. Mesh descriptor: Side Effects (Drug): explode all trees
#11. ‘adverse effect’ OR ‘drug toxicity’ OR ‘adverse outcomes’ OR ‘ side effects’ OR ‘anticholinergic toxicity’ OR ‘anticholinergic effect’ ‘Cognitive function’ OR ‘ cognitive disorder’ OR ‘ cognitive impairment’ OR ‘ dementia’ OR ‘delirium’ OR ‘physical function’ OR ‘ physical activity’ OR ‘frailty’ OR ‘falls’ OR ‘accidental falls’ OR ‘hip fracture’ OR ‘mortality’ OR ‘death’ OR ‘constipation’ OR ‘ urinary incontinence’
#12. #10 OR #11
#13. #3 AND #6 AND #9 AND #12

Embase and MEDLINE Search Strategy:

#1. 'cholinergic receptor blocking agent'/exp OR 'cholinergic receptor blocking agent'
#2. 'anticholinergic burden' OR 'anticholinergic exposure' OR 'anticholinergic' OR 'cholinergic antagonist' OR 'antimuscarinic drugs' OR 'muscarinic antagonist' OR

'anticholinergics' OR 'anticholinergic agent' OR 'antimuscarinic' OR 'antimuscarinic agent' OR 'cholinergic blocking agent' OR 'acetylcholine antagonist' OR 'cholinergic receptor antagonist' OR 'cholinergic antagonists' OR 'cholinolytics'
#3. 'intellectual impairment'
#4. 'cognitive impairment' OR 'intellectual disabilities' OR 'learning disabilities' OR 'developmental disabilities' OR 'mentally disabled persons' OR 'handicap' OR 'down syndrome' OR 'mental retardation' OR 'intellectual development disorders' OR 'psychosocial mental retardation' OR 'mental deficiency' OR 'mentally disabled' OR 'mentally handicapped' OR 'persons with intellectual disability' OR 'mentally retarded'
#5. 'adverse drug reaction'
#6. 'adverse effect' OR 'drug toxicity' OR 'adverse outcomes' OR 'side effects' OR 'drug related side effects' OR 'adverse reactions' OR 'side effects of drugs' OR 'drug side effects' OR 'adverse drug reactions' OR 'adverse drug event' OR 'anticholinergic toxicity' OR 'anticholinergic effect' OR 'anticholinergic syndrome' OR 'peripheral anticholinergic syndrome' OR 'central anticholinergic syndrome' OR 'cognitive function' OR 'cognitive disorder' OR 'cognitive impairment' OR dementia OR delirium OR 'physical function' OR 'physical activity' OR frailty OR falls OR 'accidental falls' OR 'hip fracture' OR mortality OR death OR constipation OR 'urinary incontinence'
#7. 'long term care'
#8. 'chronic use' OR 'long-term use' OR '≥ 3 months'
#9. #1 OR #2
#10. #3 OR #4
#11. #5 OR #6
#12. #7 OR #8
#13. #9 AND #10 AND #11 AND #12
#13 AND ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim) AND ([embase]/lim OR [medline]/lim) AND [english]/lim

Science Direct:

Advanced Search: ‘Anticholinergic’ AND 'Intellectual disability' AND 'Adverse drug reaction' AND 'long term use'

Appendix 2.2-2: Data Extraction Framework

Table 3.2: Data Extraction Framework	
Bibliography: 1. Title 2. Authors 3. Journal 4. Year of publication 5. Country 6. Aim and objectives	
Design and setting: **Study Population:** • Targeted population • Sample size • Age groups • Sex • Ethnic • Place of residence **Length of study:** **Reported outcomes:** **Tools used for assessing:** • Anticholinergic burden • Adverse-effect	
Results:	
Conclusion:	
Implication:	

Appendix 3.3-1: IDS-TILDA Wave 1 and Wave 4 Ethical Approval

THE UNIVERSITY OF DUBLIN
TRINITY COLLEGE

SCHOOL OF MEDICINE
FACULTY OF HEALTH SCIENCES

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School Administrator
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Prof. Mary McCarron
School of Nursing and Midwifery,
Trinity College Dublin,
24 D'Olier Street, Dublin 2

10th July, 2008

Study Title: An Intellectual Disability Supplement to the Irish Longituddinal Study on Ageing (TILDA)

Dear Prof. McCarron,

Further to the meeting of the Faculty of Health Sciences Research Ethics Committee on 27th May 2008, I am pleased to inform you that the above project has been approved without further audit.

Yours sincerely,

Dr. Orla Sheils
Chairperson
Faculty of Health Sciences Ethics Committee

Appendix 3.3-1: IDS-TILDA Wave 1 and Wave 4 Ethical Approval

Coláiste na Tríonóide, Baile Átha Cliath
Trinity College Dublin
Ollscoil Átha Cliath | The University of Dublin

IDS-TILDA,
School of Nursing & Midwifery,
Trinity College,
2 Clare Street,
Dublin 2

23rd January 2019

Ref: 181210

Title of Study: An Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (hereafter IDS-TILDA)

Dear Prof McCarron,

Further to a meeting of the Faculty of Health Sciences Ethics Committee held in December 2018. We are pleased to inform you that the above project has ethical approval to proceed.

As a researcher you must ensure that you comply with other relevant regulations, including DATA PROTECTION and HEALTH AND SAFETY.

Yours sincerely,

pp Brian Brown
Prof. Brian O'Connell
Chairperson
Faculty Research Ethics Committee

Dámh na nEolaíochtaí Sláinte
Foirgneamh na Ceimice,
Coláiste na Tríonóide,
Ollscoil Átha Cliath,
Baile Átha Cliath 2, Éire.

Faculty of Health Sciences
Chemistry Building,
Trinity College Dublin,
The University of Dublin,
Dublin 2, Ireland.

www.healthsciences.tcd.ie

Appendix 3.3-2: PIQ Medication Data Collection Templet

Name of Medication		Dosage Strength	Frequency	Route	Date first Prescribed
1.					
2.					
3.					
4.					
5.					
6.					
7.					
8.					
9.					
10.					
11.					
12.					
13.					
14.					
15.					
16.					

Appendix 3.3-3: SPSS Medication Data Collection Templet

PIN	Person Input	Medication Data Available	Medication_1	ATC-1	Dose_1	Frequency_1	More Inofr_1	Med-2

Appendix 3.3-4: The Original ACB Scale Established at Wave 1

Table 5-1 Anticholinergic Medications Reported in Study and ACB Scores

ACB Category 3 (Definite)		*ACB Category 2 (Definite)*		*ACB Category 1 (Possible)*	
Antipsychotics	**Antihistamines**	**Antipsychotics**	**Antipsychotics**	**Cardiac Therapies**	**Respiratory Drugs**
Olanzapine	Chlorpheniramine	Zuclopentixol *	Risperidone	Atenolol	Ipatropium *
Chlorpromazine	Promethazine		Haloperidol	Furosemide	Tiotropium *
Quetiapine	Hydroxyzine		Aripiprazole	Nifedipine	Theophylline
Trifluoroperazine			Fluphenazine *	Warfarin	
Pericyazine*			Flupentixol *	Dipyrimidole	
			Sulpride *	Metoprolol	
			Amisulpride*	Captopril	
			Benperidol *	Digoxin	
				Isosorbide	
				Doxazosin*	
				Bendroflumethiazide *	
				Hydrochlorothiazide *	
Antidepressants	**Gastrointestinal preparations**	**Antiepileptics**	**Antidepressants**	**Gastrointestinal preparations**	**Coricosteroids, for systemic use**
Paroxetine	Scopolamine	Carbamazepine	Escitalopram*	Loperamide	Prednisolone
Trimipramine	Atropine		Citalopram *	Prochlorperazine *	
Amitriptyline			Mirtazepine*	Ranitidine	
Clomipramine			Venlafaxine	Mebeverine *	
Doxepin			Trazadone	Alverine	
				Colchicine	
			Anxiolytics		
		Analgesics	Alprazolam	**Muscle Relaxant**	
		Nefopam	Diazepam (oral)	Baclofen *	

Appendix 3.3-4: The Original ACB Scale Established at Wave 1

Table 5-1 Anticholinergic Medications Reported in Study and ACB Scores (Cont.d)

ACB Category 3		*ACB Category 2*		*ACB Category 1*	
Anticholinergics *Biperidin** *Procyclidine** *Benzatropine*	***Urologicals/antispasmodics*** *Tolterodine* *Solifenacin* *Oxybutynin* *Festolterädine*	**Muscle Relaxants** Tizinadine*		**Analgesics** Codeine	**Antihistamines** Cetirizine Desloratidine Loratidine Levocetirizine Alimemazine Cinnarizine*

** Added by consensus*

All other medicines listed in the ACB scale but not reported in the dataset:

ACB 1: Asenapine, Chlortalidone, Clidinium, Clorazepate, Disopyramide, Fentanyl, Flavoxamine, Hydralazine, Iloperidone, Paliperidone, Quinidine, Triamterine

ACB 2: Amantadine, Belladonna, Cyclobenatpine, Cyproheptadine, Loxatpine, Meperidine, Methotrimeprazine, Molindone, Oxcarbamazeptine, Pimozide

ACB 3: Amoxatpine, Brompheniramine, Carbinoxamine, Clemastine, Clozatpine, Darifenacin, Desipramine, Dicylomine, Dimenhydrinate, Diphenhydramine, Flavoxate, Meclizine, Methocarbamol, Nortriptyline, Orphenadrine, Perphenazine, Propanthetine, Propiverine, Tribexyphenidyl, Trosopium

Appendix 3.3-5: Updated ACB Scale List of Medication

	Anticholinergic Cognitive Burden Scale Inventory and Scores INN	ATC Code	ACB Score
1	Atenolol	C07AB03, C07CB03	1
2	Alimemazine	R06AD01	1
3	Alprazolam	N05BA12	1
4	Alverine	A03AX08	1
5	Amantadine	N04BB01	2
6	Amisulpride *	N05AL05	1
7	Amitriptyline	N06AA09	3
8	Amoxapine	N06AA17	3
9	Aripiprazole	N05AX12	1
10	Asenapine	N05AH05	1
11	Atropine	S01FA01	3
12	Baclofen *	M03BX01	1
13	Belladonna	A03BA04, A03CB02, A06AB30	2
14	Bendroflumethiazide *	C03AA01, C03AB01	1
15	Benperidol	N05AD07	1
16	Benzatropine	N04AC01	3
17	Biperiden *	N04AA02	3
18	Brompheniramine	R06AB01 , R06AB51	3
19	Butyl-scopolamine	A03BB01	3
20	Captopril	C09AA01	1
21	Carbamazepine	N03AF01	2
22	Carbinoxamine	R06AA08	3
23	Cetirizine	R06AE07	1
24	Chlorphenamine	R06AB04	3
25	Chlorpromazine	N05AA01	3
26	Chlortalidone	C03BA04	1
27	Cimetidine	A02BA01	1
28	Cinnarizine *	N07CA02	1
29	Citalopram *	N06AB04	1
30	Clemastine	R06AA04 , R06AA54	3
31	Clidinium	A03CA02	1
32	Clomipramine	N06AA04	3
33	Clorazepate	N05BA05	1
34	Clozapine	N05AH02	3
35	Codeine	R05DA04, N02AJ06	1
36	Colchicine	M04AC01	1

37	Cyclobenzaprine	M03BX08	2
38	Cyproheptadine	R06AX02	2
39	Darifenacin	G04BD10	3
40	Desipramine	N06AA01	3
41	Desloratadine	R06AX27	1
42	Diazepam (oral)	N05BA01	1
43	Dicycloverine (Dicyclomine)	A03AA07	3
44	Digoxin	C01AA05	1
45	Dimenhydrinate (in combination with cyclizine)	N07CA52 , R06AA11	3
46	Diphenhydramine	R06AA02, R06AA52	3
47	Dipyridamole	B01AC07	1
48	Disopyramide	C01BA03	1
49	Dosulepin **	N06AA16	3
50	Doxazosin *	C02CA04	1
51	Doxepin	N06AA12	3
52	Escitalopram *	N06AB10	1
53	Fentanyl	N02AB03	1
54	Fesoterodine **	G04BD11	3
55	Flavoxate	G04BD02	3
56	Flupentixol *	N05AF01	1
57	Fluphenazine *	N05AB02	1
58	Fluvoxamine	N06AB08	1
59	Furosemide	C03CA01, C03EB01 , C03CB01	1
60	Haloperidol	N05AD01	1
61	Hydralazine	C02DB02	1
62	Hydrochlorothiazide *	C03EA01, C03EA01,C03AB03, C03AX01	1
63	Hydroxyzine	N05BB01	3
64	Iloperidone **	N05AX14	1
65	Ipratropium *	R03BB01	1
66	Isosorbide mononitrate	C01DA14	1
67	Levocetirizine	R06AE09	1
68	Levomepromazine (Methotrimeprazine)	N05AA02	2
69	Lofepramine **	N06AA07	3
70	Loperamide	A07DA03	1
71	Loratadine	R06AX13	1
72	Loxapine	N05AH01	2
73	Mebeverine *	A03AA04	1
74	Meclozin **	R06AE05	3

75	Meperidine /Pethidine	N02AB02	2
76	Methocarbamol	M03BA03, M03BA53, M03BA73	3
77	Metoprolol	C07AB02	1
78	Mirtazapine *	N06AX11	1
79	Molindone	N05AE02	2
80	Morphine **	N02AA01	1
81	Nefopam	N02BG06	2
82	Nifedipine	C08CA05	1
83	Nortriptyline	N06AA10	3
84	Olanzapine	N05AH03	3
85	Orphenadrine	N04AB02	3
86	Oxcarbazepine	N03AF02	2
87	Oxybutynin	G04BD04	3
88	Oxycodone **	N02AA05	1
89	Paliperidone	N05AX13	1
90	Paroxetine	N06AB05	3
91	Pericyazine *	N05AC01	3
92	Perphenazine	N05AB03	3
93	Pimozide	N05AG02	2
94	Prednisolone	H02AB06 , A07EA01, R01AD02, R01AD52	1
95	Prochlorperazine *	N05AB04	1
96	Procyclidine *	N04AA04	3
97	Promazine	N05AA03	3
98	Promethazine	R06AD02	3
99	Propantheline	A03AB05 , A03CA34	3
100	Propiverine	G04BD06	3
101	Quetiapine	N05AH04	3
102	Quinidine	C01BA01 , C01BA51, C01BA71	1
103	Ranitidine	A02BA02	1
104	Risperidone	N05AX08	1
105	Scopolamine	A04AD01	3
106	Solifenacin	G04BD08	3
107	Sulpiride *	N05AL01	1
108	Theophylline	R03DA04	1
109	Tiotropium *	R03BB04	1
110	Tizanidine *	M03BX02	2
111	Tolterodine	G04BD07	3

112	Trazodone	N06AX05	1
113	Triamterine	C03DB02	1
114	Trifluoperazine	N05AB06	3
115	Trihexyphenidyl	N04AA01	3
116	Trimipramine	N06AA06	3
117	Trospium **	G04BD09	3
118	Venlafaxine	N06AX16	1
119	Warfarin	B01AA03	1
120	Ziprasidone **	N05AE04	1
121	Zuclopenthixol *	N05AF05	2

* added by consensus to Wave 1

** New Medication included in Wave 4 compared to wave 1

Appendix 3.3-6: Categories included in Barthel Index in Wave 4

	Wave 1	Wave 4
Mobility	Please indicate the level of difficulty, if any, you have with walking 100 yards	Please indicate the level of difficulty, if any, you have with walking 100 yards
	No difficulty, some difficulty, a lot of difficulty, cannot do at all	No difficulty, some difficulty, a lot of difficulty, cannot do at all
Stairs	Please indicate the level of difficulty, if any, you have with climbing one flight of stairs without resting.	Please indicate the level of difficulty, if any, you have with climbing one flight of stairs without resting.
	No difficulty, some difficulty, a lot of difficulty, cannot do at all	No difficulty, some difficulty, a lot of difficulty, cannot do at all
Dressing	Please indicate the level of difficulty, if any, you have with dressing, including putting on shoes and socks.	Please indicate the level of difficulty, if any, you have with dressing.
	No difficulty, some difficulty, a lot of difficulty, cannot do at all	No difficulty, some difficulty, a lot of difficulty, cannot do at all
Bathing	Please indicate the level of difficulty, if any, you have with bathing or showering	Please indicate the level of difficulty, if any, you have with bathing or showering
	No difficulty, some difficulty, a lot of difficulty, cannot do at all	No difficulty, some difficulty, a lot of difficulty, cannot do at all
Grooming	Please indicate the level of difficulty, if any, you have with cleaning your teeth/taking care of your dentures	What best describes the physical help you get from someone else to clean your teeth?
	No difficulty, some difficulty, a lot of difficulty, cannot do at all	Without help, with a little help, with a lot of help, do not clean teeth, no teeth to clean
Feeding	Please indicate the level of difficulty, if any, you have with eating such as cutting up your food, use of utensils, drinking from a cup/glass etc?	Please indicate the level of difficulty, if any, you have with eating.
	No difficulty, some difficulty, a lot of difficulty, cannot do at all	No difficulty, some difficulty, a lot of difficulty, cannot do at all
Transfer	Please indicate the level of difficulty, if any, you have with getting in or out of bed.	Please indicate the level of difficulty, if any, you have with: bed – in and out.
	No difficulty, some difficulty, a lot of difficulty, cannot do at all	No difficulty, some difficulty, a lot of difficulty, cannot do at all
Toileting	Please indicate the level of difficulty, if any, you have with using the toilet, including getting up or down.	Please indicate the level of difficulty, if any, you have with using the toilet.

	No difficulty, some difficulty, a lot of difficulty, cannot do at all	No difficulty, some difficulty, a lot of difficulty, cannot do at all
Bladder continence	During the last 12 months, have you lost any amount of urine beyond your control? Did this happen more than once during a 1-month period?	During the last 12 months, have you lost any amount of urine beyond your control? Did this happen more than once during a 1- month period?
	Yes & yes, yes & no, no	Yes & yes, yes & no, no
Bowel continence	During the last 12 months, have you lost any amount of faeces beyond your control? Did this happen more than once during a 1-month period?	During the last 12 months, have you lost any amount of faeces beyond your control? Did this happen more than once during a 1- month period?
	Yes & yes, yes & no, no	Yes & yes, yes & no, no

Appendix 3.4-1 Adverse effects reported at Wave 4 associated with ACB scores at Wave 1 (n = 487)

	Falls	**Mental Conditions**	**Dementia Or Alzheimer OR N06D**	**Barthel Index**
	OD, 99% Cl, P-value	OD, 99% Cl, P-value	OD, 99% Cl, P-value	OD, 99% Cl, P-value
Wave 1 Total ACB Score				
0 (Ref)	1	1	1	1
1 – 4	1.51 (0.86,2.64), 0.15	**6.60(3.69,11.77), <0.001**	**0.39(0.15,0.97), 0.042**	0.95(0.48,1.86),0.88
5 +	**1.86 (1.03,3.38), 0.04**	**17.38(8.97,33.61), <0.001**	**0.21(0.07,0.64), 0.006**	0.87(0.37,2.01),0.74
Wave 1 Non- Anticholinergics Polypharmacy				
No (Ref)	1	1	1	1
Yes	1.30(0.81,2.08), 0.27	1.41(0.85,2.35), 0.18	1.05(0.42,2.61), 0.920	**5.66(2.06,15.57), <0.001**
Age				
55-64 (Ref)	1	1	1	1
60+	1.17(0.75,1.82), 0.50	0.88(0.55,1.42), 0.60	1.49(0.66, 3.37), 0.34	**2.08(1.10,3.93),0.023**
Sex				
Male (Ref)	1	1	1	1
Female	1.10(0.72,1.69), 0.66	0.69(0.43,1.09), 0.11	0.74(0.40,1.93), 0.74	1.13(0.63,2.02)0.68
Level of ID				
Mild (Ref)	1	1	1	1
Moderate	1.47(0.84,2.56), 0.18	0.78(0.44,1.39), 0.40	1.98(0.63,6.27), 0.24	1.39(0.74,2.62),0.30
Severe	0.94(0.49,1.83), 0.87	0.61(0.31,1.20), 0.15	1.10(0.28,4.39), 0.89	**6.32(1.95,20.55), 0.002**
Residence				
Independent (Ref)	1	1	1	1
Community Group home	0.96(0.45,2.06), 0.92	**2.38(1.07,5.31), 0.03**	4.05(0.49,33.50), 0.19	**2.43(1.17,5.03), 0.017**
Residential Care	1.14(0.50,2.57), 0.75	**3.21(1.35,7.60),0.008**	5.24(0.59,46.50), 0.14	**6.88(2.48,19.07), <0.001**
Epilepsy:				
No	1	1	1	1
Yes	1.18(0.75,1.85), 0.47	**0.57(0.35,0.93), 0.02**	1.87(0.78,4.44), 0.16	1.35(0.67,2.73), 0.40

Appendix 3.4-1 Continue

	Constipation	**Laxatives use**	**Edentulous**
	OD, 99% Cl, P-value	OD, 99% Cl, P-value	OD, 99% Cl, P-value
Wave 1 Total ACB Score			
0 (Ref)	1	1	1
1 – 4	1.09(0.65,1.85), 0.73	1.18(0.68,2.02), 0.55	0.81(0.44,1.48), 0.49
5 +	1.05(0.60,1.85), 0.86	1.42(0.79,2.53), 0.24	1.24(0.67,2.30), 0.49
Wave 1 Non- Anticholinergics Polypharmacy			
No (Ref)	1	1	1
Yes	**1.93(1.21,3.07), 0.005**	**2.04(1.26,3.29), 0.004**	1.57(0.95,2.60), 0.079
Age			
55-64 (Ref)	1	1	1
65+	1.51(0.97,2.34), 0.06	1.12(0.71, 1.77), 0.62	**4.24(2.65,6.77), <0.001**
Sex			
Male (Ref)	1	1	1
Female	1.43(0.94,2.17), 0.09	1.45(0.94, 2.24), 0.09	0.94(0.59,1.50), 0.80
Level of ID			
Mild (Ref)	1	1	1
Moderate	**1.73(1.01,2.94),0.04**	**2.60(1.48, 4.58), <0.001**	1.65(0.89,3.05), 0.11
Severe	**2.48(1.33,4.65),0.004**	**2.78(1.45, 5.32), 0.002**	1.46(0.71,2.99), 0.30
Residence			
Independent (Ref)	1	1	1
Community Group home	2.13(0.99,4.59),0.05	**6.65(2.25,19.68), <0.001**	0.99(0.42,2.36), 0.99
Residential Care	**2.61(1.16,5.90), 0.02**	**10.79(3.52, 33.06), <.001**	1.21(0.49,3.00), 0.68
Epilepsy			
No	1	1	1
Yes	**1.79 (1.14,2.79), 0.01**	1.39(0.87,2.22), 0.16	1.46(0.74, 1.97), 0.46

Appendix 4.1-1 Theoretical Domain Framework Version 2

Domain	Constructs
1. Knowledge (An awareness of the existence of something)	Knowledge (including knowledge of condition /scientific rationale) Procedural knowledge Knowledge of task environment
2. Skills(An ability or proficiency acquired through practice)	Skills Skills development Competence Ability Interpersonal skills Practice Skill assessment
3. Social/Professional Role and Identity (A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting)	Professional identity Professional role Social identity Identity Professional boundaries Professional confidence Group identity Leadership Organisational commitment
4. Beliefs about Capabilities (Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use)	Self-confidence Perceived competence Self-efficacy Perceived behavioural control Beliefs Self-esteem Empowerment Professional confidence
5. Optimism (The confidence that things will happen for the best or that desired goals will be attained)	Optimism Pessimism Unrealistic optimism Identity
6. Beliefs about Consequences (Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation)	Beliefs Outcome expectancies Characteristics of outcome expectancies Anticipated regret Consequents
7. Reinforcement (Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus)	Rewards (proximal / distal, valued / not valued, probable / improbable) Incentives Punishment Consequents Reinforcement Contingencies Sanctions
8. Intentions (A conscious decision to perform a behaviour or a resolve to act in a certain way)	Stability of intentions Stages of change model Transtheoretical model and stages of change
9. Goals(Mental representations of outcomes or end states that an individual wants to achieve)	Goals (distal / proximal) Goal priority Goal / target setting

	Goals (autonomous / controlled) Action planning Implementation intention
10. Memory, Attention and Decision Processes (The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives)	Memory Attention Attention control Decision making Cognitive overload / tiredness
11. Environmental Context and Resources (Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour)	Environmental stressors Resources / material resources Organisational culture /climate Salient events / critical incidents Person x environment interaction Barriers and facilitators
12. Social influences (Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours)	Social pressure Social norms Group conformity Social comparisons Group norms Social support Power Intergroup conflict Alienation Group identity Modelling
13. Emotion (A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event)	Fear Anxiety Affect Stress Depression Positive / negative affect Burn-out
14. Behavioural Regulation (Anything aimed at managing or changing objectively observed or measured actions)	Self-monitoring Breaking habit Action planning

Appendix 4.3-1: Topic Guide and the Supplement material

Introduction:

Hello, I would like to thank you for taking part in this study. My name is Lamya and I am PhD student in the School of Pharmacy at Trinity College Dublin.

Can I just confirm that your name is :XXX and your email address is XXX? Thank you

This study will explore your perspectives on prescribing medication with anticholinergic activity for older adults with intellectual disability and your role as a prescriber in managing high anticholinergic exposure for this group of population. For the purpose of this study, we are defining older adults as 40 years or older. The interview will last for approximately 40-50 minutes and everything you say will be confidential and will not be identified at any stage of the study. Additionally, you can stop the interview or the recording at any time. During the interview, remember that there are no right or wrong answers so please give honest responses to the questions.

Before we begin, I would like to check if you:

- read and understood the Participant Information Leaflet *[wait for reply]*
- Are you happy for the interview to be recorded *[wait for reply]*
- have any questions before commencing the interview *[wait for reply]*
- I can see you have returned the consent form to me completed, signed and dated.

If you are ready, we can start the interview now and the recording will start. [wait for response] [Start Recording]

General Questions:

We will start with some general question about you and your work.

1. Can you tell me about your current role? How long you have been practicing this profession?
2. Can you tell me about the care you provide for patients with intellectual disability?
    a. About Your approach to prescribing for older adults with intellectual disability

<u>Prescribing for older adults with intellectual disability:</u>

Now I would like to move on to discuss general prescribing practice for older adults with intellectual disability:

4. Do you find prescribing for people with intellectual disability challenging?

4.1. Can you tell me more about that?

4.2. Can you explain what you find challenging?

4.2.1. Prompt: does the number of medications, communication barriers, multimorbidity or carer involvement challenging?

4.3. Can you explain how easy or challenging is to review medicines for people with intellectual disability?

5. Could you describe the factors that are important to consider when prescribing for an older adults with intellectual disability?

5.1. Patient factors (e.g. quality of life, benefit vs adverse-effect, complexity, multimorbidity, polypharmacy)

5.2. Prescriber factors (e.g. past experience, prescribing habits and personal preferences)

5.3. Other factors (e.g. patient/relative/carer preferences, other prescribers, residential care area)

Thank you for that. Now I would like to move on to discuss anticholinergic burden in relation to prescribing to older adults (as a reminder: those 40 years and over) with intellectual disability.

<u>Anticholinergic Burden and tools used to measure it:</u>

We will start with some terms that are used in this study. Can you tell me:

6. What is your understanding of the term 'Anticholinergic Burden'?

6.1. Prompt: can you tell me if you use any tools to help you when you are prescribing anticholinergic medications?

6.2. Can you tell me how you used it?

For the purpose of this study, and to compare our results with published literature, we are defining Anticholinergic Burden as the "cumulative effect of taking one or more medications with anticholinergic activity"

We define anticholinergic activity as drugs that possess anticholinergic properties despite not being responsible for their therapeutic effect such as antipsychotic, and tricyclic antidepressant. I will share a document illustrates the background of Anticholinergic Cognitive Burden (ACB) scale which is used for the purpose of this study and a list of the most frequently prescribed medication with anticholinergic activity for

older adults with intellectual disability in Ireland. Additionally, the document illustrates a bar-chart on Anticholinergic Exposure among cohort of older adults with intellectual disability aged 40 and above. The data gathered from participants involved in Wave 1 and 4 with 9-10 years between the two waves within the Intellectual Disability Supplement to the Irish longitudinal on Aging (IDS-TILDA).

Indications and Adverse effect of Anticholinergic medication:

Now, we will go through some questions on indications and adverse effects of anticholinergic medication.

7. What are the common medications you prescribe in your specialty area that have/might have anticholinergic activity?
8. What are the indications for prescribing these medications in your professional area? What are the benefits achieved from using them?
9. What kind of possible short-term and long-term adverse effects associated with its use? can you remember a patient experienced anticholinergic adverse effect in your practice ?
10. If you observe a functioning decline (both physical and cognitive function) with your patient, How do you deal with it?

10.1. Do you consider this decline as a normal aging process? Or do you consider it could be an adverse effect associated high Anticholinergic exposures?

10.1.1. if yes, do you check the total anticholinergic exposure to rule out drug-induced adverse-effects? How?

Managing High Anticholinergic Exposure

Thank you for that. We will now move on to the next section of the interview. Here, I would like to discuss with you about managing high anticholinergic burden in older adults with intellectual disability.

11. Generally, before initiating any new treatment, do you consider anticholinergic burden before prescribing for patients with intellectual disability?

11.1. If no, why not?

11.1.1. Prompt: time, knowledge, identity (somebody's else role)

11.2. If yes, in case of identifying high exposure,

11.2.1. what would you consider as "high exposure"? can you tell me what would you do about it? Does that concern you or does it have an impact on your next action?

11.2.2. If yes, would you take action on it? (e.g. Do you conduct a medication review? Do you look for an alternative with lower AC activity? Try the possibility of de-prescribing?

11.3. Is there anything that you would consider to be beyond your responsibility in ensuring that patients receive the appropriate anticholinergic exposure?

11.4. Do you think reducing anticholinergic burden is a good thing?

11.4.1. What do you think are the benefits of addressing the high anticholinergic exposure or burden among older adults with intellectual disability?

11.5. Could you tell me about your confidence in identifying inappropriate or high anticholinergic exposure and deprescribing of anticholinergic medication by reducing/stopping or finding alternative with lower/no anticholinergic activity?

12. How do you approach reducing or stopping medicines in older adults with intellectual disability, to achieve lower anticholinergic exposure?

12.1. Prompts: Do they find stopping medicines challenging? Why?

12.2. How frequently do they tend to stop medicines?

12.3. What factors do they consider when making those decisions?

12.4. When do deprescribing decisions usually occur in your setting area? Is it at regular visits/ appointments/ during admissions/ at hospital discharge?

12.5. Who would influence your decision about whether to modify prescribed medication with anticholinergic activity? individuals/groups/agencies/carer? Anyone else

13. In case of identified high anticholinergic burden score, controlled symptoms and no adverse effects: explain how would you deal with this case?

Prompt: Would you consider lowering the exposure if possible? Or as long as the patient's symptoms are controlled and no adverse effect , you don't change it?

13.1. How important is it to you to try and change/reduce/stop medication that being prescribed for an older adult with intellectual disability who is unnecessarily exposed to high anticholinergic burden?

Now, I'd like to ask you some general questions around potential barriers and facilitators for deprescribing of anticholinergic in older adults with intellectual disability, again there are no right or wrong answers

14. Could you talk to me about barriers and facilitators in addressing the anticholinergic burden among older adults with intellectual disability?

Prompt:

14.1. What kind of **knowledge and skills** do you have as prescriber that would help you to make the necessary change to reduce anticholinergic exposure in people with intellectual disability?

14.2. What would help you to access the necessary **knowledge**? would you suggest any educational or training on the topic?

14.3. What resources might help when you encounter older adults with intellectual disability exposing to high anticholinergic burden? Updated measuring tool and deprescribing guidelines?

14.4. Have you ever felt afraid to stop or reduce the dose to reduce the anticholinergic burden for people with intellectual disability?

14.5. Having decided the best modification needed to reduce anticholinergic exposure from a clinical point of view, are there any circumstances which might prevent you from taking this action?

<u>Pharmacist Involvements in process of prescribing/ deprescribing:</u>

Now we have reached the final part of this interview and we will talk about pharmacist involvement in the process of prescribing and deprescribing for older adults with intellectual disability.

15. Can you explain how could the pharmacist contribute to the process of prescribing and deprescribing for older adults with intellectual disability?
16. Is there a pharmacist involved in the process of medication review where you are currently working? Please describe the role of the pharmacist if so.
17. What are the possible benefits and challenges in involving a pharmacist in this process?

So that brings us to the end of the interview. Before you go, is there anything else you would like to add to help reduce anticholinergic exposure in older adults with intellectual disability?

Anything you would like to say about the topic guide?

Ok, so that's the end. Thank you for giving me your time and discussing anticholinergic burden with me. [stop recording]

Would you like to review the transcript once it's ready ?

Supplements:

1. Anticholinergic Cognitive Burden Tool and List of Medication with anticholinergic activity
   Anticholinergic Cognitive Burden (ACB) scale is used to computes a total score of drugs to determine individual anticholinergic burden.
   Medicines assigned to scores based on Anticholinergic (AC) negative effect on cognition:
   - Drugs with no AC activity scored 0
   - Drugs with AC activity or in vitro affinity to M receptors but with no known clinically cognitive effects are score 1
   - Drugs with established and relevant AC effects are scored 2 or 3 based on ability to cross blood-brain barrier and reported delirium

   Total anticholinergic burden was defined as the sum of ACB scores for all medications taken.

Anticholinergic Cognitive Burden Scale Inventory and Scores INN	**ACB Score**
Carbamazepine	2
Risperidone	1
Olanzapine	3
Biperiden	3
Escitalopram	1
Loperamide	1
Diazepam (oral)	1
Quetiapine	3
Chlorpromazine	3
Cetirizine	1
Furosemide	1
Haloperidol	1
Mirtazapine	1
Scopolamine	3
Aripiprazole	1
Citalopram	1
Procyclidine	3
Alprazolam	1
Paroxetine	3
Venlafaxine	1
Desloratadine	1
Butyl-scopolamine	3
Codeine	1

Zuclopenthixol	2
Atenolol	1
Bendroflumethiazide	1
Levocetirizine	1
Prochlorperazine	1
Baclofen	1
Fesoterodine	3
Ipratropium	1
Oxybutynin	3
Promethazine	3
Theophylline	1
Tolterodine	3
Chlorphenamine	3
Diphenhydramine	3
Flupentixol	1
Mebeverine	1
Ranitidine	1
Tiotropium	1
Alverine	1
Atropine	3
Clomipramine	3
Doxazosin	1
Solifenacin	3
Trazodone	1
Trimipramine	3
Amitriptyline	3
Morphine	1
Oxcarbazepine	2
Prednisolone	1
Trifluoperazine	3
Warfarin	1
Benztropine	3
Cinnarizine	1
Digoxin	1
Dosulepin	3
Hydroxyzine	3
Lofepramine	3
Loratadine	1
Paliperidone	1
Amisulpride	1
Benperidol	1
Cimetidine	1

Clozapine	3
Cyproheptadine	2
Dicycloverine (Dicylcomine)	3
Isosorbide mononitrate	1
Metoprolol	1
Nifedipine	1
Pericyazine	3
Promazine	3
Sulpiride	1
Tizanidine	2
Ziprasidone	1

Appendix 4.3-2: Coding Framework

Prescriber's view on anticholinergic deprescribing among older adults with intellectual disability: A qualitative study protocol

Coding Scheme

	Coding categories/codes	Definition
1	**Demographics**	
1.1	Role	Data relating to the interviewee's job title
1.2	Length in job	How long has them been in this role?
1.3	Place of work	Data relating on the type and description of health services where they are working
2	**Experience of prescribing**	
2.1	Patient characteristics	Data relating to the level of ID of people who are coming to the service, their ability to communicate and availability of their medical history
2.2	Impact of family/carers	Data relating to the impact of family/ carers on prescribing
2.3	Residence	Data relating to the impact of residence type on prescribing
2.4	Other prescribers	Data relating to the impact of involvement of other prescriber on prescribing
2.5	Emotion of patient	Data relating to the impact of patient's emotion on prescribing
2.6	Appropriate prescribing	Data related to process of appropriate prescribing including deprescribing
2.7	Challenges in prescribing	Data related to any challenges in prescribing such as "difficult to diagnose", "Polypharmacy", "History" and "Multimorbidity".
2.8	Staff	Date related to staff impact on prescribing
2.9	Guidelines	Data related to guidelines used for prescribing
3	**Knowledge of ACB**	
3.1	Definition	Anticholinergic Burden definition
3.2	ACB tools/ scores	Knowledge and usage of ACB tool
3.3	Side effects	Knowledge on Anticholinergic side effects
3.4	Specific medication	Date relating to specific medication with anticholinergic activity and their adverse effects
3.5	Improve management of ACB	Data relating improving management of anticholinergic burden
4	**Any comparison to general population**	
4.1		Data relating to comparison with general population
	TDF domains *	
5	**Knowledge**	

5.1	Multi-morbidity	Data relating to interviewee's knowledge on the multimorbidity
5.2	Appropriate prescribing – polypharmacy, deprescribing	Data relating to interviewee's knowledge on appropriate prescribing, polypharmacy and deprescribing
5.3	Pharmacological	Data relating to interviewee's knowledge on amended Pharmacokinetics properties e.g. higher sensitivity to medication etc.
5.4	Prescriber knowledge on ACB, medication side effects, managing medication	Data relating to prescriber knowledge on anticholinergic medication, side effects and management of these medication.
5.5	Patient – medical history, medications	Data relating to interviewee's Knowledge of the medical conditions, specific patient characteristics and medication history of the patient (e.g. being on medication for longtime, inherited patients on medication, etc.)
5.6	Staff knowledge on ACB, medication side effects, managing medication	Data relating to staff knowledge on anticholinergic medication, side effects and management of these medication.
6	**Skills**	
6.1	Medication review and appropriate prescribing of anticholinergic medication	Data relating to the interviewee's medication review skills and appropriate prescribing of medication with anticholinergic activity
6.2	Deprescribing	Data relating to the interviewee's medication deprescribing skills
7	**Social/professional role and identity**	
7.1	Managing Medication including those from other prescribers	Data relating to interviewee's role in deprescribing and managing medication prescribed by others, including deprescribing.
7.2	Communicating with other prescribers/ healthcare professionals/ family/carer/ patient	Data relating to the interviewee's responsibility to contact other prescribers/ health care professionals with medication queries/concerns
7.3	Non-pharmacological treatment	Data relating to interviewee comfortability and or confidence to socially prescribe and provide non-pharmacological support (e.g., diet, social support groups etc.)
8	**Beliefs about capabilities**	
8.1	Identifying ACB	Data relating to interviewee's ability to identify anticholinergic medication and cumulative burden
8.2	Deprescribing incl medication from other prescribers	Data relating to interviewee's ability to deprescribe anticholinergic medication/ including those prescribed by others
9	**Optimism**	

9.1	Health record	Date relating to interviewee's optimism/pessimism regarding availability of centralized health record/ health record
9.2	Environment prescribing	Date relating to interviewee's optimism/pessimism regarding the impact of environment on their prescribing/or deprescribing (e.g. prescriber decrease the dose and staff got to other prescribers to increase it back)
9.3	Appropriate prescribing	Date relating to interviewee's optimism/pessimism regarding appropriate prescribing including deprescribing
10	**Beliefs about consequences**	
10.1	Potential impact of prescribing	Data relating to statements surrounding consequences of prescribing
10.2	Non-pharmacological treatment	Data relating to interviewee belief (or lack of) on potential impact of non-pharmacological support
10.3	Potential impact of deprescribing	Data relating to statements surrounding consequences of deprescribing
11	**Reinforcement**	
11.1		
12	**Intentions**	
12.1	Managing appropriate prescribing including deprescribing	Data relating to interviewee's intention to manage appropriate prescribing
13	**Goals**	
13.1		
14	**Memory, attention and decision processes**	
14.1	Appropriate prescribing	Data relating to interviewee's decision to manage appropriate prescribing
15	**Environmental context and resources**	
15.1	Residence	Data relating to the impact of residence on prescribing/ deprescribing of medication
15.2	Staff	Data relating to the impact of staff related factors on prescribing/ deprescribing of medication
15.3	Carer	Data relating to the impact of carer related factors on prescribing/ deprescribing of medication
15.4	Family support	Data relating to the impact of family support on prescribing/ deprescribing of medication
15.5	Multidisciplinary team	Data relating to the impact of multidisciplinary team on prescribing/ deprescribing of medication

15.6	Guidelines for appropriate prescribing	Data relating to the availability of guidelines for appropriate prescribing
15.7	Tools and guidelines for ACB	Data relating to availability of guidelines or tools for appropriate prescribing of anticholinergics
15.8	Education – for prescribers, for people who support people with ID / patient	Data relating to the impact of educating the prescriber, professional healthcare providers, carer and family for appropriate prescribing of anticholinergics
15.9	Supports – access to tests, small doses	Data relating to availability and access to medical support including tests, ECGs, small doses, social and financial support
15.10	Involvement of /communication with other prescribers/health care providers	Data relating to availability of communication channels with other prescribers
15.11	Workload	Data relating to the impact of workload on appropriate prescribing/ medication review/ deprescribing
16	**Social influences**	
16.1	Staff including health care profession	Data relating to the influences of staff to deprescribe
16.2	Family / carer	Data relating to the influences of family to deprescribe
16.3	Patient	Data relating to the influences of patient to deprescribe
17	**Emotion**	
17.1	Medication review – changing prescriptions from other prescribers	Data relating to prescriber emotions/feeling related to modify medications prescribed by other prescribers
17.2	Impact of deprescribing	Data relating to prescriber emotions/feeling about the impact of deprescribing
17.3	Healthcare workers/support team to people with ID and the patient	Data relating to emotions/feeling of carer and support of people with ID regarding deprescribing
18	**Behavioural regulation**	
18.1	Audits	Data relating on conducting audit related to medication with anticholinergics and deprescribing
18.2	Change in normal prescribing practice	Data relating to change in prescribing practice
19	**Pharmacist involvement**	
19.1	Calculate ACB score	Data relating to pharmacist involvement/support on calculating ACB score
19.2	Pharmacist Knowledge on ACB	Data relating to unique knowledge/skills of pharmacist including educating

		staff/family/carers on anticholinergics medication use
19.3	Pharmacists conduct medication review	Data relating to pharmacist involvement on conducting medication review to enhance medicine use
19.4	Pharmacist in workplace	Data relating to availability of pharmacist in workplace
19.5	Community pharmacist	Date relating to Community pharmacist involvement in providing medicinal care and support
20	**General comments**	
20.1	Useful general comments	

Appendix 4.3-3: Consolidated Criteria for Reporting Qualitative Studies (COREQ): 32-item checklist

No	Item	Guide questions/description
Domain 1: Research team and reflexivity **Personal Characteristics**		
1. Interviewer/facilitator	Which author/s conducted the interview or focus group?	LA
2. Credentials	What were the researcher's credentials?	PhD student
3. Occupation	What was their occupation at the time of the study?	NA
4. Gender	Was the researcher male or female?	female
5. Experience and training	What experience or training did the researcher have?	The PhD student had completed ' Research integrity and impact in an open scholarship era' which deepen the student's knowledge on ethical research, data collection, data storage and ownership of data.
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	The research team did not have any contact with participants prior to obtaining informed consent. Researchers had no professional or ongoing relationship with the participants.
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.*g. personal goals, reasons for doing the research*	Participants were aware that this was a research project part of LA's PhD study.
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. *Bias, assumptions, reasons and interests in the research topic*	NA
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? *e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis*	TDF was the grounded theory to identify barrier and facilitators of anticholinergic deprescribing among older adults with intellectual disability from a prescriber's perspectives. The research team conducted framework analysis.
Participant selection		

10. Sampling	How were participants selected? *e.g. purposive, convenience, consecutive, snowball*	Study was advertised through IDS-TILDA Twitter account. Invitation email was sent for stakeholders through a gatekeeper and snowball methodology was applied.
11. Method of approach	How were participants approached? e.*g. face-to-face, telephone, mail, email*	Online through Zoom
12. Sample size	How many participants were in the study?	10 participants
13. Non-participation	How many people refused to participate or dropped out? Reasons?	NA
Setting		
14. Setting of data collection	Where was the data collected? e.*g. home, clinic, workplace*	online
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	No
16. Description of sample	What are the important characteristics of the sample? *e.g. demographic data, date*	Role, length in the role and gender
Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	See “Method of Chapter 4”
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	There were no repeat interviews with the same participants.
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	All interviews were audio recorded with permission of participants.
20. Field notes	Were field notes made during and/or after the interview or focus group?	Researchers made field notes during the interviews
21. Duration	What was the duration of the interviews or focus group?	See “Results in Chapter 4”
22. Data saturation	Was data saturation discussed?	
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	Participants were asked if they were interested to check the transcripts and no transcripts returned to participants.
Domain 3: analysis and findings		
Data analysis		

24. Number of data coders	How many data coders coded the data?	Two (LA and AG)
25. Description of the coding tree	Did authors provide a description of the coding tree?	The Developed coding framework provided in Appendix 4.3-2.
26. Derivation of themes	Were themes identified in advance or derived from the data?	Derived from a three randomly selected transcripts
27. Software	What software, if applicable, was used to manage the data?	Excel
28. Participant checking	Did participants provide feedback on the findings?	No
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.*g. participant number*	Key findings of this study were supported with selected quotes in text.
30. Data and findings consistent	Was there consistency between the data presented and the findings?	All findings were derived from the data and all themes are supported by quotes.
31. Clarity of major themes	Were major themes clearly presented in the findings?	Major themes were derived from the data and are clearly defined by a paragraph title.
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Themes that are only described by few participants are also discussed in the results section of this study.

Appendix 4.3-4: DPRA Approval

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

December 03rd 2022

Study Title: Prescriber's View on Anticholinergic Deprescribing Among Older Adults with Intellectual Disability: A qualitative Study

Dear Lamya

I have reviewed the Data Protection Risk Assessment in respect of this research study and am satisfied that the intended processing of personal data for the purposes of the study as described therein is in compliance with data protection legislation, specifically the EU General Data Protection Regulation 2016 (GDPR), Data Protection Acts 1988-2018 and Health Research Regulations 2018.

Please note that the completion of a risk assessment is not a one-time exercise, but a continual process. If at any stage there are changes to the processing envisaged by this assessment please contact me.

Be advised that the Trinity College Data Protection Office may carry out a review to assess if the processing is being performed in accordance with the information provided.

I wish you the very best of luck with your research.

Sincerely,

John Eustace

Data Protection Officer
Secretary's Office
Trinity College Dublin
Dublin 2, Ireland

Appendix 4.3-5: Ethical Approval

Coláiste na Tríonóide, Baile Átha Cliath
Trinity College Dublin
Ollscoil Átha Cliath | The University of Dublin

Lamya Al Shuhaimi,
School of Pharmacy and Pharmaceutical Sciences,
Trinity College,
Dublin 2.

Ref. 2022-12-07

12 May 2023

Dear Lamya,

Re: Prescriber's View on Anticholinergic Deprescribing Among Older Adults with Intellectual Disability: A Qualitative Study

I am pleased to inform you that the above project now has approval from the School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee (SoPPS REC).

You are reminded that any significant deviation from the research description in the application requires approval from the SoPPS REC before implementation.

Please also note the reporting requirements outlined on the Committee's website (http://pharmacy.tcd.ie/research/SoPPS_REC.php), in particular the need for:

- An immediate report in writing (by email to pharmacy.ethics@tcd.ie) of any serious or unexpected adverse events, or other unforeseen events that might affect the benefit/risk ratio as outlined in the application.
- Annual reports (report form on the Committee's website).
- An end of project report (report form on the Committee's website).

Please quote the reference number 2022-12-07 in any further correspondence.

We wish you success with your research.

Yours sincerely,

Sheila Ryder,
Chairperson,
School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee.

Sheila Ryder
Chairperson
Research Ethics Committee
School of Pharmacy and Pharmaceutical Sciences

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Tel. +353 1 896 2786
E-mail pharmacy.ethics@tcd.ie
http://pharmacy.tcd.ie/research/SoPPS_REC.php

Síle Ní Mharcaigh
Cathaoirleach
Coiste um Eitic Thaighde
Scoil na Cógaisíochta agus na nEolaíochtaí Cogaisíochta

Foirgneamh Panoz, An Taobh Thoir 4/5,
Coláiste na Tríonóide,
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