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Prevalence, Patterns and Factors Associated with Multiple Medicines Use in an Ageing Population with Intellectual Disability in Ireland

A thesis submitted to the University of Dublin, Trinity College,

for the Degree of Doctor of Philosophy

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Declaration

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Summary

Background

The provision of rational and appropriate pharmacotherapy to older people with intellectual disabilities (ID) poses significant challenges due to the complexities of conditions being treated, the increased risks of adverse drug reactions, and the challenges associated with communication and atypical disease presentation. People with intellectual disabilities are often prescribed medicines to treat a variety of chronic conditions and are likely to be exposed to polypharmacy. Life expectancy for people with ID is increasing in Ireland and elsewhere. Little research has been carried out to date assessing patterns of multiple medicine use in an ageing population with ID.

Objectives

The thesis aimed to describe the patterns of, and the factors associated with exposure to multiple medicine use, by individuals aged 40 years and over with ID in Ireland, by; (i) examination of the prevalence of and factors associated with polypharmacy and excessive polypharmacy ,(ii) determining the prevalence of psychotropic drug use and psychotropic polypharmacy, including psychopharmacological combinations and associated healthcare utilisation, (iii) determining the anticholinergic burden of the population with ID, using a scale that captures total anticholinergic burden and to assess the association between higher anticholinergic burden and demographic and clinical variables, (iv) examination of patterns of antiepileptic utilisation in people with ID who report a doctor's diagnosis of epilepsy in the context of associated healthcare utilisation and control of seizures, with a view to informing health policy, and promoting safe and effective use of medicines in this population.

Methods

Objectives 1-4 are retrospective cross-sectional studies using the 2009/2010 IDS-TILDA study; a representative population of people with intellectual disabilities aged 40 years and over. Medication data (self-report/ proxy-report), and associated clinical and demographic data were drawn from Wave 1 of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA), a study on the ageing of 753 nationally representative people with an ID ≥40 years randomly selected from the National Intellectual Disability Database . Medication data was available for 736 participants (98%).

Results

Polypharmacy (use of 5-9 medicines), and excessive polypharmacy (10+ medicines) were prevalent among older people with ID; over half recorded over five medicines, and over one-fifth were exposed to ten or more medicines. Multivariate analysis revealed that living in residential settings, and having a mental health or neurological disease were most strongly associated with both polypharmacy and excessive polypharmacy, but age and gender had no significant effect. The use of multiple agents within the three most frequently utilised medication classes (the antipsychotics, antiepileptics and laxatives) further contributed to multiple medicines use.

Findings indicated that use of psychotropic agents was commonplace; 4 in 10 were exposed to psychotropic polypharmacy, and a further 2 in 10 used one psychotropic. Multivariate regression analysis revealed that those reporting mental health conditions, sleep problems, and those living in residential settings were likely to be exposed to psychotropic polypharmacy, while those with a diagnosis of epilepsy were significantly less likely, and age and gender had no significant effect. There were high levels of use antipsychotics, anxiolytics, antidepressants, and use complex interclass regimens.

The study findings revealed that 7 in 10 were exposed to medications with possible or definite anticholinergic properties (ACB $\geq$1), and almost 3 in 10 had an ACB score of 5+. A multivariate regression model revealed that older age and having a mental health condition was associated with higher anticholinergic burden, but gender, level of ID or place of residence had no significant effect Antipsychotics accounted for over one-third of the cumulative anticholinergic burden in the sample.

There was a high prevalence of epilepsy in the study population; 30.7%, with 9 in 10 of those with a diagnosis of epilepsy reporting use of one or more antiepileptics on a regular basis.. The study identified that 5 in 10 of those reporting antiepileptic use for epilepsy consumed two or more AEDs. There were 63 different polytherapy regimens recorded, reflecting the complexity of prescribing in the population. Despite the use of multiple AEDs, over half had seizures in the previous two years, and there was high utilization of all levels of health services.

Conclusions

Use of multiple medicines is commonplace for older people with ID. Living in residential settings and having a mental health condition was associated with polypharmacy, psychotropic use and higher anticholinergic burden. As people with ID continue to transition into community settings, education and interventions are needed to ensure appropriate provision of pharmacotherapy to this population needed in primary care. Older people with ID need regular multidisciplinary review of their medication regimens, to assess the benefits and risks of multiple medicines, and to avoid inappropriate prescribing.

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Table of Abbreviations

AC	Anticholinergic
ACB	Anticholinergic Burden
ASD	Autistic Spectrum Disorder
ANOVA	Analysis of Variance
ACOVE	Assessing Care of Vulnerable Elders
AED	Antiepileptic Drug
ATC	Anatomical Therapeutic Classification
BBB	Blood Brain Barrier
BNF	British National Formulary
BMI	Body Mass Index
CAPI	Computer Assisted Personal Interview
CI	Confidence Intervals
CNS	Central Nervous System
DD	Developmental Disability
DS	Down Syndrome
EPP	Excessive Polypharmacy
FDR	False Discovery Rate
FWER	Familywise Error Rate
GMS	General Medical Scheme
GP	General Practitioner
HRB	Health Research Board
HSE	Health Service Executive
ICD-10-DCR	International Classification of Disease, 10th revision, Diagnostic Criteria for Research
ID	Intellectual Disability
IDS-TILDA	Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing
IQ	Intelligence Quotient
INN	International Non-Proprietary Name
IV	Independent Variable
LD	Learning Disability
Mcg	Micrograms
Mg	Milligrams

MMSE	Mini-Mental State Examination
MR	Mental Retardation
NHS	National Health Service
NIDD	National Intellectual Disability Database
NSAID	Non-steroidal Anti-inflammatory
OR	Odds Ratio
PIN	Personal Identification Number
PIP	Potentially Inappropriate Prescribing
PIQ	Pre-Interview Questionnaire
PP	Polypharmacy
PPI	Proton Pump Inhibitor
PUD	Peptic Ulcer Disease
RCT	Randomised Controlled Trial
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SPSS	Statistical Package for Social Sciences
SUDEP	Sudden Unexpected Death in Epilepsy
SSRI	Selective Serotonin Reuptake Inhibitor
STOPP / START	Screening Tool of Older Person's Prescriptions /Screening Tool to Alert doctors to Right Treatment
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TCA	Tricyclic Antidepressant
TIA	Transient Ischemic Attack
TDD	Total Daily Dose
TILDA	The Irish Longitudinal Study on Ageing
UK	United Kingdom
VE	Vulnerable Elder
VIF	Variance Inflation Factor
WHO	World Health Organisation

Presentations and Publications

Oral presentations at National and International Conferences:

- 4th IASSID (International Association for the Scientific Study of Intellectual and Developmental Disabilities) European Congress, Vienna, Austria, July 2014
  "Prevalence and Predictors of Multiple Medicines Use among an Ageing Population with Intellectual Disability in Ireland"

  Máire O'Dwyer, Jure Peklar, Anne Belton, Philip McCallion, Mary McCarron, Martin Henman

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- Máire O'Dwyer, Jure Peklar, Anne Belton, Ian Maidment, Philip McCallion, Mary McCarron, Martin Henman

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  "Prevalence and patterns of polypharmacy in an ageing population with intellectual disability in Ireland"

  Máire O'Dwyer, Jure Peklar, Philip McCallion, Mary McCarron, Martin Henman

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- Irish Gerontological Society , 62nd Annual and Scientific Meeting, Radisson, Galway, October 2014
  "Anticholinergic Burden with Older Adults with Intellectual Disability; Relationships with Multimorbidity and Adverse Effects"

  Máire O'Dwyer, Anne Belton, Jure Peklar, Ian Maidment, Mary McCarron, Philip McCallion, Martin Henman.

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Upcoming Oral Presentations

- International Association of Gerontology and Geriatrics, 8Th European Region Congress (IAGG-ER), Dublin 2015
  "Antipsychotics in Ageing People with Intellectual Disabilities: Prevalence and Associated Risks"
  Máire O'Dwyer, Jure Peklar, Anne Belton, Ali Burke, Niamh Mulryan, Philip McCallion, Mary McCarron, Martin Henman.

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Chapter 1. Introduction

1.1. Background

1.1.1. Intellectual Disability Definition

Intellectual disability is "a disability characterised by significant limitations in both intellectual functioning and in adaptive behaviour**,** which covers many everyday social and practical skills. This disability originates before the age of 18." (1). Intellectual Disability is the now the preferred term for a condition which is referred to as Mental Retardation in the United States, Developmental Disabilities in Canada, and Learning Disability in the United Kingdom (2).

The severity of Intellectual Disability (ID) is correlated with intelligence quotient (IQ) scores as follows; mild (50-55 to approx. 70), moderate (35-40 to 50-55), severe (20-25 to 35-40), and profound (below 20-25)(3). There are wide variations in both intellectual and adaptive functioning among people with ID, and hence their capacity to live and function independently varies (4, 5). There are various aetiologies of intellectual disability, including genetic (X-linked, other chromosomal), metabolic, teratogenic (congenital infections, chemical agents), central nervous system defects, other birth defects, neonatal, perinatal, causes that are multifactorial, and causes of no known aetiology (6, 7).

1.1.2. Disorder Characteristics

Intellectual disability consists of impairments in general mental abilities in an individual that impact on adaptive functions in three areas, or domains(3, 8). These domains determine how well a person is able to cope with everyday activities.

- The *conceptual domain* includes skills in language, writing, reading, maths, reasoning, memory and knowledge.
- The *social domain* refers to empathy, interpersonal communication skills, ability to make and retain friendships, interpersonal communication skills, and similar capacities.
- The *practical domain* consists of self-management in areas including personal care, money management, job responsibilities, recreation and organisation of work and school tasks.

Intellectual disability begins during the developmental period. The disorder is considered to be chronic, and it often co-occurs with other mental conditions such as depression, autism spectrum disorder, and attention-deficit/ hyperactivity disorder(8). Most people with severe or profound ID will show some evidence of damage to the Central Nervous System (CNS), and many will have additional physical or sensory handicap (9, 10). People with ID are a heterogeneous population, encompassing a broad range of cognitive-perceptual, social and communicative deficits (11).

1.1.3. Changes in Definition of Intellectual Disability

Changes in the definition of intellectual disability reflect the transition from a medical oriented approach to disability, where disability is regarded as a person-centred trait or "deficit", to a more ecological approach, where the disability is defined in the context of the nature of interaction between the person and his/her environment, and the supports needed by an individual to enhance or maximise this interaction(2, 12, 13).

This ecological approach is captured by the World Health Organisation (2001) International Classification of Functioning, Disability and Health by emphasising the impact of disability on the broader social context (2, 14). This change is further reflected in the 2013 Fifth Edition of the Diagnostics and Statistical Manual of Mental Disorders (DSM-V), where the diagnosis of intellectual disability (intellectual developmental disability) was revised from the DSM IV diagnosis of mental retardation(3, 8). The new DSM definition also included the parenthetical name "intellectual developmental disability" to reflect the cognitive capacity deficits that begin in the developmental period. The DSM-V emphasises that diagnosis of ID should now involve clinical assessment, along with standardised testing of IQ, with severity of impairment being based on adaptive function in addition to IQ score(3, 8).

1.1.4. Genetic Basis of Intellectual Disability

A sizeable proportion of intellectual disability is attributed to genetic abnormalities (such as the case in Down Syndrome or Fragile-X syndrome), but approximately 60% of cases have no known aetiology (7, 15). Most severe forms of ID are due to defects in specific genes, or chromosomal abnormalities(16). New technologies are being developed, such as whole genome sequencing which promises to increase the understanding of the aetiology of ID, by identifying genes and mechanisms that contribute to the development of ID(7, 16). There is great variety in the phenotype

in individuals with ID, not only in levels of IQs, but also other neurobehavioral and neurological mechanisms. For example, a substantial proportion of those with ID have been shown to meet the criteria for a diagnosis of autism, with Bryson and colleagues estimating that 28% of adolescents with ID had met the diagnostic criteria for autism(17). Treatment of ID with medications is symptom orientated and conservative.

1.2. Prevalence of Intellectual Disability in Ireland

In Ireland the National Intellectual Disability Database (NIDD), was established in 1995, and collects information on people with all levels of ID, eligible for, or receiving services in a full range of residential circumstances. (18, 19). In December 2009, there were 26,066 people registered on the NIDD, which represented a prevalence of 6.15 per 1,000 population(18). Prevalence of mild ID was 2.04 per 1,000, and the prevalence rate for moderate, severe or profound ID was established as 3.65 per 1, 000. However, the NIDD registers data only on those with an intellectual disability for whom specialised health services are being provided, or who, following a needs assessment, are considered to require specialized health services in the coming five years. Almost everyone with a moderate, severe or profound intellectual disability is expected to be included on the NIDD, as they are likely to be in receipt of or require intellectual disability services. As those with mild ID are less likely to require specialized services, the number of people on the NIDD with a mild intellectual disability may, however, be underestimated (18).The ratio of males to females on the NIDD database was 1.30 to 1, and there were more males at all levels of ID(18).

1.2.1. Life Expectancy and Ageing Demographics

In most developed countries, average life expectancy for people with intellectual disability is around 60 years (20). Improvements in health and social care in developed countries for people with intellectual disabilities, have resulted in increases in life expectancy in this population, leading to a large and growing cohort of older adults with intellectual disability (21). Increase in life expectancy has also been attributed to the corresponding increase in life span seen in the general population, the control of infectious disease, improved nutrition, increase in quality healthcare provision, advocacy and quality living environments (18, 22). For people with mild ID, who do not have significant medical comorbidities, life expectancy is now approaching that of

the general population (23). By 2020, the number of people with ID aged over 65 years is projected to double from estimates made in the 1990s(24).

In Ireland, an increase in the proportion of those with ID aged 35 years and older has been observed in each iteration of the National Intellectual Disability Database(NIDD) , from 37.9% in 1996, to 48.6% in 2009(18, 22). The total number with moderate, severe or profound ID has increased by 37% since the first census of Mental Handicap carried out in the Republic of Ireland in 1974. One of the other factors contributing to this increase, is the corresponding growth in the general population over the time period. By 2009, almost half of those with moderate, severe or profound ID were aged over 35 years(18). As this is a new phenomenon, attention has been drawn to the paucity of research, in particular longitudinal studies, and incidence studies for older people with ID (25), that are needed in order to identify the care needs of older people with ID, and the need for more health services as people age(18). Furthermore, in Ireland, while the majority of adults with ID live with family, as parents and caregivers age beyond care-giving capacity, it is likely that many with ID will outlive their carers, and additional residential and therapeutic supports will be required (18).

Despite increases in life expectancy for people with ID, disparities compared to the general population still exist. The Confidential Enquiry of Premature Deaths of People with Intellectual Disabilities (2013) in the UK, suggests that, on average, males with intellectual disabilities, die 13 years earlier compared to the population in England and Wales, and on average, females die 20 years earlier(26), and that many of these deaths may be avoidable. Contributors to avoidable and premature deaths for people with intellectual disabilities include care planning, adherence to the Mental Capacity Act, living in unsuitable accommodation, and unmet and unrecognised health needs. In Ireland, Lavin and colleagues have suggested that the mortality rate for people with ID may be 10-16 times higher than that of the general population (27).

1.3. Assessment of Health in People with ID

Accurate assessment and diagnosis of psychiatric disorders and other physical disorders in people with ID can prove particularly challenging. People with ID may be poor reporters of their own health, and in most cases the history of the present illness must be determined from caregivers or family members rather than the patient (28), with increasing difficulty with diagnostic accuracy as severity of ID increases. Mental

illness may present in an atypical manner in people with ID, for example, depression as self-injurious behaviours. Conversely, behaviours such a self-talk may be normal for people with ID, but may be mistakenly diagnosed as psychosis. In general, accuracy of diagnosis becomes increasingly challenging and complex, as severity of disability and communication impairments increase (11, 28, 29). Diagnostic overshadowing occurs when and emotional or behavioural problem is misattributed to LD itself, rather than a comorbid condition(28). There are also concerns with regard to the capacity of people with ID to give informed consent to treatment, and protection of their rights (30). There have been attempts to improve recognition of mental health disorders, with use of assessments such as the psychiatric assessment schedule for adults with developmental disability (PAS-ADD), and in the mini PAS-ADD. These tools are designed to assist professional carers to make informed decisions in relation to screening and referral of potential cases to mental health services(29). The term "*dual diagnosis*" refers to the "co-existence of the symptoms of both intellectual or developmental disabilities and mental health problems" (31).

The prevalence estimates of health conditions among adults with ID based on medical records and self-reports is often an underestimation(32). People with ID often have atypical disease presentation, and may be non-verbal or unable to accurately communicate symptoms, which means there may be undiagnosed or hidden health needs in the population. People with ID may also have poor bodily awareness, and a small number may have depressed pain responses (33, 34), which further compounds detection.

1.3.1. Health Status of People with ID

A large and growing body of research has identified disparities in health status for people with ID, compared to the general population. It has been estimated that people with ID have up to 2.5 times the health problems of the general population, and different patterns of morbidity (35-37). Furthermore, health needs for people with ID are often unmet and unrecognised, and poorer health status may often be avoidable (2, 26, 38, 39). Underlying causes and barriers to health may be multiple, complex, and inter-related (40). People with ID are also at greater risk of the development of secondary health conditions (41). Despite this need, persons with intellectual disability are often under-represented in healthcare and health related research (42). Article 25 of the United Nations (UN) Convention on the Rights of Persons with Disabilities

states that people with ID should enjoy "the highest attainable standard of health without discrimination on the basis of disability". (43)

Poorer health status in the ID population is thought to be multifactorial, and include genetic predisposition to certain diseases, social determinants such as less favourable circumstances and discrimination experienced by people with ID, inability to access some generic services and health screening, and residential circumstances that may promote unhealthy lifestyle choices, and inactivity (2, 39, 44, 45). Emerson has identified five key factors in the health equalities of people with ID (39, 46) *(figure 1-1).*

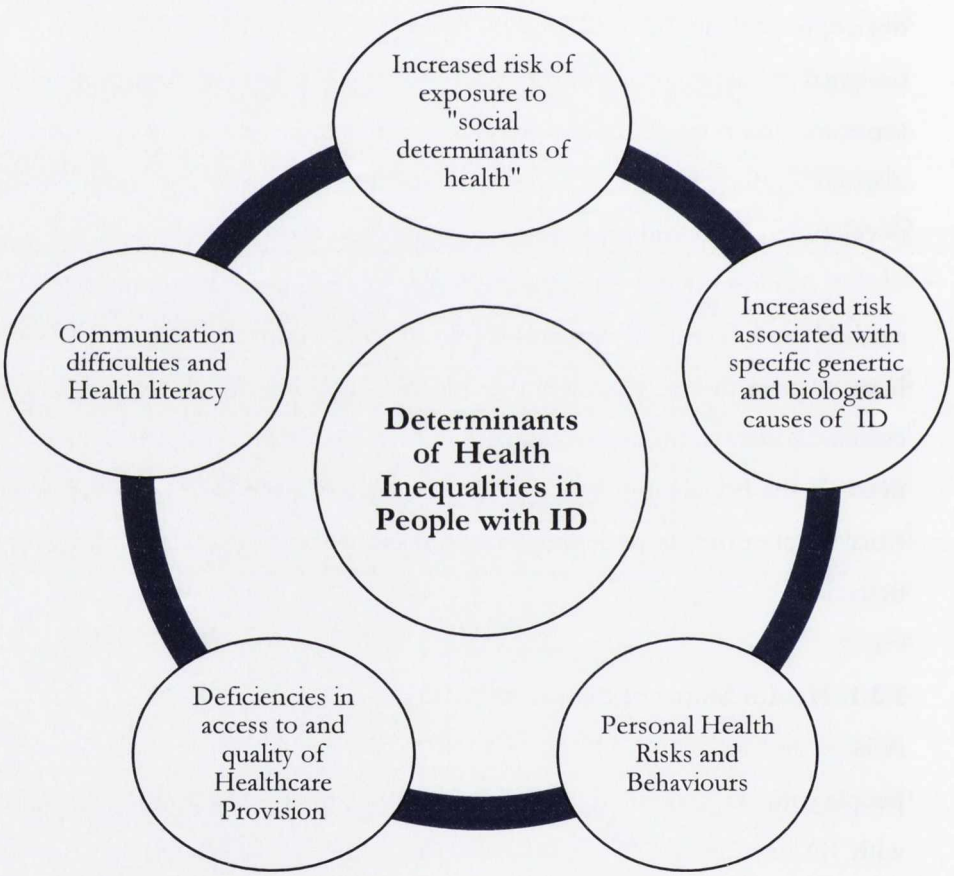

Figure 1-1 Determinants of Health Inequalities in People with ID(adapted from Emerson 2010) (39, 46)

Despite growing research, age specific differences in health of adults with ID, when compared to the general population remain poorly understood(32, 47). The European POMONOA II study examined age-specific differences in relation to

lifestyle and environmental factors, and the prevalence of medical conditions in people with ID. The study identified that rates of smoking and alcohol consumption were lower than that of the general population; over 60% had a sedentary lifestyle, and older people with ID had evidence of health disparities or inadequately managed preventable medical conditions (47).

1.3.2 Health Conditions Experienced by People with ID

People with ID may be exposed to a wide range of medical conditions that may affect a person's physical and/or mental health(41, 44). These conditions may be classified as either associated with the intellectual disability (primary), or as secondary health conditions(41)(*Table 1.1*). A number of syndromes are associated with specific health risks, for example , congenital heart disease is more prevalent among people with Down Syndrome or Williams syndrome (39, 48). People with moderate, severe or profound ID are more likely to die from congenital abnormalities, compared to the general population (49).

It is well recognised that co-morbidities are more common for people with ID, compared to the general population (44, 47, 50-52). Furthermore, people with ID, particularly as they age are likely to acquire further age-related disorders, have differing morbidity patterns and have multiple conditions or are "multimorbid" (53, 54). Older adults with ID may be particularly challenged as a result of premature ageing, age-related decline in health, increased dependency and decline in cognitive function, which may further reduce an individual with ID's ability to cope, adapt and maintain quality of life (21).

Table 1-1 Primary and Secondary Health Problems in People with ID (adapted from Van Schrojenstein Lantman-de Valk 2008) (41)

Associated	Sydrome Related	Secondary
• Epilepsy • Visual Problems • Mobility Problems, including cerebral Palsy • Mental Ill Health • Psychosis • Alzheimers Disease	• Hypgonadism • Congenital Heart Disease (Down Syndrome and William Sydrome)	• Obesity • Gatro-Oesophageal Reflux Disease (GORD) • Constipation • Fractures • Untreated Caries • Edentulous • Sexually Transmitted Diseases

1.4. Health Problems in People with ID

1.4.1. Mental Health Problems

Up until the 1980s in Ireland, and elsewhere, mental health problems were not recognised as occurring in people with intellectual disabilities, and outward manifestation of psychiatric problems or aggressive behaviours were assumed to be due to the intellectual disability(30, 55). For many years, professionals and researchers did not believe that mental health disorders could co-occur in the same person (56). Authors have argued that it in only since the early 1980s that mental health problems in people with ID began to receive attention (57). Therefore, most research in this area has taken place in the past 3.5 decades. It is now recognised however, that mental health problems are common in people with ID, and occur at a significantly higher prevalence than in the general population (58), with particularly common conditions being self-injurious behaviour, attention deficit hyperactivity disorder, anxiety, psychosis and depression(56) . Methodological differences have resulted in some inconsistencies in reported rates of prevalence of mental health conditions in people with ID, but a seminal longitudinal cohort study by Cooper and colleagues (2007) reported that 40.9% of 1023 adults with ID presented with some form of mental disorder, but when the ICD-10 DCR criteria were applied the rate dropped to 16.6%(58), with affective disorders being predominant (59). Using record linkage across health jurisdictions in Western Australia, Morgan and colleagues identified that almost a third of individuals with intellectual disability had concurrent psychiatric morbidity, and nearly 2% of people with a mental illness also had intellectual disability(6).

The aetiology of psychiatric disorders in people with ID is complex and multifactorial. Mental health problems and challenging behaviours are more prevalent in a number of syndromes associated with intellectual disability, including autism spectrum disorder, Rett syndrome, Fragile-X syndrome and Prader-Willi syndrome (48). Brain damage or dysfunction interact with other social or environmental factors, and increase the likelihood of mental illness in people with ID(29). Individuals with ID are more vulnerable to environmental factors that influence mental health, and are

less well able to adapt and to respond to change and features of their environment, and this may influence mental health. (55). Indeed, problems with mental health have been associated with life events in people with ID (55, 58).

In contrast to the general population, the prevalence of some mental health issues in people with ID has been shown to remain stable as people with ID age (21, 58, 60) . However, in Canada, prevalence of depression was found to be significantly higher among older adults with intellectual disabilities aged over 55, when compared to matched peers in the general population(61), whereas challenging behaviours may decrease with advancing age (60).

1.4.2. Behavioural Problems

The term *challenging behaviours* is an umbrella term for behaviours that include aggression, self-injury, overactivity, inappropriate sexual or social conduct, eating inappropriate objects(10), and has been defined as:

"Culturally abnormal behaviour(s) of such intensity, frequency, or duration that the physical safety of the person or others is likely to be placed in jeopardy, or behaviour which is likely to seriously limit use of or result in the person being denied access to ordinary community facilities"(62)

Best practice guidance in the UK jointly published by the Royal College of Psychiatrists, the British Psychological Society, and the Royal College of Speech and Language Therapists emphasis that the term "challenging behaviour" is not a specific diagnosis, but rather a descriptor of a range of behaviours that occur in specific contexts and have many possible causes(63).

Challenging behaviours places the health safety and welfare of the person, and the individuals and services that care for them in jeopardy (10). An individual with ID may display behaviour such as aggression in the absence of any form of psychiatric diagnosis, neurosis or personality disorder. It is also possible for an individual to present with a diagnosis of psychiatric disorder in the absence of any challenging behaviours. Furthermore, challenging behaviours and psychiatric disorders may co-exist and be inter-related (64). It has been estimated that 10-15% of people with ID exhibit challenging behaviours, with age-specific prevalence highest between the ages of 20 and 49 (39, 65-68). In Ireland, evidence suggests that over 3,000 people with ID (12% of those registered on the National Intellectual Disability Database) exhibit challenging behaviours (147), and that relatively small numbers of individuals present

with both a mental illness and challenging behaviours (55). It was reported that the prevalence of challenging behaviours in Ireland is higher among those living in residential settings, and the "Time To Move On From Congregated Settings" report indicated that 54% of those in congregated settings exhibited challenging behaviours(69).

Many causal factors have been attributed to disruptive behaviour, including social deprivation, male gender and less severe ID, while more severe ID and secondary disabilities has been associated with a range of emotional problems (including social difficulties and anxiety)(64, 70). Challenging behaviours have been shown to be affected by life events. Owen and colleagues identified that recent exposure to life events resulted in higher ratings of destructive or aggressive behaviours and/ or affective or neurotic disorders, as measured by the Psychiatric Assessment Schedule for Adults with Developmental Disability (PASS-AD) checklist(71). Dodd, upon review of the impact of bereavement on people with ID, concluded that this life event can have a negative effect on both psychiatric and behavioural functioning(72). If challenging behaviours are of extended severity, duration and intensity, they may have adverse effects on physical health (44).

1.4.3. Physical- Mental Health

Physical and mental health problems often co-exist in people with ID, and physical health problems are often related to poorer mental health (21, 44) Physical disorders may also be as a result of the side effects of psychotropic medicines, such as weight gain, and metabolic disturbances (73, 74). Furthermore, due to communication difficulties, people with ID may not be able to communicate somatic complaints and physical problems verbally, such as pain. Therefore, these physical problems may manifest as challenging behaviours in some individuals(44, 75).

1.5. Neurological

1.5.1. Epilepsy

Epilepsy is over-represented in the population with ID(28), with increasing prevalence as severity of ID increases. The prevalence of epilepsy in people with ID is high, with estimates of 14-44%, exceeding those observed in the general population, where estimates of 1.1% have been observed (76-79). Epilepsy represents a chronic, disabling condition that has a substantial impact on the quality of life(80, 81). The presence of a

presentation of atypical seizures, communication difficulties and mental health problems may complicate diagnosis and treatment of epilepsy in the population (44, 76, 82). Conversely, epilepsy and associated antiepileptic treatment may have a significant effect on the physical health of an individual, and the psychological wellbeing and may have a negative impact on quality of life (44, 81, 83, 84). Many people with ID suffer from epilepsy that is "refractory" to treatment, due to underlying abnormalities of the nervous system, and idiosyncratic responses to treatment (85, 86). People with epilepsy and ID have a significantly higher mortality rate, compared to those with ID alone(87, 88), due to sudden unexplained deaths (SUDEP), pneumonia, aspiration episodes(86, 88), and also in part due to the fact that epilepsy is positively associated with severity of ID (87).

1.5.2. Dementia

As a consequence of increased longevity now experienced by many people with ID, many are now vulnerable to cognitive decline and dementia, with adults with Down Syndrome being at especially high risk, as presence of trisomy 21 is an established risk factor for Alzheimer's disease(89, 90).

1.6. Constipation

Constipation is a common problem in people with ID; and is multifactorial; the neurological origin of ID has been suggested as a causative factor, some causes of ID such as Down Syndrome and Cerebral Palsy are associated with constipation, as has poor fluid intake, low fibre diet and inactivity (91-93). Constipation has also been correlated with use of drugs that are likely to be associated with constipation in this population, such as anticonvulsants, antipsychotics and benzodiazepines (93, 94). Constipation may often remain undetected and under-reported in this population(41). However, high levels of constipation and laxative use have been reported among people with ID living in institutional settings (94-96). Among a randomly selected adult population with ID living in an institution, 69.3% had constipation (94).

1.7. Deinstitutionalisation and its Historical Context in Ireland

Residential institutions for people with ID have a long history in Ireland and in many other countries (*Figure 1-2*). In Ireland, and in many other countries (including the USA, United Kingdom, and Sweden), there have been moves towards

"normalisation", person-centred living, community inclusion and deinstitutionalisation (97-99). The number of people with ID who reside in large institutions has been steadily decreasing in many countries such as England(99), the USA(100, 101), and Canada(102), while in Sweden no-one now resides in an institutional setting(103, 104). In some European countries such as Hungary, France, Romania and the Czech Republic, large numbers of people with ID still reside in large, poor quality congregated settings (104-106).

In Ireland, deinstitutionalisation is ongoing, but there still remains a substantial number of people in institutional care(69, 107). As of December 2009, among adults over 18 years on the NIDD (n=18038), 16% (2885) lived in residential centres, and a further 7.2% (1305) lived in other full time services (18). In the population, 1.1% resided in psychiatric hospitals. Almost half (49.3%) lived at home, a further 5.5% lived independently, and over one-fifth (21.5%) lived in community group homes (18). The "Time to Move on from Congregated Settings Report" established ,that approximately 4000 people lived in congregated settings (defined as ten or more people living together in 2011(69). When considering those living in congregated settings, people were typically middle aged; almost half were aged 40-60 years, and a further 20% were aged 60 and over. When compared with the overall population on the NIDD, those in congregated settings had higher severity of ID; 57% of those in congregated settings had severe or profound ID , compared to one-fifth of those on the NIDD (69). Concerns remain in Ireland that those who live in institutions are poorly connected to their communities (22, 108).

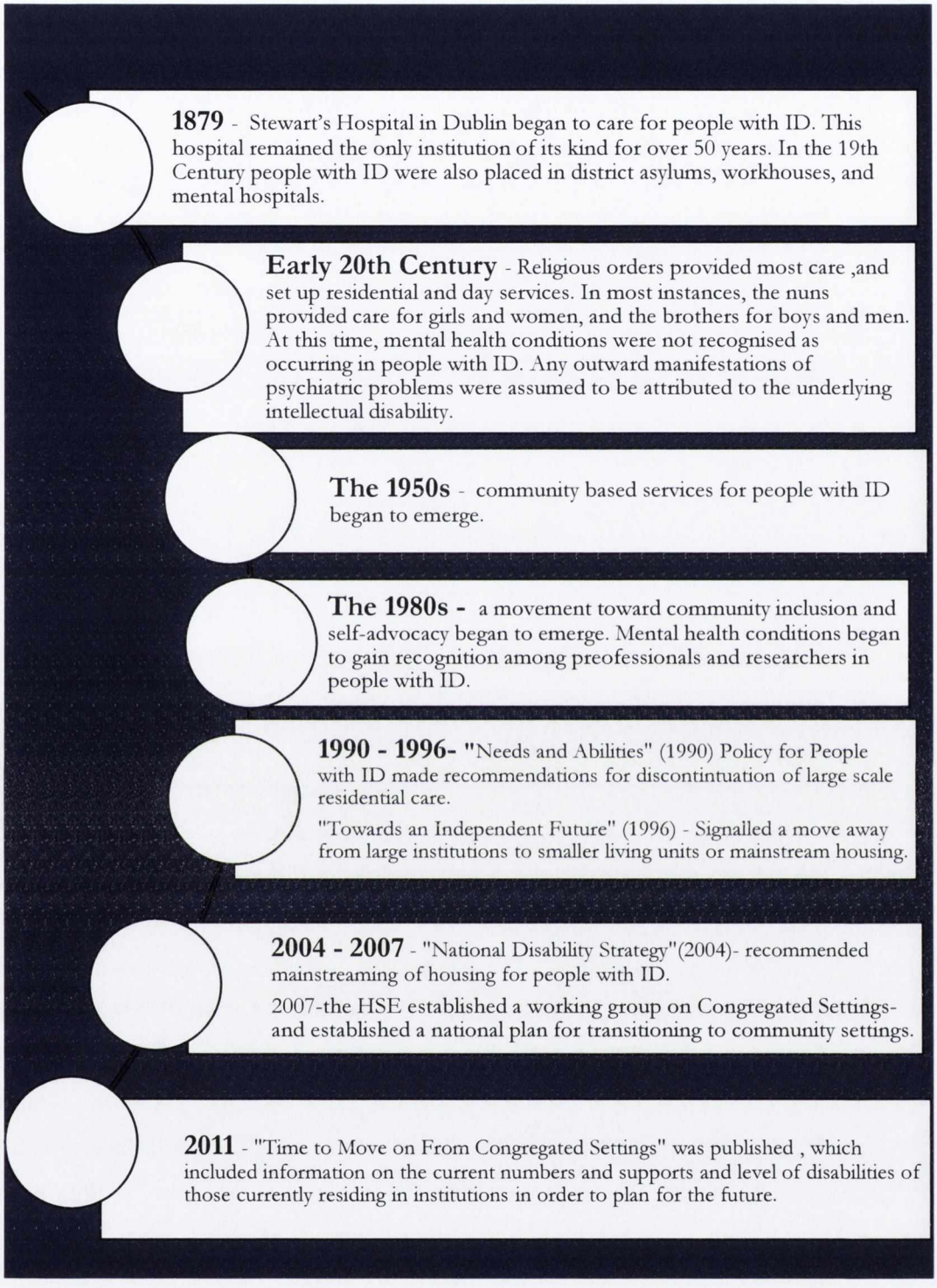

Figure 1-2 History of Institutions in Ireland (30, 69, 109, 110)

The "Time to Move on From Congregated Settings" report was published in 2011, and further analysed information on the current numbers and supports and level of disabilities of those currently residing in institutions in order to plan for the future.

The report identified 4000 people living in congregated settings (10 or more people). This report identified an older population, with high dependency and multiple disabilities living in congregated settings. Over half of these had severe or profound ID, compared to approximately one-fifth of those on the NIDD database. Over half of those living in congregated settings were middle aged (40-60 years), and one-fifth were over 60 years. Almost three-quarters of those in residential settings had lived there for over 15 years. Multiple disabilities were commonplace among those in institutional settings, with over 80% having at least one other chronic condition (69). The Vision of the report set out that "all individuals currently residing in congregated settings will have the opportunity or right to move to a home of their choice in the community"(69)

1.8. Services and Health Service Provision for People with ID in Ireland

The provision of services to people with ID in Ireland, and elsewhere has moved from a medical care model towards a social model of care that focuses on choice, social inclusion, and rights of people with ID. Multidisciplinary teams in ID services in Ireland provide person-centered care, that focuses on social, vocational and education needs of a person with ID (55). Kelly and colleagues reported that in 2009, the services most commonly availed of by adults within ID services were social work, medical services and psychiatry (18). Other services provided included community nursing, speech and language therapy, psychology and physiotherapy. Almost 98% of those on NIDD in 2009 were using day services. For adults, activation program and sheltered workshops were most common, while a minority (5%) were in supported employment(18).

The Health Service Executive (HSE) was established in 2004 by the Health Act (2004), replacing the local health boards is responsible for the delivery for the delivery of health services in Ireland(111). Those in community group homes have Intellectual Disability nurses and a range of social care staff, and access healthcare in community settings through general practitioners and other primary healthcare professionals, with referral to specialists as needed. Those in residential settings have the most medical supervision, with a greater proportion of nursing and other medical staff.

In Ireland, most mental health services for people with ID are provided by the voluntary and non-statutory sector (such as religious orders), with service-level

agreements negotiated between the Health Service Executive (government) and voluntary agencies to provide this care (55). For people who live in residential settings mental health care is provided by psychiatrists with a special interest in the psychiatry of Intellectual Disability. The rights of individuals with ID are the same as any other individual, and include citizenship, access, inclusion and community-based services (113). However, the availability of specialists in the psychiatry of ID varies across the country, with parts of the country not having any access(112). In these areas, services are provided by psychiatrists with training in the speciality of general adult psychiatry. It has been estimated that there are 20 psychiatrists who work in ID services nationally, but few multidisciplinary mental health ID teams, despite recommendations made for such teams by Vision for Change in 2006 (55)(113). It is also acknowledged that some people with ID and acute mental health disturbances have been placed in services outside of the State due to a lack of specialist services in Ireland (113).

1.9. Provision of Medicines

Prescription medications in Ireland are financed by a number of State subsidised schemes, or through private expenditure by individual patients. The General Medical Services (GMS) scheme provides medicines free of charge following a means assessment. The Health Amendment Act 2010 introduced a €0.50 levy on all prescriptions in 2010, and this was increased to €2.50 in 2013, with a cap of €25.00 per family per month. The Long Term Illness (LTI) scheme provides medicines free of charge to patients by one or more of 16 chronic conditions covered on the scheme, including diabetes and epilepsy. Most people with ID in Ireland have a medical card, which entitles the holder to free consultations with GPs, free medications (which are now subject to a prescription levy), and a range of other services. In addition, some people with ID who have chronic conditions such as epilepsy, or diabetes are entitled to a Long Term Illness Book. For those who live with family, live independently or live in community group homes, prescriptions and pharmaceutical care are received from community pharmacists. In community group homes, medications may be managed and administered by staff, or by the individual depending on the different services, and the individual's ability to manage medicines. Provision of medicines in residential settings differs by service providers. At present, there are only three pharmacists who work specifically in ID services providing pharmaceutical care, others

receive prescriptions and care from community pharmacists, or pharmacists who have specialisations in psychiatric pharmacy or clinical pharmacy.

1.10. IDS-TILDA Study

In Ireland in recent years, there has been an increased focus on ageing research and determining the successful elements of ageing, with the Irish Longitudinal Study on Ageing (TILDA) which is longitudinally following adults over 50 years of age, and the Centre for Ageing Research and Development in Ireland, which carries out a range of research projects in relation to ageing research covering the island of Ireland. People with ID have not been represented in these studies. As a consequence the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing was established. Wave One of data collection took place in 2009/2010 (22). The study aimed to explore a representative population of people aged 40 years and over with ID in Ireland, in relation to their ageing profile, health, health service needs, medication use, psychological health, social connections, employment and community participation. A values network underpinned the study with a focus on inclusion, promotion of people with ID, empowering people with ID, and promotion of best practice. The National Intellectual Disability Database served as a sampling frame for the study, and the final study contained 753 people with ID living in a range of residential circumstances. Close harmonisation between IDS-TILDA and TILDA questions was designed to enable comparison of the differences and similarities between people with ID, and with the general population to be examined. (22).

Chapter 2. Medicines Use in People with Intellectual Disabilities

2.1. Use of Medicines in People with Intellectual Disabilities

A large proportion of people with intellectual disabilities are exposed to medications to treat both physical and mental health conditions. The population with ID have been identified as being among the most medicated groups in society, with rates of prescriptions exceeding those of the general population, due to higher levels of clinical comorbidity and mental health disorders (37, 114). Medications play a critical role in maintaining health and increasing longevity in this population. The complex health needs experienced by people with ID lead to increased prescribing, with polypharmacy being more likely in this population (115). A case controlled study among people with intellectual disability who were matched with people of the same age and gender with no intellectual disability demonstrated that people with ID visited GPs 1.7 times more frequently and received four times the number of prescriptions compared to the general population(37). Adults with ID are often diagnosed with chronic somatic disease conditions, including epilepsy and gastro-oesophageal reflux disease that may require long term pharmacotherapy. Additionally drugs are frequently employed to treat psychiatric morbidities(44). Moreover, as people with ID age, they are likely to acquire age-related conditions, further increasing the likelihood of exposure to multiple medicines.

2.1.1. Polypharmacy in the Elderly

Polypharmacy is a term that has been commonly employed for many years, and is generally understood to refer to the concurrent use of multiple medicines in one individual (116). Uniform agreement on an accepted definition of a number of medicines that constitutes polypharmacy has not been arrived at, but some authorities have suggested four or five medicines (117-121). This phenomenon is increasingly common in the elderly, and has been driven by the growth of an ageing population, who are increasingly frail, coupled with the associated increased prevalence of multimorbidity. This term has been used both positively and negatively.

- "Appropriate polypharmacy" refers to prescribing multiple medicines for an individual with complex conditions, in circumstances where medicine used is prescribed according to the best evidence base(116). Polypharmacy often occurs in the context of chronic illness or physical and psychiatric comorbidity, and use of multiple medicines may be beneficial and clinically indicated (122). The overall intent for multiple medicines is to improve quality of life, to

increase longevity and to minimise drug related adverse effects. There is growing acceptance that polypharmacy may be entirely appropriate in conditions where the evidence-based recommend the use of more than one drug in the treatment of long term conditions, such as hypertension, type 2 diabetes which is complicated by coronary heart disease and hypertension(121, 123, 124). However, the evidence base for multiple medicines for co-morbid conditions remains poor (116).

- "Problematic polypharmacy", refers to prescribing multiple medicines in an inappropriate manner, where the benefit of medicines cannot be realised(116), and where potential for harm outweighs any benefit. Drug combinations may be hazardous due to interactions, the overall demand of the drug burden may be unacceptable to the patient, or medicines may be used to treat side effects of other medicines, known as the *prescribing cascade* (116, 125).

While four or more drugs was considered as high a decade ago, multiple medicine use is now commonplace, and ten medicines (also referred to as *excessive polypharmacy*), occurs frequently and constitutes a greater risk (116, 126). There is clear evidence of increased prescribing errors, increased high risk prescribing and a higher prevalence of associated adverse drug reactions (ADRs) with increased number of drugs prescribed (127, 128). Polypharmacy is an important risk factor for inappropriate medication prescribing(129). In the general population, falls, increased risk of mortality, and associated impaired physical and cognitive function have been associated with inappropriate or problematic polypharmacy(116, 122). The relationship of polypharmacy, multimorbidity and rational medicine use has received increasing attention in the general elderly population (116, 129, 130).

2.1.2. Factors Associated with Multiple Medicine Use

Factors associated with use of multiple medicines have been extensively researched in the general elderly population. The Andersen Behavioural Model of Health Service Use (131) has been previously used to examine factors associated with polypharmacy(132, 133). Rationale for using the model has accounted for the fact that factors affecting health service use, also govern the use of medicines in populations(132), with the model also helping to identify older people at risk, while controlling for other determinants of medicine use. According to the model use of health services is a function of predisposing, enabling and need factors. Predisposing

factors are socio-demographic characteristics that encourage use of health services and medicines, including age, gender, race and geographic region. Enabling factors indicate a person's ability to obtain health services (type of service and insurance status). Need factors refer to existence, or the severity of disease or condition (primary diagnosis, number of diagnoses, and reasons for healthcare use). Factors identified with multiple medicine use in the elderly population established to date include female gender, health insurance status, number and severity of conditions, increased healthcare utilization, lower socioeconomic status, and lower levels of education(122, 134, 135).

2.2. Medical Needs of People with ID

The principal medical and pharmaceutical care needs of people with ID are no different from those of the general population. However, there are also some unique challenges and additional risks in providing appropriate, evidence based effective pharmacotherapy to people with ID, as outlined in *Table 2-1*.

Table 2-1 Issues associated with Medicine Use in People with ID

Issue	Comment
Atypical Disease Presentation	Accurate diagnosis may be complicated by atypical disease presentation, with increased diagnostic difficulty as severity of ID increases(28).
Co-Morbidities	Many people with ID will have physical comorbidities that may complicate appropriate medical treatment e.g. swallowing difficulties/dysphagia. Epilepsy is over-represented in people with ID, and many psychotropic agents taken concurrently may have epileptogenic potential(28)
Frailty	Individuals with ID are at risk of earlier onset of frailty(136), making them increasingly susceptible to adverse drug reactions
Consent and Capacity for Treatment	Most people with ID will not have sufficient understanding of treatment benefits and risks, and there is therefore increased onus on the clinician or family /carers to bear the weight of medical related decision making(28).
Communication of Adverse Drug Reactions and side effects	Many people with ID may not be able to self-report side effects of medicines, due to limited communication skills.
Limited Evidence Base	There is less information about safety of medications in people with ID. ID is often an exclusion criteria from participation in Randomised Controlled Trials(137). Consequently, use of medicines is often based on extrapolation from the general population(29).
Increased sensitivity to medicines	People with ID are more likely to experience drug-related side effects (138). People with ID may handle drugs differently, due to greater variations in physical stature and physiological functioning (139) Many will have existing brain pathology which may increase neuropsychiatric adverse effects.
Prescribing Cascade	Due to impaired ability to communicate side effects, people with ID may be at increased risk of the "the prescribing cascade" or "incremental prescribing".
Monitoring requirements	Non-compliance or intolerance with some blood tests or other monitoring procedures such as ECGs, may result in safety issues with some medicines, or may result in these medicines not being prescribed(115).
Age-related changes	Medicines which may have been previously acceptable may now pose risks as people age.

2.3. Polypharmacy Studies in the Population with ID

Some of the key studies that examine multiple medicine use (including psychotropic and non-psychotropic medicines) among people with ID are presented in *Table 2-2*.

Table 2-2 Studies Examining Multiple Medicine Use in ID populations

Title, year, country	Aim	Setting, Population, Sample Size	Definition of multiple medicine use	Results
Prevalence and factors associated with polypharmacy in Victorian adults with intellectual disability(140) Haider et al., 2014, Victoria, Australia	To describe the prevalence of medicine use and polypharmacy (Defined as five or more concomitant medicines), and to investigate the factors associated with polypharmacy in a population of people with intellectual disability	897 adults aged 18-82 years (mean age 42 years), with all levels of ID (74% had mild or moderate ID. Participants drawn randomly from the Victorian Population Survey of People with ID. This study contained participants from an administrative database of people with ID who had sought assistance from the Victorian Department of Human Services.	Concomitant use of five or more medicine	In the population, 76% used medicines, and 21% were exposed to polypharmacy. At multivariate analysis, polypharmacy was associated with older age, unemployment, increased health checks and general practitioner visits. Those with epilepsy, diabetes, stroke, cancer and osteoporosis had more polypharmacy.
Atlas on the Primary Care of Adults with Developmental Disabilities in Ontario(141) Ouellette-Kuntz et al., 2013 Ontario, Canada	To explore prevalence and patterns of medication use, with emphasis on those with multiple medicines (defined as two or more) in adults with ID	52,404 Adults with ID. Aged 18-64 years who were receiving income support from the Ontario Disability Support Program, and were eligible to have medications paid for under the Ontario Drug Benefit Program,	Patterns and number of medicines used on a given date in 2009 (from pharmacy claims data) Multiple medicines classed as two or more, also used threshold of five or more dispensed medicines	Of the sample, 26% were dispensed 2-4 medicines, and 21.5% had five or more medicines. 39.5% had no medicines dispensed. Antipsychotics (21.1%), benzodiazepines (13.1%) and SSRI antidepressants were most commonly dispensed. The number of medicines increased with age, and among those with high morbidity levels and was higher among women (univariate). Those with a psychiatric diagnosis had a greater prevalence of multiple medicine use compared to those with no psychiatric diagnosis (29.4% had polypharmacy, compared to 13.4

Title, year, country	Aim	Study Population, Sample Size	Definition of multiple medicine use	Results
Medication use among Australian adults with intellectual disability in primary healthcare settings: A cross-sectional study (142) Doan et al., 2013 Brisbane, Australia	To investigate the extent of medication use in Australian adults with ID living in the community and accessing generic primary health care, and to explore associations between demographic and medical variables and psychotropic medication use	117 adults with ID living in the community in Brisbane (mean age 35 years), all levels of ID. Derived from a larger Randomised Controlled Trial : the Advocacy and Health Study	Numbers, and classes of medicines and supplements taken. Medication data reported by person with ID and/or carer, health assessment carried out by GP	Of the 117 participants, 79% reported currently taking medicines, a median of 3 medicines. Psychotropics were most frequently reported by 35%, followed by anticonvulsants (26%), and analgesics and gastrointestinal medicines (25%). Having a psychiatric illness or challenging behaviours were significantly associated with increased odds of using psychotropics.
The documentation of health problems in relation to prescribed medication in people with profound intellectual and multiple disabilities(95) 2009 The Netherlands	To document if there was an associated health problem documented in the noted for frequently prescribed medicines among people with profound intellectual and multiple disabilities	254 adults from 8 residential settings (*46% male, 54% female). All had profound intellectual and multiple disabilities (PIMD) – an estimated intelligence quotient of 25, and profound or severe motor disorders	Medication use was defined as a prescribed medication in the previous year, use of five or more prescribed medications in the previous year was also analysed (medication and health data from pharmacy and case records).	Of the 254 participants, 89% were prescribed one or more medicines over the course of one year, and 40% were prescribed five or more medicines. Overall 92% had a documented reason for medicines use. Most frequently reported classes were the laxative (65%), anticonvulsants (56%), and drugs for peptic ulcer and Gastro-Oesophageal Reflux Disease (52%)
Health problems of people with intellectual disabilities: the impact for general practice(37) 2007 The Netherlands	To analyse health problems and prescription patterns of people with intellectual disabilities registered with GPs, and the differences in health problems between people with intellectual disabilities and control persons (without intellectual disabilities).	868 individuals with ID, and 4305 controls (people without ID). Each individual with ID was matched to 5 people without ID with regard to age, sex and practice. Individuals came from 87 GP practices.	Numbers of acute and repeat prescriptions. All therapeutic classes analysed	People with intellectual disabilities paid 1.7 times more visits to GPs nd received four times as many repeat prescriptions. Psycholeptics, anticonvulsants and psychoanaleptics were the most frequently reported repeat prescriptions for people with ID. Different morbidity patterns

2.4. Classes of Therapeutic Drugs

2.4.1. Psychotropic Medicines

Over the past 40 years, psychotropic use, including antiepileptics among people with ID has been the topic of much research. Singh and colleagues evaluated the relevant literature between 1966 and 1996, and concluded that prevalence rate for psychopharmacological and or antiepileptics in large institutions were higher than in community settings, with between 44 and 60% in institutions reporting use, with many studies not differentiating between antiepileptics used for epilepsy or those used for mood stabilising indications(143).

The greater use of psychotropic agents, in particular the antipsychotics, remains an established finding in the more recent ID literature (142, 144-148), these agents are frequently prescribed to manage both mental health conditions and challenging behaviours(148-151), and their widespread use has been subject to criticism and concerns relating to the quality of prescribing (147, 148, 152-154). There is less information available about the safety and efficacy of these agents in people with ID (29), and especially in the elderly, and information about use of these drugs is often based on extrapolation of knowledge from the general population(29).

The extensive use of psychotropic medicines in people with ID remains a controversial area, and the area of research that has received most attention. Antipsychotic agents have been the most broadly reported medicines for people with ID and co-morbid psychopathology (56, 153). While antipsychotic pharmacotherapy has an important role in managing psychopathology, the role of antipsychotics in dealing with challenging behaviours has less evidence and more risk of harm (56). Where no diagnosis of mental illness is present, guidelines recommend that challenging behaviour should be managed with behavioural, environmental and psychological interventions, with use of antipsychotics only when risk to the patient or others is great, where rapid short term intervention is necessary, or where other treatments have failed (11, 155, 156). Consensus guidelines regarding the use of psychotropic medications in people with ID for challenging behaviours have been developed (156). However, pharmacotherapy has been a mainstay of managing challenging behaviour, since chlorpromazine was first introduced for the treatment of challenging behaviour over 40 years ago(148). Emerson and colleagues reported that among 500 adults with ID with challenging behaviours in a range of residential supports in the UK were more likely to receive antipsychotic medicines, as opposed to behavioural support (157). In

the UK, the 2012 Department of Health Review "Transforming Care: A national response to Winterbourne View Hospital" highlighted "deep concerns" about overuse of psychotropic medicines for people with ID(158, 159).

In some cases, where challenging behaviours may arise from a psychotic or affective illness, the short term use of a psychotropic agent may be considered appropriate or rational, as is recommended to calm disturbed patients whatever the underlying psychopathology (160). Concerns exist, however, that medication is commonly being prescribed with the therapeutic target, being the behaviour (the symptoms), as opposed to the underlying cause(11, 148). Physical health problems ranging from ear infections, premenstrual problems, dental pain, seizures and gastrointestinal disorders have been identified to cause or exacerbate problem behaviour, as have side effects associated with antiepileptic medications, but these medical causes for challenging behaviours may be frequently missed in people with ID(75, 161-163). There are few studies of high quality in relation to medication efficacy in long term treatment of challenging behaviour in the absence of mental illness, or of the associated risks with treatment, however, upon review of the literature key findings that have emerged include:

- A randomised controlled trial of typical (haloperidol) and atypical (risperidone) antipsychotics versus placebo for aggressive behaviour in people with intellectual disability found no significant advantage for either antipsychotic(164).
- Use of antidepressants in people with ID in residential settings is more likely to be associated with mental ill health, while use of antipsychotics and anxiolytic agents is more often associated with use to treat problematic behaviour(145, 165)
- Antipsychotics are often more frequently utilised to treat challenging behaviour rather than schizophrenia in this population, despite little or no evidence for their effectiveness and some evidence of detrimental side effects(166, 167)j.

Despite these findings, these agents, particularly the antipsychotics may be prescribed continuously for many years and for many individuals, often resulting in chronic adverse effects. Upon review of the literature, findings here include;

- Substantial potential for deleterious side effects such as tardive dyskinesia, akathisia, pseudo-Parkinsonism in the case of first generation antipsychotics such as chlorpromazine and haloperidol(138).
- Increased risk of metabolic side effects and weight gain in the case of the atypical antipsychotics(74).
- Behavioural side effects associated with use of benzodiazepines are more frequently experienced by people with ID, and are often under-recognised and may be inadvertently confused with other psychiatric and behavioural problems(168).

2.4.2. Psychotropic Polypharmacy

People with ID are frequently treated with more than one psychopharmacological agent (114, 169-171). There are clinical situations in psychiatry where use of more than one psychotropic medication from the same or different class may be indicated, justified and considered "rational polypharmacy". The addition of an antipsychotic agent to a mood stabiliser for acute mania for example, or the short-term use of a benzodiazepine in the early stage of a treatment of a patient with major depression alongside an antidepressant represent examples of rational or empirically supported polypharmacy(172, 173). However, there is general agreement that use of multiple agents may be irrational and increase risk of adverse effects, drug interactions, non-compliance and medication errors and mortality particularly in the elderly(172, 174). One small study by Mahan and colleagues found a greater prevalence of side effects including general effects on the CNS in people with ID taking two or more psychotropics than those who reported one. Specific side effects scales have been developed(175).

2.4.3. Antiepileptics

As people with ID are at increased risk of both mental health disorders, and epilepsy, using a combination of medications from both groups is common (114, 176, 177). Furthermore, as many antiepileptics work as mood-stabilisers, their application in mood disorders is also commonplace. Use of antiepileptic polytherapy may be necessary in this population to treat epilepsy that may be refractory to a single agent(178). Concurrent use of psychotropics in the population with epilepsy may be complicated by the fact that some psychotropics, including the first generation antipsychotics have epileptogenic potential (28, 114).

Some of the key studies to date in the ID literature examining centrally acting drugs (including psychotropics and antiepileptics) in the ID population, are presented in *Table 2-3.*

Table 2-3 Studies relating to Centrally Acting Drugs in People with ID

Title, year, country	Aim	Setting, Sample Size,	Definition of Centrally Acting Medicine	Results
Prevalence of Psychotropic Drug Use in Adults with Intellectual Disability: Positive and Negative Findings from a Large Scale Study. Tsiouris et al., 2012 (144) USA	To examine the prevalence and factors associated with psychotropic drug use among adults with ID in New York state	4,069 adults with ID (including autism spectrum disorder) living in a range of settings who received services from the New York State for People with Developmental Disabilities in 2006-2007 (this represented 47% of those who used services).	Psychotropics consisted of antipsychotics (typical and atypical); mood stabilizers (anticonvulsants, and lithium); antidepressants; antianxiety agents; anti-impulsives; stimulants; and hypnotics.	58% received psychotropics, 39% used typical antipsychotics, and 6% typical, 23% antidepressants, 19% mood stabilisers, and 16% antianxiety agents. Almost 50% had a psychiatric disorder, 38% had a psychiatric disorder and challenging behaviours, and 13% used psychotropics for behaviour alone. There were differences in use varying by geographic region.
Antiepileptic drugs with mood stabilizing properties and their relation with psychotropic drug use in institutionalized epilepsy patients with intellectual disability Leunnisan 2011(179) The Netherlands	To investigate whether the use of mood-stabilising antiepileptics in patients with ID and epilepsy is associated with a different use of psychotropic drugs	Retrospective cohort study of 246 patients with ID and epilepsy in an institution in the Netherlands. The mean age of the study population was 47.9 years. Data was gathered from electronic patient files.	In the population, antiepileptics were used for control of epilepsy, they were not used primarily for mental or behavioural symptoms. Mood-stabilising antiepileptics studied were carbamazepine, valproic acid, and lamotrigine Psychotropic drugs were divided into four groups; antipsychotics, antidepressants, anxiolytics, and ohers (including lithium, propranolol, psychostimulants) Clobazam, clonazepam, diazepam, midazolam and clorazepate were not included in the anxiolytics group.	Almost all (98.4%) took an entiepileptic, with 72.4% taking 3 or more antiepileptics. Carbamazepine was the most commonly reported AED, followed by valproic acid and lamotrigine. 41.5% took psychotropics, antidepressants by 14.6% of patients, 30.5% took antipsychotics, and 11.8% took anxiolytics. There was a significantly lower use of antidepressants in those using lamotrigine. There were significantly less prescriptions of anxiolytics among those using AEDs with mood-stabilising properties. An inverse relationship between the drug load of the mood stabilising antiepileptics alone or combined and the use of psychotropic drugs.

Title, Year , Country	Study Aim	Study population, Sample Size	Definition of centrally acting medicines	Results
Emerging Trends in the Use of Drugs to Manage Challenging Behaviour of People with Intellectual Disability McGillivray Australia (152) 2006	To investigate patterns, and combinations of psychotropic use in people with ID who had been reported to have had chemical restrain in Victoria, Australia.	Retrospective sample. N=873 All had ID and were subject of report to the Intellectual Disability Review Panel in 2000 concerning the use of chemical restraint IDPS Act in Victoria, Australia. Age range 6.8 – 87.7 (mean of 37.0 years) Notification forms for monthly report to IDRP concerning use of chemical restraint by staff for each person who received a restrictive intervention. Gender, Age, type of medication from March 2000 and or 1993.	Six groups: antipsychotics, antidepressants, anticonvulsant / mood stabilisers, psychostimulants, antianxiety / sedatives and others. Anti-anxiety and sedative drugs were combined to form a single group. Clonazepam was reclassified from an anticonvulsant to an anxiety sedative. Lithium was classes with the anticonvulsants in a group called anticonvulsants / mood stabilisers. Anticholinergics were included in others.	4.5% of the population were chemically restrained. Antipsychotics thioridazine, haloperidol and chlorpromazine were most widely reported (60.0% of those in 200, and 81.4% in 1993).In 2000, 21% received antidepressants, an increase on 9.7% in 1993. Increase in anticonvulsant or mood stabilisers was noted: 16.3% in 2000 versus 11% in 1993. Intraclass polypharmacy: in 1993 13.8% of those administered antipsychotics had intraclass polypharmacy, compared to 8.4% in 2000.In 2000 53.8% were routinely administered more than one different class of drug (interclass polypharmacy).
Psychotropic medication in adults with mental retardation: Prevalence, and prescription practices(147) Holden 2004 Norway	To investigate prevalence of psychotropic use in people with ID living in the community in Norway, and the relationship with prescribing guidelines	Retrospective sample. 300 participants drawn from people with mental retardation who were receiving health or educational services. All were adults and living in community settings. A caregiver or parent was given a questionnaire about demographics, mental health conditions, problem behaviour and psychotropic medication use.	First-generation neuroleptics, second-generation neuroleptics, SSRI antidepressants, other antidepressants, anticonvulsants, anxiolytics, mood stabilisers and stimulants.	Of the population, 37.4% received any psychotropic agent. 19.4% used typical antipsychotics, 12.2% used atypical antipsychotics, 85% used SSRI antidepressants, 2.4% used other antidepressants, 5.1% used anticonvulsants, 1.4% used anxiolytics. On average, medications had been used for 5.5 years(first generation antipsychotics for 9 years). 54.3% of medications were indicated for psychiatric diagnosis alone, or with problem behaviours. 23.7% of all antipsychotics recorded had a psychosis diagnosis.

Title, year, country	Study Aim	Study Population, Setting	Definition of centrally acting medicines	Results
Statewide Longitudinal Survey of Psychotropic Medication Use for Persons With Mental Retardation: 1994 to 2000 (180) Spreat et al., 2004 USA	To examine longitudinal patterns of psychotropic medication use between 1994 and 2000.	All available 3187 people in 2000 represented 84% of the total service population with ID registered for services. Another sample contained 2248 persons who lived in residential facilities in 1994 and 2000. A third sample was 200 individuals who lived in residential facilities in 1994 and 2000, and 167 individuals who were in residential facilities in 1994, and supported living arrangements in 2000.	Psychotropic medication classes; anxiolytics, antipsychotics, antidepressants, soporific/hypnotics, or sedatives , and anticonvulsants to treat mental illness	In 2000, 34.3% took a psychotropic, antipsychotics were most frequent (20%), then antidepressants (15.8%), anxiolytics (11.1%), and anticonvulsants for mental illness(6.9%). 31.7% of those in nursing homes took antipsychotics, compared to 19.6% in supported living. Use of antidepressants was more consistent across settings. Use of antidepressants increased from 5.5% in 1994, to 15% in 2000. Overall there was increased use of psychotropic medications for those who moved from an institutional setting to a community setting.
Patients with and without intellectual disability seeking outpatient services : diagnoses and prescribing pattern (181) Hurley et al., (USA) 2003	To examine differences in diagnosis and psychotropic use for individuals with and without intellectual disability from adults with attended an outpatient psychiatric appointment.	N=300 100 adults with mild ID, 100 adults with moderate/severe/profound ID 100 Adults with no ID from patient charts in a hospital psychiatric department All DSM diagnosis available.	Medication prescribed at end of evaluation appointment. Classes as antidepressants, mood stabilisers (antiepileptics and lithium), anxiolytics, antipsychotics, cholinesterase inhibitors and stimulants. "Total Drug Classes"- no. different classes taken	People with ID reported significantly more antipsychotic use (32%) versus non-ID (14%), lower use of antidepressants (27% versus 40%), and greater use of mood stabilisers (28% versus 14%) and were less likely to be prescribed anxiolytics. Interclass polypharmacy was greater among ID subjects compared to non-ID. People with ID were more likely to present with aggression, or physical complaints and non-ID subjects more often with depression and anxiety.

Title, year, country	Study Aim	Study Population, Setting	Definition of centrally acting medicines	Results
Receipt of psychotropic medication by people with intellectual disability in residential settings(145) 2000 Robertson et al., UK	To examine the patterns and factors associated with psychotropic use, particularly antipsychotics across three different residential settings for adults with ID	N=500 86 lived in community, 133 in residential , 281 in community dispersed housing	Medication data taken regularly or as required was distinguished. Adaptive Behaviours Scale Used Aberrant Behaviour Checklist and PAS-ADD used to screen for mental health and autistic spectrum. Psychoactive medication classes: hypnotics, anxiolytics, antipsychotics (oral or depot), antidepressants, antiepileptics, anti-Parkinson drugs (categorised regularly or as required).	People living in residential settings were significantly more likely to receive psychotropics on a regular and as required basis. Antipsychotics were reported to be used on a regular basis by 56% in residential settings, 27% in dispersed housing and 17% in village communities. 11% of those living in residential settings received antipsychotic and antidepressant combination. Factors associated with antipsychotic use included more challenging behaviours, having no mobility problems, living in a residential setting. Mental health as was not a key predictor of use.
Prevalence of psychotropic and anticonvulsant drug use among North Dakota Group Home Residences (182) 1997 Burd et al., USA	To examine the prevalence and factors associated with psychotropic or anticonvulsant use among individuals with ID living in group homes.	N =1384 Individuals with ID living in group homes, had IQ measures for ID Mean age 41 years, 12% of the cohort was 61 years or over 19% psychiatric diagnosis, 23% have seizure diagnosis	Psychoactive Medications (neuroleptics, antidepressants, anti-anxiety agents, anticonvulsants, stimulants, lithium, beta blockers, antihypertensive, clonidine, hydroxyzine, antiparkinson medications. Medication use analysed in the presence or absence of psychiatric or seizure diagnosis. Multiple medicines and polypharmacy defined as use of more than one psychotropic or anticonvulsant medicine.	38% of participants were taking one or more psychotropic and/ or anticonvulsant medicines. Anticonvulsants were used by one quarter of the residents. 20% of the sample used medicines other than anticonvulsants. 11% were taking more than one medication. (polypharmacy) :28% of those who were receiving psychotropic or anticonvulsant medicines were receiving multiple medicines Those who reported a psychiatric diagnosis were 3.4 times more likely to report multiple medicines.

2.5. Other vulnerable populations

Some other vulnerable populations have similarities to people with ID, and so present similar therapeutic challenges. Elderly patients with dementia are difficult to assess, have multimorbidity, polypharmacy, may be frail, have cognitive decline and live in residential facilities of various types (61, 183, 184). Interventions regarding quality and appropriateness of medication use in other vulnerable populations such as those with dementia, those who reside in nursing homes, are frail and have complex comorbidities have focused on maintenance of quality of life, prevention of further disability, and prevention of further functional and cognitive decline (116, 185). As such there have been studies on the effect of sedative burden of medicines, the anticholinergic burden of medication regimens, and the use of medicines that may increase risks of falls as therapeutic targets to improve outcomes in vulnerable populations (186-191). People with ID have a high likelihood of exposure to medicines with significant sedative and anticholinergic potential, due to high rates of exposure to centrally acting medicines, however total sedative or anticholinergic burden has not been determined in this vulnerable population.

2.6. Medication Review

Polypharmacy underlines the need for careful medication review. Similar to people with ID, other vulnerable populations such as the frail elderly, those with dementia, and those in care homes need regular review of medication regimens. Clinical medication review led by pharmacists in elderly populations in primary care, and those in care homes have demonstrated significant reductions in number of inappropriate medicines, or interventions and medicines optimisation, and to a lesser extent improvement in some patient outcomes including falls (192, 193). A structured medication review represents an opportune time to review the effectiveness of medications, as well as their adverse effects.

Despite their complex pharmaceutical care needs, and evidence of multiple medicine use among people with ID, to date, there have been few studies published regarding medication review in people with ID (194). A narrative review examining pharmaceutical care interventions for people with ID, and pharmacist contribution to multidisciplinary teams caring for people with ID from 1994-2014 identified only ten articles reaching the inclusion criteria (194). While the evidence base was limited, studies did demonstrate that pharmacists did have an impact identifying therapy related

problems through medication review, and improving outcomes for people with ID (195, 196)

2.7. Limitations of Studies Identified in the ID literature to Date

Upon appraisal of studies in the literature regarding pharmacotherapy in people with ID to date;

- Many studies have employed clinic or convenience samples. As a result, sample sizes are often small, and are not representative, and thus may not have sufficient power to carry out multivariate analysis. Population level studies are rarely carried out in the ID population.
- There is a lack of consensus in relation to the methods used to study polypharmacy in this population, including measurement, and methods of data analysis (197). Many studies focus on use on multiple medicines solely in terms of psychotropic agents, as opposed to capturing the overall burden of medicine use. Studies often have not differentiated between anticonvulsant use for epilepsy, or for mood-stabilising indications. Their focus has been on specific therapeutic classes of psychotropics, such as antipsychotics or specific diagnostic groups. Few studies to date have examined the prevalence and patterns of combinations of psychopharmacological agents in the population (114).
- Much of the existing literature concerning psychotropic drug use in people with ID has considered adolescents or younger adults, whereas the middle-aged, the elderly and comparisons of those in residential settings compared with those living independently are few.
- Many studies regarding patterns of medicine use in people with ID have conducted bivariate analysis only, and did not adjust for confounders that may influence medicine use(197).
- Few studies have examined factors associated with medicine use, including age, gender, multiple conditions, and organisational variables including healthcare utilization.
- Studies to date in the ID population have not examined specific patterns of medication use that affect cognitive and functional status in vulnerable populations, such as sedative load, cumulative anticholinergic burden, or falls-increasing medicines.

2.8. Aims and Objectives

The overall aim of the thesis is to describe the patterns of, and the factors associated with exposure to multiple medicine use, by individuals aged 40 years and over with ID in Ireland, with a view to informing and promoting safe and effective use of medicines in this population. This aim will be achieved through four specific objectives;

1. To examine the prevalence of polypharmacy and excessive polypharmacy in a population of people with ID aged 40 years and older, and to determine the factors associated with polypharmacy and excessive polypharmacy in the population.
2. To identify the prevalence of psychotropic drug use and psychotropic polypharmacy, to treat mental health conditions in the ageing population with ID, and to examine the patterns and combinations of psychotropic medications employed. To identify the factors associated with psychotropic use and psychotropic polypharmacy.
3. To determine the anticholinergic burden of the population with ID, using a scale that captures total anticholinergic burden, and to assess the association between higher anticholinergic burden and demographic and clinical variables.
4. To examine the patterns of antiepileptic utilisation in people with ID who record a doctor's diagnosis of epilepsy in the context of healthcare utilisation, control of seizures, and use of concurrent medicines.

Objectives 1-4 are retrospective cross-sectional studies using the 2009/2010 IDS-TILDA population, of a representative population of people with intellectual disabilities aged 40 years and over.

2.9. Thesis Outline and Structure

The studies addressing the four objectives of the thesis are presented in *Chapters 3-6,* respectively.

Chapter 3 introduces the IDS-TILDA study and cohort, the methods used to gather medication data in the population, and examines the overall patterns and prevalence of multiple medicine use, and factors associated with multiple medicine use in the population.

Chapter 4 presents the prevalence, patterns and combinations of psychotropic medicines employed in the study population. This chapter also examines factors

associated with psychotropic use and psychotropic polypharmacy, and health care utilisation for mental health conditions in the population.

Chapter 5 examines anticholinergic burden for the study population, as determined by use of the Anticholinergic Cognitive Burden Scale (amended by consensus). This chapter also presents the therapeutic classes that contribute to anticholinergic burden. Multivariate analysis then identifies factors associated with higher anticholinergic burden. The relationship between anticholinergic burden and potential for anticholinergic adverse effects is also examined.

Chapter 6 describes the prevalence and patterns of antiepileptic medications used to treat participants who recorded a doctor's diagnosis of epilepsy. Use of medications to treat acute seizures is also examined, as are patterns of epilepsy review, seizure frequency and associated healthcare utilisation. Concurrent use of medications that may affect the seizure threshold for those with epilepsy is also presented in this chapter.

The thesis findings are summarised in *Chapter 7*, and implications for future research and healthcare delivery to people with ID are highlighted. It is hoped that findings from this research will contribute to a growing body of research regarding safe and appropriate use medicine use in the ageing population with intellectual disabilities, and will serve to increase awareness of the complex pharmaceutical care needs of people with ID.

Chapter 3. Patterns of Drug Use and Factors Associated with Polypharmacy and Excessive Polypharmacy in Ageing People with Intellectual Disability

3.1. Introduction

With the growing number of older adults and associated increases in age-related chronic disease, multiple medicines use has increased and polypharmacy is now commonplace (122, 198). Medications play a critical role in maintaining health in vulnerable older people (83), management of chronic conditions with two or more medicines is increasingly recommended (199), and in some circumstances polypharmacy may be considered therapeutically beneficial (116). In the older population, the safe and appropriate use of medicines in the elderly is emerging as an issue of key importance (200).

However, polypharmacy is also a risk-factor for adverse drug reactions, drug-drug interactions, drug-disease interactions, falls and increased hospitalizations, all of which are associated with higher healthcare costs and reductions in quality of life (122, 128, 201). The combination of the early onset of lifelong disorders and the ageing process predisposes people with ID to a higher disease burden at an earlier age and differing patterns of health needs (32, 38), with up to 2.5 times the number of health problems reported for the general population (35, 36, 41, 202) and a higher incidence of co-morbidities such as psychiatric conditions, epilepsy, dental disease, dementia and osteoporosis (32, 36). Furthermore, people with ID are more likely to be exposed to health inequalities and social determinants of poorer health such as poverty, unemployment and discrimination (39). In Ireland and in other developed countries, increasing emphasis on deinstitutionalization and community integration also means greater utilization of primary health care services where there may not be specialist knowledge of the unique issues for people with intellectual disability as they age.

Regardless of the health care setting, detection and diagnosis of illness are more complex for this population (32, 36, 203) and may contribute to both the overuse and underuse of medicines. Mental health and neurological concerns often offers a therapeutic rationale for the use of multiple drugs, from within the relevant therapeutic groups(145). Unsurprisingly, use of multiple drugs and long-term use of some types of drugs in this population may cause preventable harm (204, 205). This risk of harm and complexity of prescribing is further compounded by both age-related adversity risk and the presence of organic dysfunction associated with the intellectual disability which may lead to idiosyncratic responses to drugs (206-208). Greater variation in people's

physical stature and physiological functioning may result in increased drug sensitivity (115, 209). The evidence base for the use of medicines in this population is often lacking as the presence of an intellectual disability is often an exclusion criterion from Randomized Controlled Trials (210, 211). Consequently, use of these drugs is often based on extrapolation of evidence drawn from the general elderly population (29), even though a body of knowledge points to differences in the severity and combinations of co-morbid conditions in people with ID as they age(53).

Limitation of polypharmacy and of psychotropic use has been encouraged as one of the core elements of "good physical health" in elderly people with ID (32, 36). Polypharmacy has also been identified as a key indicator of quality of healthcare for people with ID as polypharmacy may cause harm and require clinical attention in this population (205). However, studies relating to the patterns , prevalence and predictors of polypharmacy exposure in older adults with ID are scarce (32, 197), particularly in those with a high burden of multimorbidity. Given the potential for increased adverse consequences for people with ID from multiple drug use and from frequent reliance on general population data and recommendations, it is important that there be studies of the patterns of drug use particular to people with ID.

To address this need, the primary objectives of this study were:

1) to determine the prevalence and patterns of polypharmacy and excessive polypharmacy , and the relationship of medicine use to patterns of medical conditions in a representative sample of ageing people with intellectual disability,

2) to identify factors associated with polypharmacy and excessive polypharmacy in an ageing population with intellectual disability.

3.2. Methods

3.2.1. Study Design

Medication Data were drawn from the 2009/2010 first wave of data collected for the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA) (22). IDS-TILDA is a multi-wave longitudinal study of older adults with ID designed to explore their ageing profile, physical and behavioral health, health service needs, psychological health, medication use, social networks, living situations, community participation and employment. For the purposes of analysis

for this chapter and the subsequent chapters, this study is cross-sectional. We have followed the STROBE (the Strengthening the Reporting of Observational Studies in Epidemiology) standardized reporting guidelines for cross-sectional studies to ensure uniform conduct and reporting of our research (212). All participants who had medication information available have been included in our study (736, 98%).

3.2.2. IDS-TILDA Sample and Study Sampling Methods

The IDS-TILDA sample was randomly selected from Ireland's National Intellectual Disability Database (NIDD), which collects information on 26,000 people with all levels of ID, eligible for or receiving services and in a full range of residential circumstances (18)(19). The NIDD includes persons of all levels of ID in Ireland. Permission to use the NIDD as the study sampling frame was granted from the National Intellectual Disability Database Committee. Inclusion criteria for the study were: age over 40 years with intellectual disability and written consent to participate and/or family/guardian written agreement, where required. Age 40 years was selected to reflect the lower longevity of people with ID, thereby ensuring that there would be sufficient subjects for future waves of data collection and because this would provide opportunities to offer insight into ageing for those who may age prematurely(22).

Each person on the NIDD is assigned a personal identification number (PIN). Consistent with inclusion and exclusion criteria, staff at the NIDD randomly selected 1800 PINs. To preserve confidentiality, IDS-TILDA issued the invitation packs to the regional disability database administrator (RDDA), and the RDDA addressed and posted the pack to the person associated with each PIN number. The invitation pack contained summaries of the project and consent forms, including easy to read consent forms, and were directed to the person with ID and families and support staff(22).

3.2.3. Site and Service Level Ethical Approval

Ethical approval for the study was received from the Faculty of Health Sciences, Trinity College Dublin, and from all 138 service providers.

3.2.4. Consent Process

A potential participant who received the invitation pack was encouraged to read the study material, the accompanying letter and the consent either independently, or with support from a key worker or family member. If they were will to partake, they then

returned the consent form. The study employed a system of "process consent", whereby at the time of interview consent was reaffirmed, and the right to withdraw at any time from the study was upheld. It was recognised that some people would be unable to self-consent, in these cases a family member or guardian was requested to review the information and materials and signed a letter of agreement supporting the person with ID's participation in the study. Self-consent was obtained for 20% of participants, 13.7% self-consented and also returned a family letter of agreement to partake, and 62% were deemed unable to self-consent, and a letter of agreement was received from a family member or guardian(22). Everyone who was issued a PIN number was registered on the NIDD, and therefore had an intellectual disability. The person's level of ID was checked and confirmed from case notes at the time of the face-to face interview.

3.2.5. Data Protection

In accordance with the Data Protection Act (1988), all participants were made aware that all data collected will be retained for the duration of the study, using encrypted computer storage in a locked facility.

3.2.6. Sample

The recruited, consented and protocols completed sample was 753 persons with an ID, aged between 41 and 90 years. The overall response rate of 46% of approached participants represented 8.9% of the total population aged 40 and over registered on the 2008 NIDD database. The sample was representative in key demographic variables of the NIDD population from which it was drawn. The demographics of the sample are presented in *Figure 3-1.*

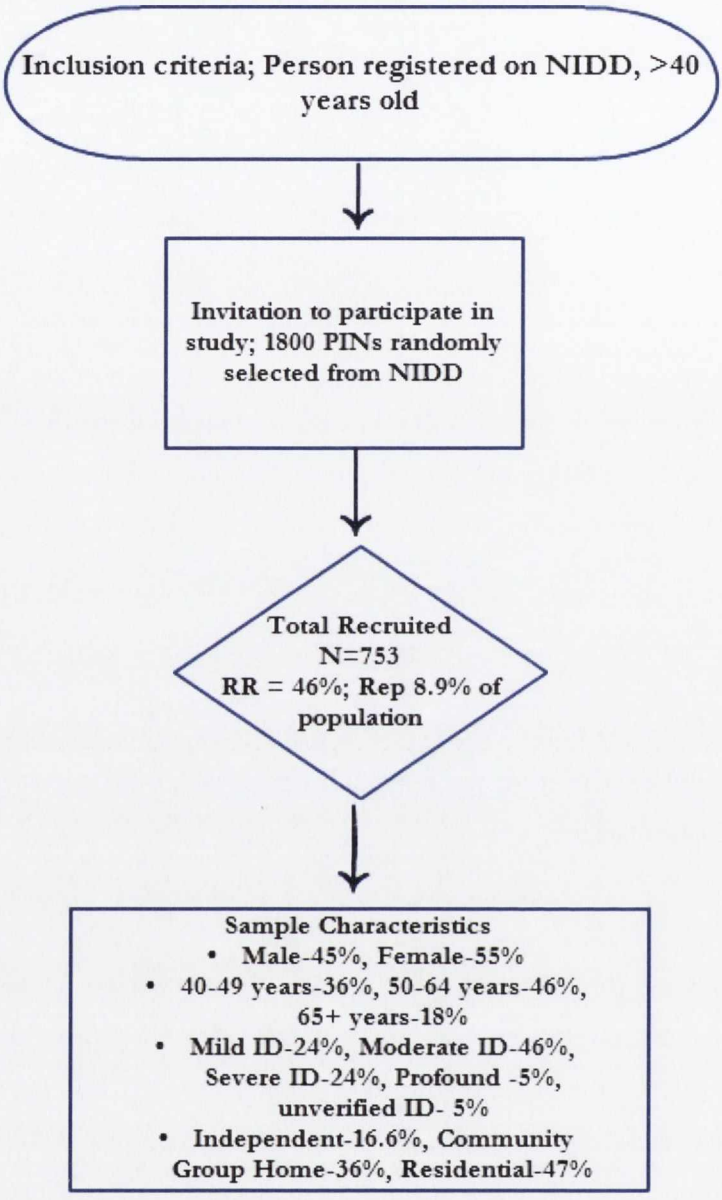

Figure 3-1 Flow Diagram for Study Sample and Demographic Characteristics

RR= Random Representativeness Rep= Representing

Participants, and therefore prescribers came from all over Ireland and from 138 different ID service providers as demonstrated by the map below in *Figure 3-2.*

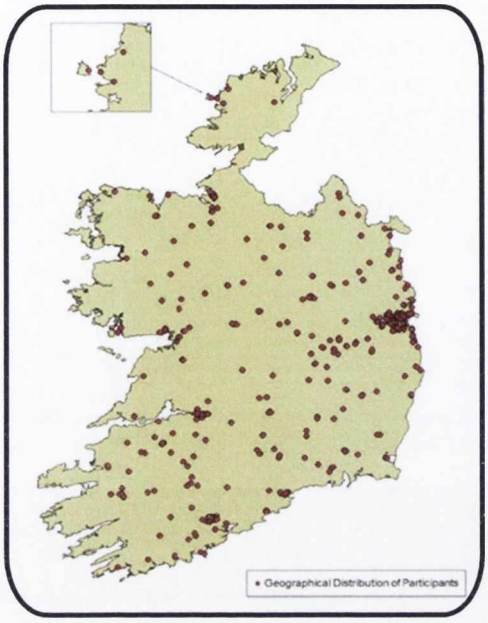

Figure 3-2 Geographical Distribution of Study Participants

Comparisons of the demographic characteristics between the NIDD and IDS TILDA sample are presented in *Table 3-1*, along with p-value for z-test of proportions in *Table 3-2*.

Table 3-1 Comparison with NIDD and IDS-TILDA

	NIDD		*IDS-TILDA*	
	%	*N*	*%*	*N*
Level of ID*				
Mild	28.2	2341	23.9	166
Moderate	45.2	3756	46.5	323
Severe/Profound	26.6	2209	29.5	205
Gender				
Male	50.8	4305	44.8	330
Female	49.2	4165	55.2	406
Age at Wave 1				
40-49	46.8	3970	36.1	266
50-54	41.1	3482	45.7	336
65+	12.0	1018	18.2	134

Table 3-2 p-value for Z-test of proportions

	IDS-TILDA at Wave 1 vs NIDD 2008
Mild	**0.0132**
Moderate	0.5094
Severe/Profound	0.1067
Male	**0.009**
Female	
40-49	**<0.001**
50-54	**0.0175**
65+	**0.0025**

3.2.7. Data Collection and Measures

A pre-interview questionnaire (PIQ) was sent to each participant at least one week in advance of a face to face interview. The PIQ covers demographical information including age, level of ID, aetiology of ID, physical and mental health status (including physician confirmed diagnoses of physical and mental health concerns), healthcare utilisation and medication usage. The purpose of this preliminary questionnaire was to give respondents time to source the information required, thereby increasing the reliability of reported data. Additional data were gathered in a subsequent face to face interview and PIQ reports were also confirmed in this interview, this was aided by the use of a Computerized Assisted Personalised Interview (CAPI).

Interviews were completed by field workers who had completed a comprehensive three day course in the administration of the protocol, and all were experienced in the care of people with ID. A number of different interviewing styles were offered to the participants given their differing levels of ID and abilities to communicate; a respondent only interview conducted directly with the individual (n=147; 19.5%), a proxy interview completed with a family member or carer most familiar with the person (n=265; 35.2%) or an interview with the person was supported by a familiar family member or carer (n=314; 41.7%). A small number of participants required a combination of these approaches (n=27, 3.6%). Proxy is defined as "the authority given to a person to act for someone else" (213). The study required that the proxy had known the person with ID for a minimum of six months, where possible. Some questions included self-report items, to be completed only if possible with the person with ID, and other questions could be either completed by the person, the carer or staff. In addition, in order to improve accuracy of information, PIQ entries, including medications and doctor's reports of conditions were verified at time of interview.

The design and implementation elements of the study and responsibilities of this author (Máire O'Dwyer), and those of the IDS-TILDA study are outlined in *Table 3-3.*

Table 3-3 Contributions and Study Responsibilities

Study Elements	Responsibility
Study Design, Ethical Approval	IDS-TILDA (Overall responsibility with Principal Investigators Professor Mary McCarron and Professor Philip McCallion)
Recruitment of participants, consent	IDS-TILDA
Design of study instruments, including medication data collection	IDS-TILDA
Field work and data collection	IDS-TILDA
Data input from Pre-Interview Questionnaire into SPSS database	IDS-TILDA (all checked by Máire O'Dwyer)
Medication Data cleaning and ATC Coding	Maire O'Dwyer, Jure Peklar. Maire O'Dwyer had final responsibility for the integrity and accuracy of the medication data
Medication classification into therapeutic classes	Maire O'Dwyer (consensus with Martin Henman, Ian Maidment, Niamh Mulryan and Jure Peklar)
Definitions e.g. polypharmacy, creation of derived medication variables	Máire O'Dwyer (ACB coding checked by Anne Belton)
Other derived variables creation e.g. sleep variables	Máire O'Dwyer

3.2.8. Medication Exposure Measures

For the purpose of this chapter, and subsequent chapters, our primary outcome of interest was medication exposure.

Participants/ proxy were asked the following question in the pre-interview questionnaire

"*Can you tell me what medications (including prescribed or over the counter) and supplements you take on a regular basis(like every day or every week) ?" (22).*

Medicines were recorded by brand/generic name, including prescription and non-prescription, over the counter (OTC), herbal and alternative medicines and any

food supplements taken, and where available the dose and frequency. The accuracy of this information was further improved by cross checking the medication information in the face to face interview and data were gathered and verified for 736 (98.0%) of participants. These 736 participants were the study population for our study.

3.2.8.1. Classification of Medicines

For the purposes of this analysis, medications and supplements were recorded using the World Health Organisation Anatomical Therapeutic Chemical Classification (ATC) classification code, International Non-Proprietary name (INN name), and brand name where available.

The ATC system is an internationally used system to code medications, controlled by the World Health Organisation Collaborating Centre for Drug Statistics Methodology (214). The ATC system classifies drugs into different groups according to the system or organ on which they act and/or their chemical or therapeutic characteristics. Drugs are classified in groups at five levels. Drugs are classified into 14 main first level groups, with one therapeutic or pharmacological second level subgroup. The third and fourth levels then consist of the chemical/pharmacological or therapeutic subgroups, and the fifth level consists of the chemical substance.
The complete classification of olanzapine illustrates the code structure below:

N	**Nervous System** *(1st level, anatomical main group)*
N05	**Psycholeptics** *(2nd level, therapeutic subgroups)*
N05A	**Antipsychotics** *(3rd level, pharmacological subgroup)*
N05AH	**Diazepines, Oxazepines, Thiazepines, Oxepines** *(4th level, chemical subgroups)*
N05AH03	**Olanzapine** *(5th level, chemical substance)*

Thus, under the ATC system, all olanzapine medications are coded as N05AH03. In addition to coding, data was cleaned and duplications were removed, for example, if a participant recorded taking two strengths of a particular medicine, for the purpose of analysis, this was treated as one medicine. Two pharmacists (Máire O'Dwyer, Jure Peklar) then independently reviewed the original hard copy pre-interview questionnaires and confirmed all entries into the dataset and classified all use of medications. Full doses and frequencies were available in 12.6% of cases, 34.6% had

dose information but incomplete information about frequency, and for 54.1% of participants the names of medicines were recorded but doses were not all complete. Information on the duration or the cost of prescription was not collected.

3.2.8.2. Medicine Definition

Medication use was defined as regular use (every day or every week), this included oral, parenteral, topical, and ophthalmological and inhaled medicinal products.
Concurrent use was defined as the regular use of at least two medications(215).
For the purpose of this study, food supplements herbal medicines, and homeopathic medicines were excluded from the definition of a medicine.

In our study, we defined a food supplement according to the Directive 2002/46/EC of the European Parliament and of the Council, of 10 June 2002: "'Food supplements' means foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities"(216).

Furthermore, certain medicines were re-classed, by consensus decision (Máire O'D, Martin Henman, Jure Peklar) according to their indications and previously reported classes in other pharmacoepidemiological studies,

- Rectal diazepam (N05BA01) and buccal midazolam (NO5CD08) were categorised as "medicines used to treat acute seizures" as per their SmPC indications.
- Lithium (N05AN01) was reclassified as a mood stabiliser, as its primary use in this cohort was to treat manic depression / depression.
- Clobazam was reclassified as an antiepileptic, as it is primarily used for this indication.
- Prochloroperazine was included in the antiemetic/antinauseant grouping (A04) as sufficient dosing data was available to suggest that it was primarily being used in low doses (5-10 mg) as licensed for Meniere's syndrome or nausea and vomiting in Ireland rather than 75-100 mg indicated in psychosis.
- Midazolam was removed from the definition of a hypnotic/sedative, as its primary indication is a rescue medication for seizures.

Of the 736 participants, 7.6% (56) reported taking no medicines on a regular basis. Data extraction for the 680 participants with medication use yielded 4297 medicines (excluding supplements).

3.2.8.3. Polypharmacy definition

For the purposes of this chapter, the primary outcome of interest (the dependent variable) was whether a subject was exposed to no polypharmacy, polypharmacy or excessive polypharmacy.

There is no universally agreed definition of polypharmacy, however, we drew on published studies for the following definition (120, 122, 217)

- Excessive polypharmacy (EPP): concurrent use of ten or more different drugs.
- Polypharmacy (PP): the use of five to nine drugs.
- No polypharmacy: taking four or less drugs (included those taking no medicines).

3.2.9. Chronic Health Conditions.

Each participant/ caregiver respondent reported if the individual with ID had ever been diagnosed by a doctor/relevant health professional with one or more of 12 chronic health conditions (53). Ten of the conditions were drawn from the Charlson Co-Morbidity Index (218) : heart disease; endocrine disease; eye disease; hypertension; joint disease; lung disease; gastrointestinal disease; liver disease; cancer; and stroke (*Appendix 6).* In addition, due to the reported higher prevalence of neurological and mental health conditions in persons with ID, two conditions were added: neurological disease (which includes cerebral palsy, epilepsy, multiple sclerosis, Parkinson's disease, spina bifida, muscular dystrophy, Alzheimer's disease, dementia, organic brain syndrome or senility and serious memory impairment) and mental health problems (emotional, nervous or psychiatric condition, hallucinations, anxiety condition, depression, emotional problems, schizophrenia, psychosis, mood swings and manic depression) (53). The full list of the conditions included in each chronic condition are listed in *Appendix 6.* Participants were further characterized into those who were, or were not multimorbid. *Multimorbidity* was defined as the co-occurrence of two or more of these chronic health conditions in one person (219). A continuous variable was also created for each participant with number of these reported chronic conditions. However, for the purposes of further detailed analysis in our study, lung disease, liver

disease, stroke and cancer were not included in further analysis, as each had a prevalence of <5% in the sample.

3.2.9.1. Pain

The prevalence of reported pain was measuring using the response to the question "Are you often troubled with pain?" (n=714), and participants/proxy who reported pain then graded the severity of pain (mild, moderate, severe) (n=225)

3.2.9.2. Self-rated health.

All participant/caregiver respondents rated the person with ID's health on a five point scale from poor to excellent (n=730). A derived binary variable was then created with those with excellent/very good/good self-rated health compared to those with fair/poor self-rated health.

3.2.9.3. Health Care Utilization, and Health Insurance Status

Participants were asked in the pre-interview questionnaire the number of occasions in the previous year they had accessed a range of primary, secondary and tertiary care services including GP, outpatient, Accident and Emergency and nights in hospital.
In terms of health insurance status, of those who reported type of cover (n=728), almost all (97%) reported a full medical card, which entitles the card holder to free medicines, GP visits, and other medical services, 1.1% had a GP visit card (where GP visits are free of charge and a person pays for medication), and 1.9% reported having neither cover. Due to the homogeneity of the response, this factor was not studied in further detail.

3.2.9.4. Education status

Participants were asked about the highest level of education they received. Here, 32% reported no formal education, 30.8% primary education, 3% some secondary education, and 11.2% other education, including special needs schools. It was beyond our scope to examine the influence of this variable on polypharmacy status in more detail, as level of education attainment was low.

3.2.9.5. Employment Status

Of the sample, 6.6% were in paid employment (220), and there were insufficient numbers employed to determine any effect size.

3.2.9.6. Marital status

Participants were asked their marital status in the pre-interview questionnaire; 99% were unmarried, this factor was not examined in further detail due to homogeneity of response.

The demographic and clinical variables described in the study are presented in *Figure 3-3.*

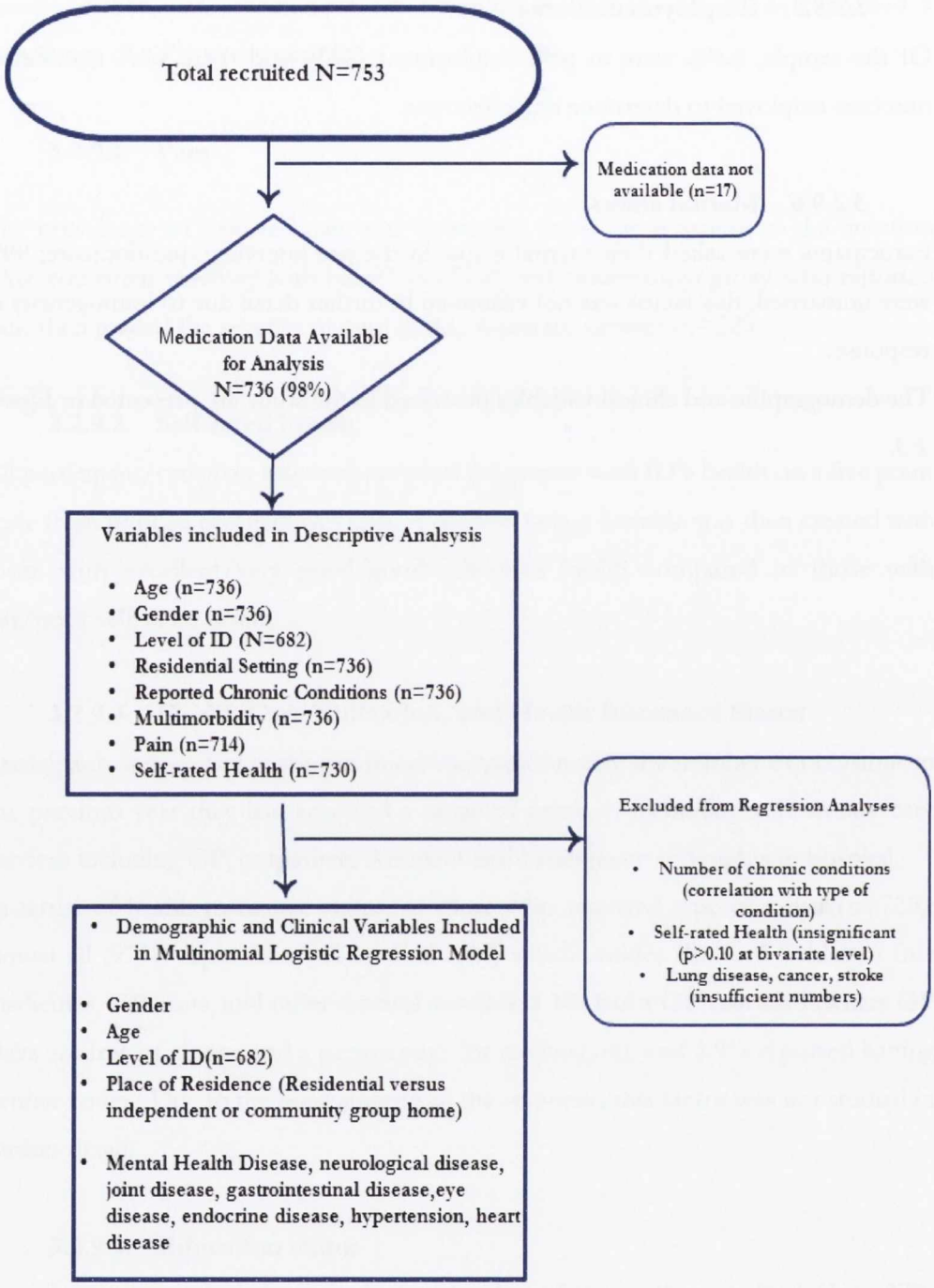

Figure 3-3: Flow chart for the study

3.2.10. Statistical Analysis

Statistical analyses were carried out using the Statistical Package for Social Sciences, version 20.0 (SPSS Inc.). The characteristics of the eligible sample were expressed as percentages, means with standard deviations (±SD) and 95% confidence intervals (C.I.s) as appropriate to the variable.

Figure 3-4 provides a profile of number of medicines used by participants in the cohort. This line has a profile but no intrinsic value, its purpose is to convey a profile of medicine use in the cohort.

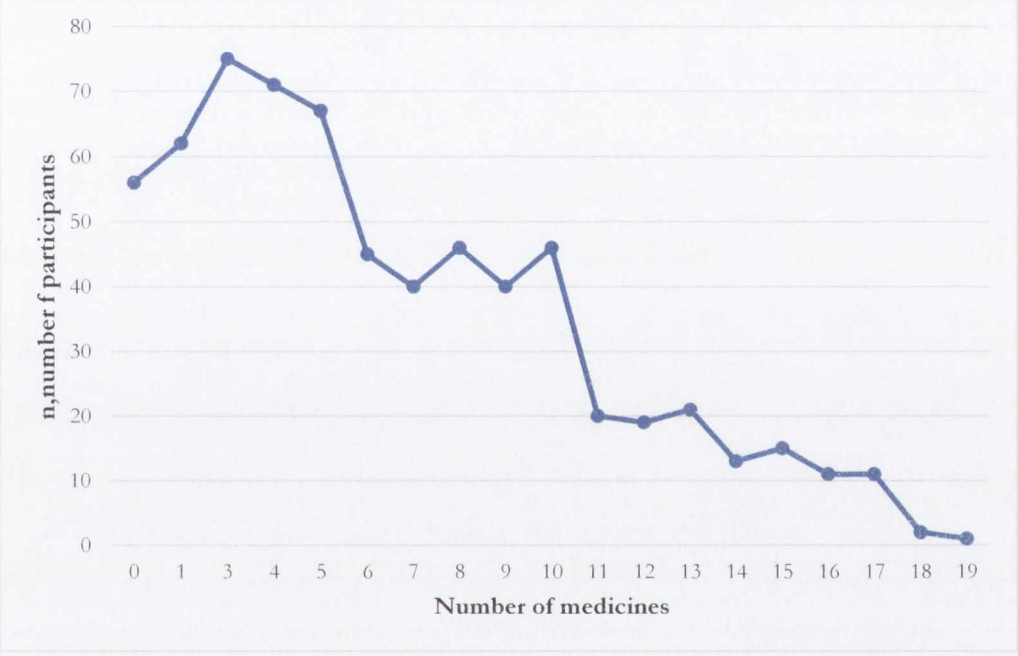

Figure 3-4: Distribution, number of medicines reported (n=736)

The overall prevalence of no polypharmacy, polypharmacy and excessive polypharmacy exposure was calculated as a proportion of the total eligible population (n=736). Descriptive statistics at bivariate level summarised the population reporting no polypharmacy exposure, polypharmacy and excessive polypharmacy. A chi-squared (χ^2) test for independence was used to test for a significant association between the three polypharmacy groupings. For continuous variables, a one-way Analysis of Variance (ANOVA) was used to test for a significant difference between means. Bivariate analysis was initially used to examine associations between the dependent (polypharmacy exposure) and explanatory variables.

3.2.10.1. Multivariate Regression

Multinomial logistic regression was performed to identify factors associated with polypharmacy and excessive polypharmacy exposure. In this model, the outcome (dependent) variable had three possible outcomes and the individuals who reported no polypharmacy exposure (0-4 medicines) were the reference category (*figure3.5*).

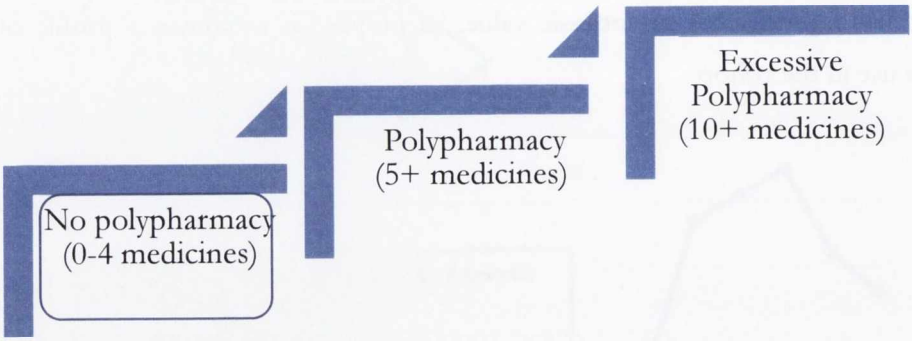

Figure 3-5 : Levels of Polypharmacy Exposure for Multinomial Logistic Regression (reference category is no polypharmacy

3.2.10.2. Factors Associated with Polypharmacy, Candidate Variables

The behavioural model of Health Services use proposed by Andersen et al. was used and adapted to identify factors potentially associated with multiple medicine use in our ageing population (131). This model has been used previously to evaluate multiple medicine use in older populations (133). In this model, the use of health services consists of predisposing, enabling and need factors. Candidate variables that were within our scope of analysis and were considered for inclusion in our model were:

- Predisposing variables: age, gender, level of ID, place of residence,
- Enabling factors: healthcare utilization
- Need factors: self-rated health, type of chronic conditions, and number of conditions.

We excluded the following candidate variables from further analysis:

- Health care utilisation due to correlation with chronic conditions.
- Number of conditions (correlation with individual chronic conditions).

3.2.10.3. Testing for Multicollinearity

Collinearity (or multicollinearity) occurs where the correlations among the independent variables are strong. It may also be described as "interdependence among explanatory variables" (221). Multicollinearity may result in increased standard errors, and unreliable estimation results in regression models. Thus, it has the potential to make some variables statistically insignificant, while they should be otherwise significant. To test for multicollinearity between the independent factors, we employed two strategies;

1) We examined *Variance Inflation Factors (VIF)* , and

2) *Correlation coefficients* of the independent variables.

Variance Inflation Factors (VIF) (and tolerance) is based on "the proportion of variance the i^{th} independent variable shares with other independent variables in the model" (222). If no two X variables are correlated, then all the VIFs will be 1. Although there is no universal agreement criteria for which the VIF level is indicative of multicollinearity, for our study, we examined VIFs between variables, we employed a cutoff of VIF of >2 . If the VIF for one of the variables is around or greater than 2, there is collinearity associated with that variable. All VIFs were below the threshold of 2.

Spearman's correlation coefficient is a non-parametric measure of statistical dependence or correlation between two variables. The correlation coefficient may also be described as "a measure of the relative weight of the factors they share" (223).A coefficient of 0 indicates no relationship between two variables, when two variables are perfectly related the coefficient is 1 (224). The Spearman's correlation coefficients were interpreted using Dancy and Reidy's categorisation (225). Here, correlations of ± 1 is interpreted as a perfect correlation, values between ± 0.7 to ± 0.9 are interpreted as strong correlations, values in the range ± 0.4 to ± 0.6 are categorized as moderate correlations, r -values between ± 0.1 to ± 0.3 are weak correlations and a value of 0 is zero correlation, implying there is no correlation. All of the correlations fell below 0.4, indicating only weak correlations indicating no concerns.

All demographic variables were included in the final adjusted multivariate model (age, gender, level of ID). Those who lived independently or in community group homes were included as a single variable, as the subpopulation of those reporting excessive polypharmacy in the independent setting was small (n=5). Only those with verified ID (n=682) were included in regression analyses. The remaining

variables with a significance of $p<0.10$ at bivariate level, were selected for inclusion in the multivariate model. Self-rated health was insignificant at bivariate level, and so was not included in the model. Variables were entered into the multivariate model simultaneously.

The R^2 (the percentage of variance explained by the model) is presented. The full model containing all predictors was statistically significant, χ^2 (28, N=658) = 325.7, P<0.001 indicating that the model was able to distinguish between those who reported polypharmacy, excessive polypharmacy and no polypharmacy. Results are presented as Odds Ratios (O.R.s), with corresponding 95% Confidence Intervals. Type I error was set at 0.05 for all p-values and confidence intervals. All p-values reported are two-sided. Interpretation of the results for a specific risk factor is based on the odds of being, for example, exposed to excessive polypharmacy rather than being exposed to no-polypharmacy.

3.2.10.4. Sample Size and Power

Sample size and power was a critical consideration for the study, with particular attention required for using multinomial logistic regression as our analysis method. Tabachnick and Fidell outline important issues for determining sample size when employing multiple logistic regression(226). In this study, the alpha level (α) was set at 0.05 or $p\leq0.05$ and the power level was set at 0.80 or beta (β) at 0.20. We employed the following equation described by Tabachnick and Fidell; $N \geq 50 + 8m$ (where m is the number of IVs) for testing the multiple correlation or $N \geq 104 + m$ for testing individual predictors(226). Our final model contained 12 predictors, and for 658 participants in the regression analyses, sample size required would be 146, so our sample size far exceeded this for 80% power.

3.3. Results

3.3.1. Demographics and chronic conditions

Table 3-4 includes details of the demographic and clinical characteristics of the sample with valid medication data (n=736). There were slightly more females than males. Mean age of participants was 54.1 years (S.D. 8.8, range 41-90 years), with almost half (45.7%) aged between 50- 64 years. Almost half (46%) of the sample with recorded level of ID (n= 682) reported moderate ID. Most participants (83.4%) lived in either

community group homes or residential care with 16.6 % living independently or with family.

Females reported a higher mean number of chronic conditions; 2.7 (±2.7) compared to males; 2.2 (±1.5). A greater proportion of men reported fair/ poor self-rated health; 10.7% compared to 4.1% of females. The five most frequently reported chronic conditions found in at least one fifth of participants; eye (51.3%), mental health (47.7%), neurological (36.3%, of which 30.7% had epilepsy), gastrointestinal (26.7%) and endocrine (21.7%). The number of concomitant diseases ranged as high as seven, with 71% reporting multimorbidity (i.e. two or more chronic conditions). (53).

Table 3-4: Baseline Characteristics of the Eligible Study Population (n=736)

Characteristic	N(%) 736	Male 330	Female 406
Age			
40-49 years	266(36.1)	133(40.3)	133(32.8)
50-64 years	336(45.7)	139(42.1)	197(48.5)
65+ years	134(18.2)	58(17.6)	76(18.7)
Level of ID (n=682)			
Mild	166(23.9)	70(23.0)	93(24.6)
Moderate	323(46.5)	139(45.7)	177(46.8)
Severe	168(24.2)	76(25.0)	91(24.1)
Profound	37(5.3)	19(6.2)	17(4.5)
Residential Setting			
Independent	122(16.6)	58(17.6)	64(15.8)
Community Group Home	265(36.0)	121(36.7)	144(35.5)
Residential	349(47.4)	151(45.8)	198(48.8)
BMI Category(n=574)			
Underweight (BMI<18.5)	12(2.1)	6(2.2)	6(1.9)
Normal Weight (18.5-24.99)	214(37.2)	108(40.1)	109(34.8)
Overweight (25-29.99)	173(30.1)	90(33.5)	84(26.8)
Obese (≥30)	175(30.4)	65(24.2)	114(36.4)
Mean (±S.D.) Conditions	2.5(±1.5)	2.2(±1.5)	2.7(±1.5)
Self-rated Health (n=730)			
Excellent	90(12.1)	35(10.8)	51(12.6)
Very Good	270(36.2)	114(35.1)	151(37.3)
Good	278(37.3)	131(40.3)	143(35.3)
Fair	79(10.6)	32(9.8)	46(11.4)
Poor	28(3.8)	13(4.0)	14(3.5)

3.3.2. Drug Use

Almost all (92.4%; 680), participants reported taking one or more medicines, with a maximum of 19, a mean (±SD) of 5.7 (±4.4) medicines. Of this, almost a half (46.3%)

took less than 5 drugs (mean (±SD) of 2.0(±1.5)), 32.2% polypharmacy (5-9 drugs with a mean (±SD) of 6.8(±1.5)) and 21.5% excessive polypharmacy (≥10 drugs with a mean (±SD) of 12.6(±2.4)). Multiple drug use increased slightly with age from 5.0 (±4.3) for those aged 40-49 years, to 5.7(±4.4) for those aged 50-64 years but substantially to 7.7(±4.3) in those over 65 years of age.

Results from the bivariate analysis are presented in table *3-2*. Residential setting was significantly associated with polypharmacy and excessive polypharmacy ($p< 0.001$) ranging from a mean (±SD) of 2.4(±2.8), for those living independently, to 4.9(±3.8) for those living in community group homes and 7.5(±4.5) medicines for those in residential settings *(Table 3-5)*. The level of ID was significantly associated ($p<0.001$, $n=682$) with polypharmacy and excessive polypharmacy, 47.3% of those with polypharmacy had severe/profound ID and almost one-third (29.3%) of those with severe/profound ID reported excessive polypharmacy. Less than 5% of those living independently reported excessive polypharmacy.

Table 3-5: Bivariate associations between explanatory variables and polypharmacy status (n=736)

Characteristic	Total Population	No polypharmacy (0-4 drugs)	Polypharmacy (5-9 drugs)	Excessive polypharmacy (≥10 drugs)	p-Value[a]
	736	341	237	158	
Demographics					
Gender					
Male	330	163(49.4)	101(30.6)	66(20.0)	0.334
Female	406	178(43.8)	136(33.5)	92(22.7)	
Age group					
40-49 years	266	142 (53.4)	74 (27.8)	50 (18.8)	**<0.001**
50-64 years	336	160 (47.6)	113 (33.6)	63 (18.8)	
≥65 years	134	39 (29.1)	50 (37.3)	45 (33.5)	
Level of ID (n=682)					**<0.001**
Mild	163	100 (61.3)	35 (22.1)	28 (17.2)	
Moderate	316	161 (50.9)	93 (29.4)	62 (19.6)	
Severe/profound	203	47 (23.1)	96 (47.3)	60 (29.6)	
Residential Setting					**<0.001**
Independent	122	106 (86.8)	18 (14.8)	5 (4.1)	
Community Group Home	265	151 (57.0)	83 (31.3)	33 (12.5)	
Residential	349	100 (28.7)	136 (39.0)	120 (34.4)	
Drug use (mean±S.D.)	5.8 (±4.4)	2.1±1.4	6.7±1.5	12.6±2.4	**<0.001**
Chronic Diseases					
Eye Disease	380	265 (69.7)	111(29.2)	74 (19.5)	**0.032**
Mental Health	356	103 (28.9)	142 (39.9)	111 (31.2)	**<0.001**
Neurological	268	70 (26.4)	110 (41.0)	88 (32.9)	**<0.001**
Gastrointestinal	198	50 (25.2)	71 (35.9)	77 (38.9)	**<0.001**
Joint Disease	153	50 (32.7)	59 (38.6)	44 (28.8)	**<0.001**
Endocrine Disease	162	57 (35.2)	56 (34.6)	49 (30.2)	**<0.001**
Hypertension	112	32 (28.6)	42 (37.5)	38 (33.9)	**<0.001**
Heart Disease	89	32 (36.0)	30 (33.7)	27 (30.3)	**0.024**
Reported Pain (n=714)	334	83(24.9)	82 (24.6)	73 (21.8)	**<0.001**
Pain severity (n=225)	90	34 (37.7)	32 (35.6)	24 (26.7)	0.64
Mild					
Moderate/severe	135	47(34.8)	44 (32.6)	44 (32.6)	
Self-rated health(n=730)					
Excellent/very good/ Good	625	288 (46.1)	208 (33.3)	129 (20.6)	0.44
Fair/poor	105	50 (47.6)	29 (27.6)	26 (24.8)	

3.3.3. Number of chronic conditions, medicine use

Those who were multimorbid (≥2 conditions) reported a mean (±SD) of 6.8(±4.4) drugs compared to 3.1(±3.3) drugs for those who have one chronic condition or no chronic conditions. A profile of mean number of medicines related to mean number

of reported conditions is presented in *Figure 3-6*, and demonstrates a corresponding increase in mean number of medicines with increasing number of conditions reported. Those reporting excessive polypharmacy reported a higher average number of chronic conditions; a mean (±SD) of 3.5 (±1.5), compared to those in the polypharmacy group; 2.8 (±1.4) and the no polypharmacy group; 1.8 (±1.2).

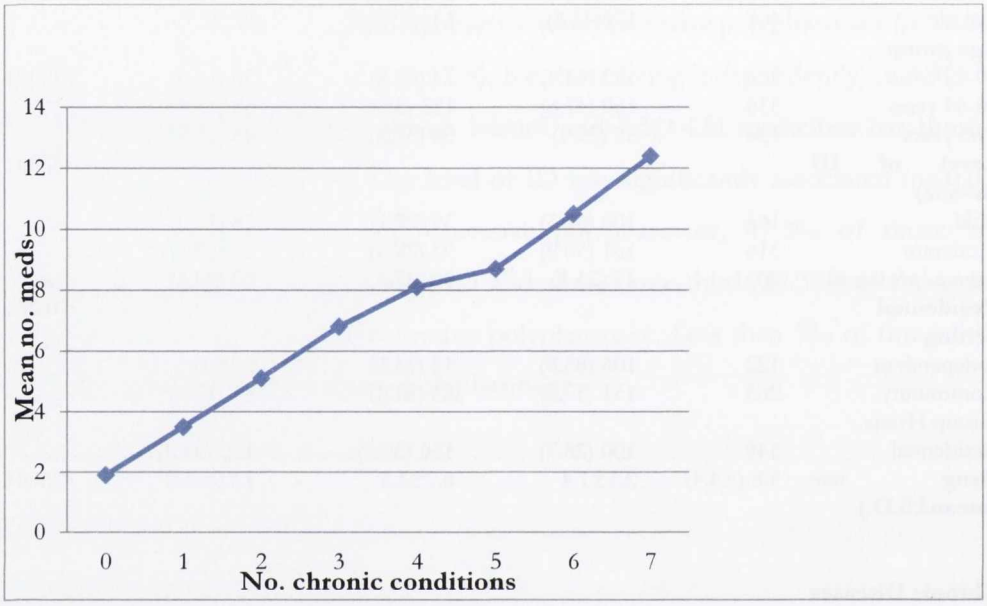

Figure 3-6 Profile of mean number medicines versus mean number reported chronic conditions

3.3.4. Therapeutic Drug Classes and Reported Conditions

Table 3-6 presents the frequently reported therapeutic classes by polypharmacy status. Drugs for mental health conditions, neurological disease and gastrointestinal conditions / symptoms were the most frequently reported with the antipsychotics (43.2%), antiepileptics (39%), laxatives (37.8%) all used by more than one in three of the cohort .

Almost two-thirds (64.6%) of the excessive polypharmacy group and over half (54.9%) of the polypharmacy group reported use of one or more antipsychotics, compared to 26% of people in the no-polypharmacy group. (*Table 3-3).* The most frequently reported antipsychotics were the typical agents risperidone and olanzapine. Antiepileptics were the second most frequently reported therapeutic class reported by 39% (287) of participants. Antiepileptics represented 63.1% of the excessive polypharmacy, 54% of the polypharmacy and 16.7% of the no-polypharmacy group. Of the 287 participants who reported antiepileptic medications, 71.4% (205) reported

a diagnosis of epilepsy, and this was considered to be their primary indication. The majority of other 82 participants (78.8%) had a doctor's diagnosis of an emotional/ nervous or psychiatric condition, and these agents were likely to be used primarily for this indication.

Laxatives were reported by three-quarters of the excessive polypharmacy group, half of the polypharmacy group, and 12.3% of the no-polypharmacy group. The most frequently reported agents were lactulose (A06AD65) reported by over half (51%) of those who reported laxative use and macrogol combinations (A06AD11) by 43%. Of those reporting laxatives, 12.7% reported use of enemas (A06A). Of the sample, 43% reported that constipation was a problem, and almost one-fifth reported a doctor's diagnosis of chronic constipation.

In terms of gender and frequently reported classes, there was no significant association between antipsychotic use and gender ($p=0.27$), or antiepileptic use and gender ($p=0.23$). Females were more likely to report laxative use; 40.8% of females reported laxative use compared to 31.7% of males ($p=0.009$).

Prevalence of other psychotropic agents was high, with over one quarter (26.2%) of the cohort reporting use of antidepressants (43.7% of the excessive polypharmacy group), almost one quarter (23.5%) reporting use of anxiolytics of the excessive polypharmacy group), and 13.3% reporting use of hypnotic/ sedatives (34.4% of the excessive polypharmacy group).

Over one quarter of participants reported gastrointestinal conditions, including constipation. In addition to laxatives, other drugs for GIT conditions were commonly reported, with 24% of participants reporting drugs for peptic ulcer disease (PUD)/ gastroesophageal reflux disease (GORD) ; almost half (49.0%) of those in the excessive polypharmacy reported use of these agents. Proton Pump Inhibitors were also frequently reported by 21.7% of participants and 44.5% of those in the excessive polypharmacy group.

Use of anticholinergic agents were recorded by 16.3% of the cohort. There was a substantially higher frequency of use of anticholinergic agents among the excessive polypharmacy group, with one third reporting use, compared to 22.3% of the polypharmacy group and 4.1% of the no-polypharmacy group. Reported prevalence of Parkinson's disease was low in the cohort; <1%, . Of those reporting anticholinergic use, 91% reported concurrent use of antipsychotics.

Rates of reported hypertension and heart disease were lower; 15.2% and 12.1% respectively. Lipid modifying agents were the most frequently reported cardiovascular agents, reported by one-quarter of participants. There was a lower frequency of use of other cardiovascular agents; antithrombotics (10.6%), agents acting on the renin-angiotensin system (6.5%),

In terms of pain (714), 238 reported experiencing pain. In terms of pain severity (n=225), 40.0% reported mild pain and 60.0% reported moderate/ severe pain. Of the analgesics reported. paracetamol was most frequently used by over one third (34.2%) of the cohort, use of more potent analgesics was less, with 2.3% of participants reporting use of paracetamol /codeine combinations, and 0.8% reporting use of opioids. In terms of anti-inflammatory analgesics, 10% reported use of oral NSAIDs.

Endocrine disease was reported by over one fifth of the cohort (22%), and drugs for thyroid were most commonly reported (17.9%), followed by oral anti diabetics (5.5%), Insulin and analogue use was negligible.

Antihistamines were reported by 8.8%. First generation antihistamines were reported by 3.2% of participants and 8.3% of the excessive polypharmacy group, while second- generation antihistamines were reported by 5.6% and 11.5% of those reported excessive polypharmacy.

Eye disease was the most commonly reported condition in the cohort, with half of participants reporting eye disease (53). Of those reporting eye disease, 27.2% (98) reported having cataracts, 5% (18) reported age –related macular degeneration, and 2.8% (10) reported glaucoma. There were a wide range of other eye conditions reported including blepharitis, hypermetropia and bilateral keratoconus. However, reported prevalence of use of eye preparations was low; the majority of those reporting ophthalmologicals were reporting lubricant preparations (ATC Code S01X); 2.8% of participants, 1.1% of the cohort reported antiglaucoma and miotic preparations.

Table 3-6: Proportions of drugs users in the therapeutic classes reported by >5% of the sample (n=736)

	ATC Code	Total Population 736	No polypharmacy (0-4 drugs) 341	Polypharmacy (5-9 drugs) 237	Excessive polypharmacy (≥10 drugs) 158
Antipsychotics	N05A	319 (43.2)	89 (26.1)	128 (54.0)	102 (64.6)
Antiepileptics*	N03A	287 (39.0)	60 (17.6)	128 (54.1)	99 (63.1)
Laxatives	A06A	278 (37.8)	42 (12.3)	117 (49.4)	119(75.3)
Analgesics	N02B	277 (37.6)	52 (15.2)	107 (45.1)	118 (75.1)
Antidepressants*	N06C	193 (26.2)	51 (15.0)	83 (35.0)	69 (43.7)
Anxiolytics*	N05B	173 (23.5)	24 (7.0)	70 (29.5)	79(50.0)
Lipid Modifying Agents	C10A	187 (25.4)	69 (20.2)	62 (26.2)	56 (35.7)
Drugs for PUD/ GORD	A02B	177 (24.0)	30 (8.8)	70 (29.5)	77 (49.0)
Drugs for thyroid conditions	H03A	132 (17.9)	49 (14.4)	48 (20.3)	35 (22.3)
Anticholinergic Agents Preparations	N04A	120 (16.3)	14 (4.1)	53 (22.3)	53 (33.8)
Hynotics and Sedatives*	N05C	100 (13.6)	6 (2.1)	40 (16.9)	54 (34.2)
Antithrombotics	B01A	78 (10.6)	11 (3.2)	37 (15.6)	30 (19.1)
NSAID Drugs	M01A	73 (9.9)	12 (3.5)	25 (10.5)	36 (22.9)
Antipropulsives	A07D	68 (9.2)	5 (1.4)	20 (8.4)	43 (27.3)
Antihistamines	R06A	65 (8.8)	10 (2.9)	25 (10.5)	30 (19.1)
Drugs Affecting Bone	M05B	59 (8.0)	11 (3.2)	22 (8.4)	26 (16.6)
Propulsives	A03F	56 (7.6)	1 (0.3)	20 (8.4)	35 (22.3)
Inhaled Adrenergics	R03A	53 (7.0)	5 (1.5)	17 (7.2)	31 (19.7)
Expectorants	R05C	51 (6.9)	4 (1.2)	16 (6.8)	31 (19.7)

	ATC Code	Total Population	No polypharmacy	Polypharmacy	Excessive Polypharmacy
Agents acting on the renin-angiotensin system	C09A	48 (6.5)	9 (2.6)	18 (7.6)	21 (13.4)
Oral Antidiabetics	A10B	41 (5.6)	6 (1.8)	18 (7.6)	17 (10.8)

*Other therapeutic classes reported by <5% in decreasing prevalence; selective calcium-channel blockers (C08C), beta-blocking agents (C07A), Antifungals for topical use (D01A), other drugs for obstructive airway disease, inhalants (R03B), antiemetics and antinauseants *(A04A), other ophthalmologicals (S01X), other systemic drugs for obstructive airways (R03D).*

**modifications described in methods*

The ratio of number of drugs in relation to the most frequently reported conditions and pain is presented in *Table 3-7*. Those with gastrointestinal, neurological, and mental disease reported the higher number of related drugs to treat these conditions with 4.2, 2.8 and 2.5 drugs from the relevant ATC group, respectively. Those with eye disease had 0.13 agents.

Table 3-7 Ratio Drugs: Conditions in the Sample (N=736)

	Number reporting Conditions	Number receiving medicine from Relevant ATC Group	Ratio Drug: Condition
Eye Disease	380	50	0.13: 1
Mental Disease	356	885	2.5:1
Neurological	268	746	2.8:1
Gastrointestinal	198	827	4.2:1
Endocrine	162	195	1.2:1
Pain (Mild/ Moderate/ Severe)	225	371	1.6:1

3.3.5. Intraclass Polypharmacy

Intraclass polypharmacy (concurrent use of >1 agent within the same class), was observed in all of the three most frequently reported therapeutic classes, with one quarter (25.7%) of those who reported antipsychotic use reporting antipsychotic polytherapy (maximum 4 concurrent antipsychotics reported) and 39.7% (n=114) of the those who reported AED use reporting AED polytherapy (maximum of 5 concurrent AEDs reported).

Of the participants that reported antipsychotic polytherapy (n=82), 49% (n=41) were exposed to excessive polypharmacy, 31 (38.3%) reported polypharmacy and 10 (12.3%) were in the no polypharmacy category. In the case of the participants reporting antiepileptic polytherapy (n= 114), 43.8% (n= 50) were in the excessive polypharmacy group, 40.8% (n= 47) were exposed to polypharmacy and 14.9% (n=17) were in the no-polypharmacy group. In terms of those who reported use of laxatives (n=276); 47.1% (130) reported concurrent use of 2 or more laxatives (maximum 5). Of those reporting laxative polytherapy (130), 60.7 % were exposed to excessive polypharmacy, 33.8% were exposed to polypharmacy and 5.4% were in the no-polypharmacy. Of those reporting laxative polytherapy, half (50.8%) reported a doctor's diagnosis of chronic constipation.

3.3.6. Therapeutic Classes, Residential Setting

Prevalence of the three most frequently reported therapeutic classes (antipsychotics, antiepileptics and laxatives) by place of residence is presented in *Figure 3-7*. There was a significant association between antipsychotic ($p<0.001$), laxative ($p<0.001$) and antiepileptic ($p<0.001$) use and residential setting. A higher proportion of participants living in residential settings reported use of antipsychotics, antiepileptics and laxatives compared to those living independently or in community group homes. This difference was particularly pronounced in the case of laxative use with 54.2% of those living in residential settings reporting use of a laxative compared to 28.7% of those living in community group homes and 9.0% of those who lived independently.

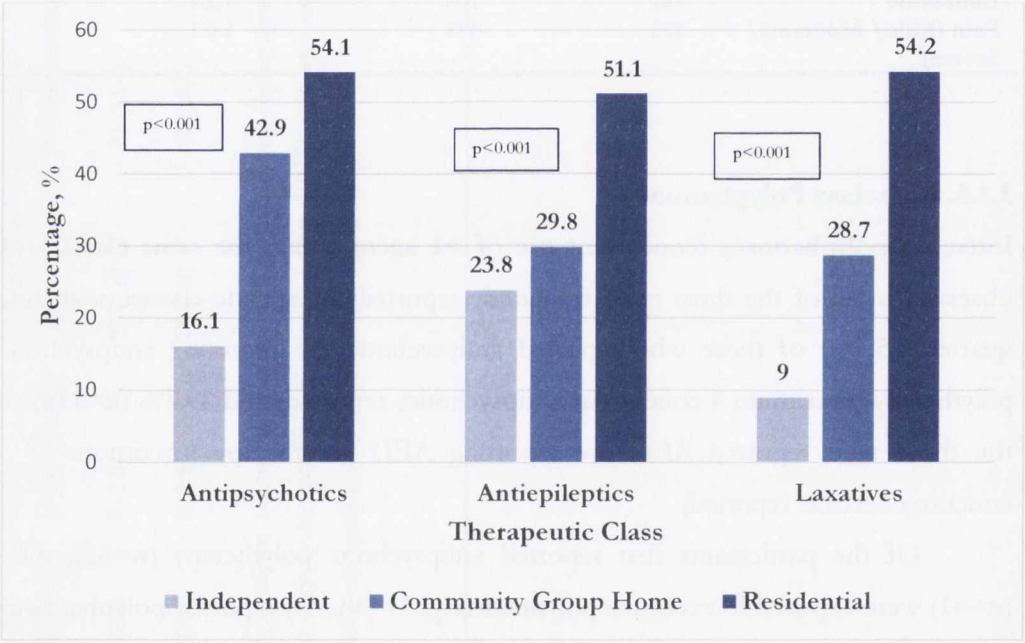

Figure 3-7 Proportion of participants receiving three most frequently reported therapeutic classes according to residential status (n=736)

3.3.7. Health Care Utilisation and Polypharmacy Status

Patterns of use by healthcare utilization are presented in *Table 3-8*. Over 40% of the sample reported 6 or more GP consultations in the previous year. There was a significant bivariate association ($p<0.05$), between number of GP consultations and polypharmacy status, number of outpatient visits and being admitted to general

hospital; with those exposed to excessive polypharmacy reporting the greatest frequency of use of these services.

Table 3-8 Healthcare Utilization in the Previous 12 Months by Polypharmacy Status (N=736)

HealthCare Utilization	Total Population 736 n(%)	No Polypharmacy 341 n(%)	Polypharmacy 257 n(%)	Excessive Polypharmacy 158 n(%)	p-value
General Practitioner Visits (n=644)					
0-1	90(14.0)	64(21.3)	16(6.2)	10(6.3)	**<0.001**
2-5	272(52.2)	146(48.5)	86(40.2)	40(31.0)	
6+	282(42.8)	91(30.3)	112(52.3)	79(61.2)	
Outpatient Visits(n=678)					
0	339(50.0)	187(59.7)	105(47.7)	47(32.4)	**<0.001**
1	117(17.3)	45(14.4)	46(20.9)	26(17.9)	
2+ visits	222(32.7)	92(25.9)	69(31.4)	72(49.6)	
Accident and Emergency admissions (n=700)					
0	567(81.0)	273(83.7)	179(79.2)	115(77.7)	0.21
1+	133(19.0)	53(16.3)	47(20.8)	33(22.3)	
Nights in Hospital (N=688)					
0	610(91.1)	293(92.4)	200(88.1)	117(81.3)	**0.002**
1+	78(8.9)	24(7.6)	27(11.9)	27(28.7)	

Significant p-values (<0.05) in bold

3.3.8. Factors Associated with Polypharmacy and Excessive Polypharmacy

Results from the multinomial logistic regression are presented in *Table 3-9*. The model contained 12 explanatory variables. The model as a whole explained 39.0 %(Cox and Snell R Squared) and 44.3% (Nagelkerke R Squared) of the variance in polypharmacy

status. These results demonstrate consistency across a number of factors discriminating polypharmacy and excessive polypharmacy from no polypharmacy exposure. Living in a residential setting, reporting having a mental health, neurological, endocrine condition or hypertension were associated with both polypharmacy and excessive polypharmacy exposure at both levels, compared to those who were not exposed to no polypharmacy, controlling for all other factors in the model. Those with severe/profound ID were likely to be exposed to polypharmacy, but not excessive polypharmacy. Gastrointestinal disease was significantly associated with excessive polypharmacy only. Gender, age, eye disease, heart disease or joint disease were not significantly associated with polypharmacy or excessive polypharmacy.

Table 3-6: Factors Associated with Pharmacy and Polypharmacy, Multinomial Logistic Regression (n=658)

	Polypharmacy Categories			
	Polypharmacy (5-9 medicines)		Excessive Polypharmacy (10+ medicines)	
Characteristic	**OR (95% CI)**	**P-Value**	**OR (95% CI)**	**P-Value**
Gender				
Male	1.00		1.00	
Female	0.95(0.62-1.45)	0.81	0.93 (0.55-1.56)	0.78
Age				
40-49 years	1.00		1.00	
50-64 years	1.12 (0.71-1.77)	0.64	0.75 (0.43-1.34)	0.33
65+ years	1.63 (0.87-3.07)	0.13	1.79 (0.87-3.68)	0.12
Level of ID				
Mild	1.00		1.00	
Moderate	1.34 (0.79-2.30	0.77	0.77 (0.39-1.51	0.45
Severe/Profound	**4.06 (2.08-7.91**	**<0.001**	1.38 (0.62-3.10	0.43
Residence				
Independent/Community Group Home	1.00		1.00	
Residential	**2.08 (1.33-3.25)**	**0.001**	**6.90 (3.88-12.25)**	**<0.001**
Conditions				
Mental Health				
No	1.00		1.00	
Yes	**3.98 (2.59-6.11)**	**<0.001**	**6.05 (3.55-10.31)**	**<0.001**
Neurological				
No	1.00		1.00	
Yes	**3.67 (2.32-5.80)**	**<0.001**	**6.08 (3.51-10.53)**	**<0.001**
Gastrointestinal Disease				
No	1.00		1.00	
Yes	1.10 (0.66-1.84)	0.73	**2.66 (1.51-4.67)**	**0.001**
Joint Disease				
No	1.00		1.00	
Yes	1.52 (0.89-2.58)	0.12	1.33 (0.71-2.51)	0.37
Endocrine Disease				
No	1.00		1.00	
Yes	**2.06 (1.23-3.47)**	**0.006**	**3.69 (2.00-6.80)**	**<0.001**
Eye Disease				
No	1.00		1.00	
Yes	0.67 (0.44-1.00)	0.05	0.68 (0.39-1.17)	0.17
Hypertension				
No	1.00		1.00	
Yes	**3.09 (1.65-5.80)**	**<0.001**	**3.68 (1.78-7.63)**	**<0.001**
Heart Disease				
No	1.00		1.00	
Yes	1.20 (0.63-2.31)	0.58	1.51 (0.71-3.22)	0.28

Reference category = no polypharmacy (0-4 medicines), p <0.05 is significant, all significant factors in bold
Cox and Snell r^2 = 0.39 Nagelkerke r^2=0.44

3.4. Discussion

3.4.1. Principal Findings

Polypharmacy and excessive polypharmacy were commonplace in ageing people with intellectual disability in our study with over half of the sample reporting five or more medicines, and 1 in 5 with ten or more medicines (excessive polypharmacy). To our knowledge, no previous study has examined prevalence, patterns and factors associated with polypharmacy and excessive polypharmacy in a representative ageing population with intellectual disabilities. In our multivariate model, after adjusting for confounding factors, we identified that those living in residential settings were likely to be exposed to polypharmacy and excessive polypharmacy, while severe/profound ID was associated with polypharmacy only. Furthermore, those with mental health conditions, neurological conditions, endocrine disease and hypertension were likely to be exposed to polypharmacy and excessive polypharmacy, but gender or age had no significant effect. In parallel, we observed high rates of use of agents to treat mental health and neurological conditions and lower rates of use of medicines to treat cardiac conditions, previously reported different common disease pathways of elderly people with ID compared to the general population (47, 227). We established that the high prevalence of intraclass polypharmacy among the antipsychotics, antiepileptics and laxatives in particular, further contributed to utilization of multiple medicines in the cohort. While eye disease was the most prevalent condition in the population, we identified a low use of ophthalmological preparations.

3.4.2. Polypharmacy Comparisons

Making cross-study comparisons of polypharmacy prevalence has limited value, as estimates of the prevalence often vary due to the differences in the definition of number of medicines that constitute polypharmacy (122). However, the prevalence rate of polypharmacy, and in particular that of excessive polypharmacy established in our study were higher than rates that have been reported in the general elderly community dwelling population, where, using the same definition of five or more medicines, rates of 4-42% have been reported (135, 228, 229). The prevalence of excessive polypharmacy was similar to one study of elderly nursing home residents (230). While they are not directly comparable, prevalences determined in our cohort are higher than those reported for the general Irish population over 50 years where

rates of polypharmacy and excessive polypharmacy were reported as prevalences of 19% and 2% respectively (217). However, we would expect the older population with ID to use more medicines due to the established higher prevalence of complex multimorbidity, in particular psychiatric conditions and epilepsy, and frailty present in elderly people with ID (53, 136), which often necessitate a greater frequency and complexity of medical interventions. In a Dutch National survey of general practice differences between 712 individuals with ID and controls (patients with no ID who were matched on age and sex), those with ID received four times more repeat prescriptions compared to controls (37).

Moreover, there are a number of methodological concerns relating to studies carried out in the ID population. Many studies that have reported prevalence of multiple medicine use in people with ID have focused on specific drug classes or therapeutic areas such as antiepileptic polytherapy (176, 231) and psychotropic polypharmacy (144, 145, 149, 232) in isolation, as opposed to broader definitions of polypharmacy employed in the general elderly population. In addition, comparisons are further limited by the fact that many ID studies have tended to employ small sample sizes, convenience(152) or clinic samples (181, 233), and often only included those living in institutional settings , and older people (particularly over 65 years) were rarely studied. Given the fact that people with ID are living longer, and are acquiring age related conditions in addition to predisposing conditions, we felt it was important to capture the total drug burden.

The prevalence reported in our study is higher than a recent Australian study of a community dwelling population with ID in the state of Victoria, who had used health services, which included 897 people with ID aged from 18-82 years (over 90% were under 60), and all levels of intellectual disability, where over 20% reported the use of 5-9 medicines (140). However, this study did not report on specific patterns of medicine used in the population. Van der Heide and colleagues examined documentation of health problems in relation to prescribed medicines to adults with profound and multiple intellectual disabilities intellectual disability living in residential settings in the Netherlands found that 40% of individuals (n=101) were prescribed 5 or more medicines over the course of a 1-year period ; in our study 71.9% of those living in residential settings reported use of 5 or more medicines (95). Medication use patterns were explored among 52,404 adults aged 18-64 years with developmental disabilities receiving primary care services and support from the Ontario Disability

Support Group, who were dispensed medications covered by the Ontario Drug Benefit Program in October 1, 2009 (141). This study had a prevalence rate of 42.1% in those aged 55-64 years for polypharmacy (≥5 medicines), and 3% for 11 or more medicines; in our study prevalence of polypharmacy was 35.1% overall for those living independently or in community group homes. The Dutch study (95), only looks at those prescribed medicines for any reason in an institution. Both the Australian and Canadian studies selected their cohorts by use of health services which may mean that those with no medicines or chronic conditions would be under-represented or absent(140, 141). Polypharmacy was identified as an independent factor associated with prescription errors in a study of 600 older individuals with ID who reported medicine use age 50 years and over randomly selected from the Healthy Ageing Intellectual Disabilities Study (HA-ID) in the Netherlands(234), which included participants from independent and residential settings, with most prescription errors detected relating to drugs acting on the central nervous system (43.2%).

3.4.3. Frequently Reported Classes

The most frequently reported therapeutic drug classes in our study were the antipsychotics (42.3%), antiepileptics (38.7%) and laxatives (36.9%). This pattern of frequently used medications is similar to another study of ID patient prescription practice in Dutch general practice (37) , and may reflect the predisposition of people with ID to co-existing illnesses such as seizure disorders, mental health and gastrointestinal conditions. Psycholeptics (antipsychotics, anxiolytics and hypnotics), followed by anticonvulsants were also the most frequent repeat prescriptions issued to patients with intellectual disability visiting general practitioners in the Netherlands (37).The use patterns identified in our study were also similar to those found in a large Canadian study of people with intellectual disabilities who were eligible for the Ontario Drug Benefit Program and who examined medication use on a given date in 2009, where antipsychotics were the most commonly dispensed class, and antiepileptics and laxatives were among the most frequent classes(141). Our study findings are in contrast to those reported in the general elderly population, where cardiac therapies, analgesics, gastrointestinal agents and antithrombotics are the therapeutic classes more frequently implicated in polypharmacy (217, 228, 235, 236).

According to our findings, antipsychotics represented the most frequently reported class, confirming results of previous studies in the ID population where

antipsychotics represent the most common psychotropic class (145, 181, 237, 238), both to treat mental health conditions, and for behavioural problems which may be outside their licensed indication(145, 239), but are in contrast to the prevalence reported in the general older population in Ireland where prevalence of 1.2% and 2% have been reported(188, 240). On the one hand, in our current study there was evidence for high levels of mental health concerns; almost half of the population reported a mental health condition, but a limitation was that we did not use the term challenging behaviours, and so cannot directly compare with studies that have done so. The levels of reported use of antipsychotics were higher for those who reported excessive polypharmacy, with two thirds reporting use. While our findings do not permit conclusions to be drawn with regard to rationality or appropriateness of medicines used, the widespread use of these agents requires further evaluation since there are many well established risk factors associated with long term use including weight gain , glucose dysregulation and hyperlipidaemia in the case of the second generation (138, 241), and extrapyramidal symptoms and cognitive decline in the case of the first-generation agents(206). People with ID may be more susceptible to these side effects compared to the general population(242).

Antiepileptics were the second most commonly reported class in our study, with almost 40% exposed to these agents. In our sample, seven in ten of those with AED use had a doctor's diagnosis of epilepsy. It is established that rates of epilepsy in the ID population, far exceed that of the general population. Furthermore, it is also likely that some of these agents were used for their mood stabilising indications. Anticonvulsants were identified as the second most common class of repeat prescriptions issued to people with ID receiving general practitioner services in the Netherlands(37). The rate of use in our study was higher than reported in previous studies where prevalences of 8 and 26% has been reported (141, 142) but less than reported by Van Der Heide and colleagues among an institutionalised population with profound and multiple disability in the Netherlands(95).

Laxative use was reported by over one third of the sample, and by three-quarters of those who reported ten or more medicines, reflecting the high prevalence of constipation established in our study; 43% reported constipation as a problem and almost one fifth reporting a doctor's diagnosis of chronic constipation. Our findings also revealed a significant association between laxative use and residential settings, with over half reporting use, in contrast to over one-quarter in community group homes

and less than 10% living independently. These findings are consistent with other studies in the ID population, where high levels of constipation and laxative use have been reported for people with ID living in institutional settings (94-96).

3.4.4. Intraclass Polypharmacy

Notably, within the three most frequently reported therapeutic classes in our study, we identified a high prevalence of use of multiple agents from within the same therapeutic class (intraclass polypharmacy), further contributing to polypharmacy and excessive polypharmacy in the population. The practice of intraclass polypharmacy has been an acknowledged phenomenon in the ID population (50, 152). The use of multiple agents from the same therapeutic class may in some incidences be necessary, for example, antiepileptic polytherapy for individuals whose epilepsy is not controlled from use of a single agent (243, 244), and laxatives with different mechanisms of action, and may serve as an indicator of treatment intensification. These findings are in contrast to the general population, where increasing prevalence of polypharmacy has been attributed to different patterns of treatment intensification of therapy for common chronic conditions such as diabetes and cardiovascular disease(235, 245, 246) .We were limited with regard to ascertaining the appropriateness of these regimen due to the cross sectional study design; and it was not possible to determine clinical response to previous monotherapy regimens. In addition, we did not have information on length of exposure to intraclass regimens or severity of associated conditions. However, the longitudinal nature of our study will allow us to gather data about length of exposure to these regimens.

This pattern of practice may be of concern in the case of the antipsychotic agents as there is mounting evidence that risk of adverse reactions or side effects increases with numbers of drugs taken (175, 247). More specifically, there are findings that concomitant use of two drugs from the same class in the ID population often did not enhance clinical efficacy but was more likely to compound side effects (152, 171). Indeed, Kalachnik noted that intraclass polypharmacy could only be justified in rare circumstances(248). While emphasising that there is little research in relation to the prevalence and consequences of drugs interactions in people with ID, Sommi and colleagues suggest that genetic factors and altered metabolism increases risk (171, 247)) "Duplicate drug class prescriptions" is regarded as a potentially inappropriate

prescription as determined by STOPP (Screening Tool of Older Person's Prescriptions) criteria in the elderly (249).

We identified a high prevalence of antiepileptic polytherapy; almost 40% of those using AEDs used more than one agent, with a maximum of five concurrent agents reported. It is acknowledged that in The ID population, seizures are often "pharmacoresistant", refractory to treatment(250) and may necessitate use of multiple agents, but use of multiple agents carries increased risk of drug-drug, drug-disease interactions and adverse drug events.

The high prevalence of laxative polytherapy identified in our study is a new finding. The higher prevalence of constipation and use of multiple laxatives is likely to be multifactorial; the neurological origin of ID has been suggested as a causative factor (91), as has poor fluid intake, inactivity and low fibre diets (92). The higher prevalence of disease and decrease in age related functional ability have been proposed as mechanisms for increased risk in the general elderly population. However, while we do not have specific information as to the cause of constipation, and while acknowledging that constipation is likely to be multifactorial, it is likely that side effects of certain medication classes are likely to contribute to the presentation of constipation, specifically the significant use of drugs with anticholinergic side effects, and may reflect "the prescribing cascade" to some extent(125).

Furthermore, we identified that over 60% of those reporting laxative polytherapy were exposed to excessive polypharmacy, almost half of those reporting antipsychotic polytherapy were exposed to excessive polypharmacy and 43.8% of those reporting AED polytherapy reported use of 10 or more medicines. Thus, in addition to intra- and inter-class polypharmacy, these patients are also taking a wide variety of other medicines, further increasing the cumulative drug burden and increasing the risk of drug-drug and drug-disease interactions. Many previous studies in the ID population have reported prevalence and risks associated with intra- and inter- class polypharmacy(152), but this has not been previously studied in the context of a patient's cumulative drug burden, and constitutes an area for further study.

3.4.5. Factors Associated with Polypharmacy and Excessive Polypharmacy

Our multivariate analysis identified no significant association between polypharmacy exposure and gender ; the prevalence of multiple medicine use was equally high in males and females, a finding which is consistent with some previous ID studies (140,

233), but contrasts to those reported in the general elderly population, where women are more likely to report polypharmacy across all ages and access medical care(135, 228, 246).

While over half of our study population were aged between 50 and 64 years, our findings indicated that after adjusting for relevant confounding variables, age was not associated with polypharmacy exposure or excessive polypharmacy exposure. These findings are contradict recent findings by Haider and colleagues in Australia who identified that older age was associated with polypharmacy exposure(140). However, these findings were adjusted for age and ID severity, but not clinical conditions. Ouellette-Kuntz reported at univariate level that older adults with ID reported a greater number of medicines, but the study did not include people over the age of 65 (141). Our findings contrast with findings in the general population, where increasing age has been consistently been identified as a key determinant of polypharmacy exposure (185, 235, 251) . The correlation between polypharmacy and older age in the general population may be in part explained by increased number of age-related morbidities in some studies (252). Use of multiple drug therapy increases the likelihood of inappropriate medicines being prescribed(116). Our findings of the lack of association between age and multiple medicine use may be due to the earlier onset of disease burden, and presence of long standing co-morbidities such as epilepsy, endocrine and mental health conditions in this population, meaning that people with ID acquire multiple medicines from a young age.

After adjusting for confounding variables, our multivariate analysis revealed that place of residence was strongly associated with polypharmacy exposure, with those living in residential settings being more likely to be exposed to both polypharmacy and excessive polypharmacy. Our findings revealed that almost 40% of those living in residential settings reported 5-9 medicines and one-third reported ten or more medicines. These findings are consistent with several studies in the ID population where greater medicines use, in particular psychotropic drug use has been reported in institutional settings (145, 167), however demographic and clinical variables were not controlled for in these analyses. Lower rates of use reported for independent and community settings for people with ID in our study may in part reflect the tendency for individuals with complex mental health problems, severe ID, challenging behaviours and other chronic morbidities to remain or to be placed in institutional care. To be explored further for those living in residential settings, are the

contributions of being older, having a higher burden of chronic disease and more severe ID, and having greater access to healthcare professionals. In the general elderly population, the rate of prescribing of medicines has also been reported to be lower in community settings compared to extended care or institutional settings (253, 254). That IDS-TILDA will track its sample longitudinally may offer new opportunities to better understand the impact of "place" on polypharmacy practices. The influence of place of setting and pattern of medication use of particular relevance in the current context in Ireland, as there are renewed efforts to move people with ID from institutional settings into the community (69). Many participants who partook in Wave 1 of the study and who were in the excessive polypharmacy group and residing in institutions will be placed in community settings. Thus, the complex pharmaceutical care needs of people with ID will be increasingly managed in community settings. In the coming years it will be important to monitor what happens to medication practices upon movement into the community.

Our multivariate findings indicated that severe/profound ID was associated with polypharmacy exposure, but not excessive polypharmacy. There have been inconsistent findings in the ID in relation to the influence of ID severity on multiple medication patterns; Haider and colleagues noted a significant association between ID severity and polypharmacy, while previous studies investigating polypharmacy and cognitive function in people with ID found no association between psychotropic polypharmacy and severity (140, 181). Some conditions that may necessitate multiple therapy have a greater prevalence in those with severe/profound ID, such as epilepsy(87). While we did not have information about side effects, given the high risk of ADRs associated with use of multiple medicines (255, 256) , the potential that those with severe/profound ID may be at greater risk of the prescribing cascade, and the diminished communication abilities of individuals with severe/profound ID, detection of side effects and adverse drug reactions in these participants has been and will prove difficult, highlighting the need for extra caution in use and monitoring, and training for carers on monitoring for side effects, particularly as those with severe ID move into community settings where less formal supervision and access to healthcare professionals will be available.

Our regression model identified a number of chronic conditions associated with polypharmacy and excessive polypharmacy. As expected, and consistent with the ID literature (140, 182, 233, 257), we found that mental health and neurological

conditions were the strongest and most consistent predictors of both polypharmacy and excessive polypharmacy, they are both conditions which may necessitate lifelong therapy and multiple therapeutic interventions. The association between polypharmacy and mental health conditions and neurological disease, may also, be in part explained by the fact that the provision of medical care in this population tends to be reactive in nature i.e., if complaints or obvious symptoms are recognised or brought to the attention of medical practitioners (181, 258), and these diseases may be more symptomatic and therefore recognised and treated. Gastrointestinal disease was associated with excessive polypharmacy only, while endocrine disease and hypertension were less prevalent, but were also associated with both levels of polypharmacy exposure. Few studies in the ID literature to date have examined this relationship between medical comorbidities other than seizure and psychiatric morbidities and polypharmacy (197). Ouellette-Kuntz reported that among a large group people with ID receiving primary care services, those comorbid psychiatric diagnoses reported multiple medicines at a greater frequency, however, this was at univariate level only, and adjustments for confounding variables were not carried out. Haider and colleagues identified stroke, cancer, epilepsy, osteoporosis and diabetes, but not depression as significantly associated with polypharmacy among adults with ID in Victoria, Australia(140).

While we could not include the number of chronic conditions in our multivariate analysis, when considering the effect of chronic conditions on polypharmacy status, it is important to note that the majority of people reported more than one chronic conditions; 71% were multimorbid (53). As expected, as the number of conditions reported by an individual increased in our study, so did polypharmacy and excessive polypharmacy exposure; nine out of every ten participants reporting excessive polypharmacy were multimorbid, with an average of 3.5 conditions. The relationship between polypharmacy in older age and multimorbidity is well established in the general population (129, 259). In the ID population, a Canadian study also reported that multiple medicine use was higher for those with higher morbidity levels (141). Individuals with multimorbidity may be prescribed several drugs, each of which is recommended by a disease-specific guideline, but the result is that the overall drug burden is high and has the potential to be harmful (219, 260) . Furthermore, most individuals who report use of five or more medications are taking a unique

combination of drugs with effects that cannot be predicted from literature and studies (135, 261).

In the general elderly population, socioeconomic status, health insurance status, marital status and educational attainment have been identified as key determinants of multiple medicine use (122, 134, 228, 262, 263), with those of lower socioeconomic status being more likely to be exposed to polypharmacy. For our study, it was not possible to examine the effect of these characteristics in detail, as our sample was uniform with respect to many of these variables, almost all held a full medical card, few were employed, nearly all were unmarried and levels of educational attainment were low. However, it is likely that these factors influence patterns and frequency of medication use. Deprivation, and social exclusion have been associated with poorer health outcomes for people with ID (39, 264, 265). Given the low level of education and literacy established in our population, tailored and appropriate education for patients and carers regarding medicines is needed. To further examine these issues, Wave 2 of the IDS-TILDA study contains questions in relation to knowledge of carers in relation to medication administration, medication side effects and education received.

3.4.6. Health Care Utilization

A significant association between GP, outpatient consultations and nights spent in hospital and polypharmacy exposure was identified at the bivariate level, with those reporting polypharmacy or excessive polypharmacy accessing these services more frequently. We also identified that healthcare for the sample was being accessed most frequently at a primary care level, with less than one in ten spending nights in hospital during the previous year. The area of the relationship between healthcare utilization and polypharmacy exposure has not been studied in detail in the ID literature, but Haider and colleagues reported an association between five or more GP visits and other healthcare checks and polypharmacy exposure(140). Morgan identified that patients with ID and epilepsy in institutions were less likely to be admitted to hospital compared to those in community settings and had lower use of outpatient services(266).

There is the potential that the health needs of those with severe ID or multiple morbidities may be treated within institutional settings, because of the high availability of medical and many acute services may be provided in the institution, or the threshold

for admission to secondary care may be higher(266). It may be that with deinstitutionalisation there may be greater use of acute services, but also of referral to specialists, and that the volume and pattern of these changes in utilisation are difficult to extrapolate from the present situations. The Canadian Consensus guidelines for adults with ID in primary care settings recommends a comprehensive review of medicines at regular intervals (e.g. every three months)(205). Recommendations are also made that staff, patients and carers are educated about the appropriate use of medicines and over the counter preparations.

In the general population, increased health care utilization has been linked to polypharmacy, with Jorgensen reporting that visiting a primary care physician five or more times per year increased the risk of using five or more medicines by 15 times(267). On the other hand, those who have more complex health conditions may utilize health care at a greater frequency. In our study, almost all of participants had a full medical card, which entitles card holders to free GP visits and a range of other healthcare services, thus there is no economic barrier to access.

In the general population, older individuals who display multimorbidity may often visit multiple clinicians between primary and secondary care settings to manage these chronic conditions and may also have increased likelihood of hospitalization (130, 268).

3.4.7. Self-rated health

An association between polypharmacy and self-reported health have been found in other studies of the elderly (122, 235, 269), however, we identified no significant association between self-rated health and polypharmacy status. This is in contrast to a recent study in the ID population, where poor self-rated health was significantly associated with polypharmacy(140). However, given that we examined self-rated health as opposed to self-reported health, the effect of proxy respondents must be taken into consideration. While use of proxy respondents is useful and necessary, especially for people with severe ID, the validity of proxy respondents has been called into question, in particular for questions that require more subjectivity (270). Furthermore, carers of people with ID have tended to perceive the person that they are caring for to be healthier than the results suggested by a medical exam (39, 50, 271). This too is an area for further research, to determine as to whether this was due to multimorbidity

and perhaps severity of ID, undiagnosed diseases or unsuccessful treatment with multiple medicine use and/or side effects of medicines (145).

3.4.8. Study Strengths

This study has a number of key strengths. Firstly, to our knowledge this is the first study to examine patterns and factors associated with polypharmacy and excessive polypharmacy in a representative older population with ID. The large sample size, combined with the representativeness of the national ID population in Ireland means that these findings have the potential to be generalised to other populations with ID, and that our multivariate analysis had sufficient power. The use of proxy respondents who knew participants well (more than six months), meant that it was possible to include those with severe or profound ID. Our descriptive analysis and multivariate model considered a wide range of demographic, clinical, health care utilization and socioeconomic status, which provided a more holistic approach to examining factors affecting polypharmacy in this population. While we cannot rule out residual confounding, in our multivariate analysis we took into account demographic and other clinical potential confounders. We could not directly correlate the use of a particular class of medication to the diagnosis, it is likely that the association between conditions and that the number of medicines that we found is reliable.

The use of the two thresholds for multiple medicine use (i.e. polypharmacy and excessive polypharmacy) has not been utilised before in an ID population to our knowledge. The most up to date research suggests that polypharmacy is now commonplace, and the threshold of 10 or more medicines captures greater risk(116, 126). All medication data was independently examined and coded by two pharmacists, which increased the accuracy of medication information.

3.4.9. Study Limitations

There are a number of methodological limitations to be considered when interpreting the results for our analysis.

First, both chronic conditions and medication use reported was based on participant or proxy self-report, and thus may be liable to a misclassification bias(272). However, several steps improved the accuracy of this information: cross-checking of the medicines and chronic condition information in the pre-interview questionnaire (PIQ) at time of interview and participants receiving the PIQ at least one week in

advance of the interview, giving them sufficient time to gather information about their medicines use. Such verification of information at the time of interview is reported to have greater reliability than self-report recall methods (215).

Secondly, we do not know the extent to which answers in the face to face interview, for example in relation to self-rated health or pain, were influenced by the combination of responses styles; some interview directly with participants, some with proxy only and some adopted a hybrid approach. In keeping with the goals of inclusion of our study, of including all people with ID in the research regardless of level of ID is very important. Those with severe or profound ID were more likely to have a proxy only interview or a mixed answer style. Proxy respondents enabled non-verbal participants, or those with severe ID to partake. The validity of proxy responses on more subjective items has been called into question (270). Further research is warranted to determine the effect of the differing response styles and inclusive research.

Thirdly, we did not collect information about the length of exposure to medications, and thus we did not have information about length of exposure to polypharmacy and excessive polypharmacy. In addition, we did not have full information in relation to dose and frequency of medications. We have addressed these limitations in Wave two of the longitudinal study, and amended our data collection form to collect length of exposure and dosing information.

Fourthly, we did not have information about the severity of reported medical conditions, or previous response to medical interventions, therefore commenting on appropriateness or rationality of medication regimens was beyond the scope of our study.

Fifthly, we did not collect information as to whether people experienced side effects associated with therapies, or attitudes and knowledge in relation to medicine use.

Sixthly, the definition of polypharmacy in terms of numerical threshold of drugs does not in itself imply whether it is appropriate to prescribe multiple medicines. However, polypharmacy is a risk factor for inappropriate prescribing.

Seventh, the cross-sectional multivariate analysis examined associations between multiple medicine use and a range of explanatory variables, but it does not address cause and effect. While our model was adjusted for a range of patient and clinical characteristics, multivariate methods cannot rule out residual confounding, particularly

with respect to disease severity that is difficult to provide a precise measure of in an epidemiologic study. We could not include those with unverified ID in the multivariate model. Future waves of the study will provide additional data in relation to causation and the implications longitudinally of polypharmacy exposure in this population.

Eighth, we did not have information in relation to compliance or adherence to medication regimens.

Ninth, it was beyond the scope of the study to examine prescriber characteristics, and the influence of implicit prescriber variations and decision making on patterns of medicine use. Implicit prescriber decision making

3.4.10. Conclusions

Our findings suggest that a significant proportion of ageing people with ID are exposed to polypharmacy and excessive polypharmacy to treat multiple morbidities. Our findings support the idea of distinct patterns of multimorbidity in this population, particularly mental health conditions and neurological conditions that place ageing people at significant risk of exposure to polypharmacy and in particular excessive polypharmacy. In addition, our study suggests that often it is intraclass polypharmacy, especially in the case of the antipsychotics, antiepileptics, and laxatives that is contributing to the use of multiple medicines in the population. Medications represent a critical intervention to prolong life and improve the quality of life of older people. However, it is also important to balance that exposure to polypharmacy may not be synonymous with inappropriate treatment with a concern that polypharmacy is an important risk factor for inappropriate medication prescribing (122, 273).

By identifying patterns of multiple medicines use and factors associated with polypharmacy and excessive polypharmacy this study has begun a process to identify at risk groups, raise awareness of the unique challenges in providing appropriate pharmacotherapy to this population and encourage frequent and more rigorous monitoring of medicines. . In particular, regular collaborative medication reviews with the incorporation of a clinical pharmacist in a multidisciplinary team have been demonstrated to lead to improvements in the quality of prescribing and patient care in other populations (274). This is particularly important, as ageing people with ID represent a growing cohort who are particularly vulnerable to adverse drug events.

What is already known about this topic:

- With the growing number of older adults, use of multiple medicines is now commonplace to treat age-related chronic diseases.
- While polypharmacy may be therapeutically beneficial in the elderly, it is also a risk factor for adverse drug reactions, drug-drug and drug-disease interactions, and may contribute to falls and hospitalisation.
- In the general elderly population, polypharmacy has been well studied, and is associated with increasing age, living in institutional settings, female gender, and conditions such as hypertension, diabetes, depression, cardiovascular disease, and respiratory conditions.
- People with ID are now experiencing increased longevity, and are likely to have been exposed to multiple medicines from a younger age due to the higher prevalence of health concerns, particularly mental health and neurological diseases.
- Despite this, there have been minimal studies of factors and patterns associated with multiple medicine use in older people with ID.

What this study adds:

- Polypharmacy (use of 5-9 medicines), and excessive polypharmacy (10+ medicines) were prevalent among older people with ID; over one-fifth were exposed to ten or more medicines.
- Our findings revealed that living in residential settings, and having mental health, neurological disease were most strongly associated with both polypharmacy and excessive polypharmacy, but age and gender had no significant effect.
- Findings from our study also suggested that often it is intraclass polypharmacy, especially in the case of the antipsychotics, antiepileptics and laxatives that is contributing to the use of multiple medicines in the population.
- Older people with ID should have frequent multidisciplinary reviews of their medication regimens to assess for the risks and benefit of use of multiple therapies, and to avoid inappropriate prescribing.
- Intervention studies aimed at enhancing the appropriateness of prescribing should pay particular attention to people with ID who are taking multiple medicines.

Chapter 4. Prevalence, Patterns and Factors Associated with Psychotropic Drug Use and Psychotropic Polypharmacy in an Older Population with Intellectual Disability

4.1. Introduction

Use of psychotropic agents in the elderly is of important clinical significance (275), and these agents have improved the quality of life and function for many people diagnosed with psychiatric disorders (144). In the general population, mental and behavioural disorders are estimated to account for 12% of the global disease burden, and the World Health Organisation, upon review of evidence for the treatment of mental health conditions concluded that "a combined psychosocial and pharmacological approach is likely to yield best results"(276). However, there is ongoing international concern about the levels of use of psychotropics in older people (275, 277, 278), particularly those who live in residential care (279, 280). There is accumulating evidence of adverse cognitive effects associated with psychotropic agents in the elderly(281).

Adults with intellectual disabilities are characterised with having a higher prevalence of mental health concerns compared to the general population (114), and as outlined in *Chapter 1,* up to 62% of adults with ID exhibit behaviour that may be deemed socially inappropriate or be considered as "challenging behaviour" (156, 282, 283).

Psychotropic agents are frequently employed to treat psychopathological conditions (147, 232, 233, 257, 284). Additionally, many people with ID receive these agents on a long-term basis to treat behavioural problems in the absence of a psychiatric diagnosis (285) for which these medications may not have been indicated (239, 257, 286). Their use has been a cause for some concern due to limited empirical data in relation to efficacy, but given that people with ID have historically been under-represented in Randomised Controlled Trials (114, 148, 154, 170, 287), the robustness of scientific studies in this population may often be lacking (153). While much of the available research has focused exclusively on effectiveness of these agents in the suppression of symptoms or maladaptive behaviours, there has been little consideration for the potential for detrimental effects of these medications on positive social behaviours such as learning, and social and adaptive behaviours (288). Furthermore, the challenges presented by difficulties in communication, assessment and diagnosis, recognition of side effects, use of medications without explicit patient consent , co-ordination of social and behavioural interventions with pharmacotherapy (138, 165, 284, 285, 287) and the relative paucity of high-quality data to inform the use of medicines in this population (165, 289), give rise to increasing concern.

Prevalence of psychotropic use for people with ID has been reported to range from 40-44% for long-stay hospitals or institutional settings, to -32% for community based residential care and 9-10% for those living in independent settings (145, 167, 232, 290, 291). Findings from the study in *Chapter 3* indicated that all of the main classes of psychotropics were frequently prescribed, with participants living in residential settings being particularly likely to be exposed to intraclass polypharmacy with antipsychotics. In the context of deinstitutionalisation, there has been public and political debate about quality, location and types of mental health care services for people with ID(158).

Despite the fact that many adults with ID experience psychotropic polypharmacy (292-294), few studies focus on use of multiple agents and ,in particular, on patterns of psychotropic combinations (including psychotropic polypharmacy) used in older adults with ID (114, 295). Limitation of polypharmacy and, in particular psychotropic use has been suggested as one of the core elements of "good physical health" in elderly people with ID (32, 36). This study aims to address these gaps in information by examining the prevalence, patterns and factors associated with psychotropic use in general and psychotropic polypharmacy in a representative sample of ageing people with ID.

To address this aim our primary objectives were;

1) To determine the prevalence of psychotropic drug use and psychotropic polypharmacy;

2) to examine combinations of psychotropics in individuals, by assessing intraclass polypharmacy and interclass polypharmacy;

3) to examine the use of psychotropics in relation to reported mental health conditions and the utilization of psychiatric healthcare;

4) to determine the demographic and clinical factors associated with use of single psychotropic agents and psychotropic polypharmacy.

4.2. Methods

4.2.1. Study Design

Data from the first Wave of IDS-TILDA was analysed for this study(22). All participants with information on medications (736, 98.0%) have been included in this study. For more information on the study design, participants and medication data collection, refer to *Chapter 3*.

The flow chart for the current study is presented in *Figure 4-1*.

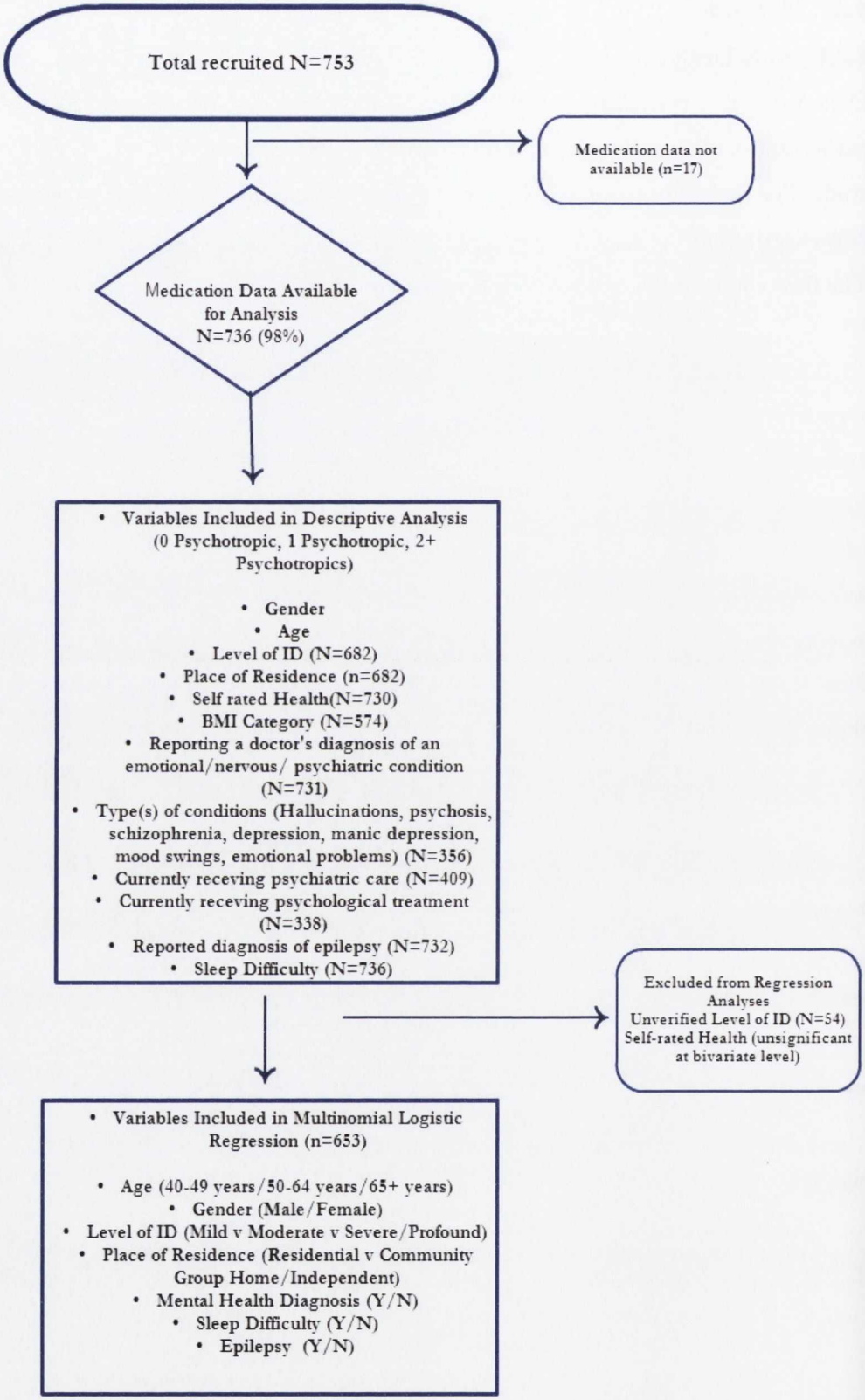

Figure 4-1 Flow chart for study

4.2.2. Psychotropic Definition

The primary outcomes of interest (the dependent variables) for this study were whether a subject had any psychotropic use, and whether a subject was exposed to use of multiple agents (psychotropic polypharmacy).

For the purposes of our study, we focused on the five major classes of psychotropic medicines used in adults:

1) antipsychotic agents (ATC N05A);

2) antidepressants (ATC NO6A);

3) anxiolytics (ATC N05B);

4) sedative / hypnotics (ATC N05C);

5) mood – stabilising agents (which included anti-epileptics (N03A) for indications other than epilepsy and lithium (N05AN01)).

A detailed list of these medications and therapeutic classes in our dataset is provided in *Table 4-1.*

This psychotropic agent classification is based on standard references, published literature, and consensus agreement between two pharmacists (Máire O'Dwyer, Martin Henman) and a Psychiatrist specialising in the treatment of people with ID (Niamh Mulryan). We counted the mood-stabilising antiepileptic medicines in our definition of a psychotropic when the patient did not report a doctor's diagnosis of epilepsy (80% of these had a doctor's diagnosis of emotional/nervous or psychiatric condition). In the case of clonazepam we reclassified this agent from an antiepileptic to an anxiolytic in participants (5) who had no diagnosis of epilepsy and had a psychiatric diagnosis.

In addition, as described in *Chapter 3;*

- Prochlorperazine was not classed as an antipsychotic
- We reclassified lithium (ATC N05AN01) as a mood stabiliser, lithium has been considered within the category of mood stabilisers previously (169, 181).
- We removed rectal diazepam from the definition of an anxiolytics, as its primary indication is for acute seizure control(296), buccal midazolam was also re-classed as for acute seizure control.
- Clobazam (ATC N05BA09) was removed from the definition of an anxiolytic in those with a diagnosis of epilepsy, as it is primarily used in epilepsy.

For the purposes of our study we employed the following definitions;

- **Psychotropic polypharmacy** :concurrent use of two or more psychotropic agents in one individual (278, 297).

In addition, we also examined patterns of use of multiple agents within and between classes using the following definitions:

- **Intraclass polypharmacy**: use or two or more agents from within the same therapeutic class (141, 168, 298). For the purpose of intraclass polypharmacy we regarded anxiolytics and hypnotics to be considered as one class (anxiolytics/hypnotics), all have a similar mechanism of action, and to enable comparability with other studies.
- **Interclass polypharmacy** : use of two or more medications from different therapeutic classes (299). For the purpose of our analysis here, the four classes were antipsychotics, antidepressants, mood stabilisers and anxiolytics/hypnotics.

Information in relation to these outcomes was combined to form the following variables;

1). A binary variable was created with those reporting use of any psychotropics (1, 0).

2). A continuous variable captured the number of psychotropics reported by an individual (range 0- 7).

3). A categorical variable was created to capture those reporting 0, 1 or 2 or more psychotropics (psychotropic polypharmacy) (0,1,2).

4). A binary variable for those reporting intraclass polypharmacy (1,0)

5). A continuous variable for the number of interclass polypharmacy combinations (range 0-5).

Data extraction from the 680 cases who reported using medications yielded 4297 medicines (excluding supplements). Further extraction resulted in 1003 reported psychotropic medications (57 different medications) for 436 participants *(Table 4-1);* this represented 23.3% of all medicines reported in the total sample.

Table 4-1 Psychotropic Medications reported in the study

Antipsychotics	Antidepressants	Anxiolytics*	Hypnotics* / sedatives	Mood stabilizers
Atypical	**TCAs**	**Benzodiazepine derivatives**	**Benzodiazepine derivatives**	**Antiepileptics**
Aripiprazole	Amitriptyline	Alprazolam	Flurazepam	Carbamazepine
Amisulpride	Clomipramine	Bromazepam	Flunitrazepam	Lamotrigine
Olanzapine	Dosulepin	Chlordiazepoxide	Lortemazepam	Valproic Acid
Quetiapine	Doxepin	Diazepam (oral)	Nitrazepam	
Risperidone	Lofepramine	Lorazepam	Temazepam	
Sulpride	Trimipramine	Prazepam	Triazolam	Phenytoin
Zisprasidone		*Clonazepam*		Phenobarbitone
	SSRIs		**Benzodiazepine-related/ z-drugs**	Pregablin
Typical	Citalopram		Zolpidem	Gabapentin
Benperidol	Escitalopram		Zopiclone	Levetiracetam
Chlorpromazine	Fluoxetine			
Fluphenazine	Paroxetine	Buspirone	**Other**	*Lithium*
Flupentixol	Sertraline		Melatonin	
Haloperidol				
Periciazine				
Trifluoroperazine	Duloxetine			
Zuclopentixol	Mianserin			
	Mirtazepine			
	Trazadone			
	Venlafaxine			

Medications were coded according to their primary psychoactive/ mental disorder. Medications in italics may be listed under different categories in the WHO ATC. In these circumstances, their coding category was decided upon by consensus and according to other pharmacoepidemiological studies.

** Considered together as one class for intraclass and interclass definitions*

4.2.3. Antipsychotic Dose Data

For the purposes of examining dosage regimens of the four most frequently reported antipsychotics (risperidone, olanzapine, chlorpromazine and haloperidol) , total daily doses (TDD) for each (if available) were extracted and compared to recommended doses listed in the British National Formulary (BNF) and The Maudsely Prescribing Guidelines in Psychiatry 11th edition as outlined in *Table 4-2(28).* Mean dose was calculated, and we examined if participants were exposed to doses higher than recommended dose or maximum dose as per the BNF and Maudsely Prescribing Guidelines.

Table 4-2 Recommended and maximum doses for Haloperidol, Chlorpromazine, Risperidone and Olanzapine according to the BNF and The Maudsely Prescribing Guidelines in Psychiatry.

	British National Formulary		Maudsley Prescribing Guidelines in Psychiatry 11th Ed.
Antipsychotic	**Recommended dose**	**Route of Administration**	**Maximum Dose**
Haloperidol (ATC N05AD01)	5-10mg daily (Max 30mg)	Po	30mg daily
Chlorpromazine (ATC N05AA01)	75-300mg daily (Max 1g)	Po	1000mg daily
Risperidone (ATC N05AX08)	4-6mg daily (Max 16mg)	Po	16mg daily
Olanzapine (ATC N05AH03)	5-20 mg daily (Max 20mg)	Po	20mg daily

4.2.4. Mental Health Conditions and Variables

Participants or their carers / proxy were asked to answer questions in relation to mental health diagnoses in the Pre-Interview Questionnaire. Participants were asked:

1. "Have you ever received a doctor's diagnosis of an emotional/nervous or psychiatric condition?"
2. "What type(s) of condition conditions (hallucinations, manic depression, mood swings, depression, anxiety, psychosis, schizophrenia, don't know, none of these conditions).
3. Do you have other emotional, nervous or psychiatric condition(s)?
4. What emotional / nervous or psychiatric condition(s) do you have? (Open text answer).

5. Do you now get psychiatric treatment for your condition (s) such as attending a psychiatrist?

6. Who gives you psychiatric treatment for your condition(s)? (Psychiatrist, General Practitioner, Other)

7. Do you now get psychological treatment for your condition(s) such as counselling or behaviour support? 8. Who provides you with psychological treatment?.

In addition, for the purpose of some of the analysis those who reported hallucinations or psychosis or schizophrenia were grouped together to describe those with a psychotic disorder.

Participants and/or proxy answered questions in relation to sleep difficulties (four categories) in the face to face interview (*Appendix 6*). A binary variable (any sleep problem) was created from these four variables (300).

4.2.5. Explanatory variables

Potential predictors of the use of psychotropics and/or psychotropic polypharmacy were identified through a review of the literature and included:

1. Predisposing variables: age, gender, level of ID, living circumstances, co-morbid epilepsy, physical health conditions, sleep problems, educational attainment, socioeconomic status , marital status, health perception;

2. Enabling factors: institutional setting, health care access, health insurance status, functional abilities;

3. Need factors: reporting a mental health condition, a sleep problem, type of mental health condition, severity of mental health conditions.

4.2.5.1. Candidate Variables Excluded

For the purposes of further descriptive and multivariate analysis, we excluded the following variables from further analysis

- Marital status: 99% of the participants were unmarried.
- Educational attainment: Levels of educational attainment were uniformly low.
- Severity of mental health conditions: We did not have information about severity of mental health conditions.
- Socioeconomic status: Of the population almost three-quarters (73.5%) were unemployed, 6.6% were in paid employment, 7.4% were in perceived employment, and a further 12% were in sheltered employment (220).

- Health Insurance status: 97% of the sample had a full medical card (22).
- Healthcare Utilization: Psychiatric and Psychological consultations were examined at a descriptive level only, due to correlation with mental health conditions.

4.2.6. Statistical Analysis

Data analyses were performed using SPSS Version 20. Descriptive statistics summarised the population reporting use of 1 psychotropic, 2 or more psychotropics (psychotropic polypharmacy), and those reporting no psychotropic exposure. The overall prevalence of psychotropic drug use was calculated as a proportion of the total eligible population (n=736). The prevalence of specific psychotropic classes and drugs was then calculated as a proportion of those who reported psychotropic use. Participants were further classified by use in bivariate analysis of no psychotropics, 1 psychotropic and ≥2 psychotropics by age, gender, and level of ID, residential setting, Body Mass Index, mental health conditions, epilepsy and health conditions. Multinomial logistic regression was used to identify factors associated with use of one psychotropic and psychotropic polypharmacy. In this model, the outcome variable had three potential outcomes and individuals who reported taking no psychotropic medications were the reference category (*Figure 4-2*).

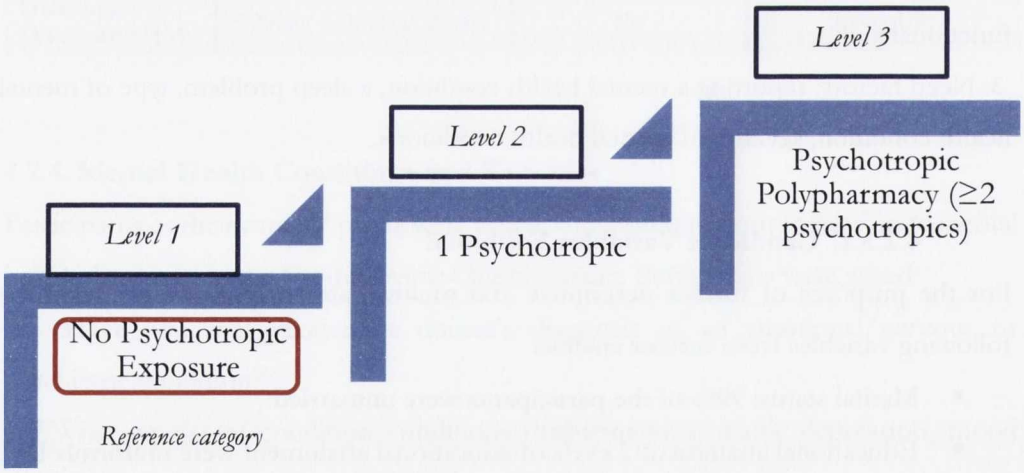

Figure 4-2 : Levels of Psychotropic Exposure for Multinomial Logistic Regression (reference category: no psychotropic exposure)

All demographic factors were included in the model (gender, age, level of ID). Those with unverified level of ID (n=54) were excluded from regression analyses. For the purposes of the multivariate analysis, those living independently and in community group homes were grouped together in a single variable due to insufficient numbers in the independent variable. Explanatory variables that had a $p<0.10$ at bivariate analysis were considered for inclusion in the final multivariate model. Self-rated health was unsignificant at bivariate level ($p=0.31$), and so was not included in the model. We employed two strategies to examine multicollinearity between explanatory variables (see *Chapter 3* for further details); examination of variance inflation factors, with a VIF of >2 being considered the cut-off, and we also examined Spearman's correlation coefficient, with correlations of greater than 0.4 being considered significant. All variables fell below the specified thresholds, indicating no concerns. All factors were entered into the model simultaneously. The full model containing all predictors was statistically significant, χ^2 (18, N=653) = 368, $P<0.001$ indicating that the model was able to distinguish between those who reported one psychotropic, psychotropic polypharmacy and no psychotropic exposure. The interpretation of the results for a specific risk factor is based, on the odds of being, for example, exposed to psychotropic polypharmacy rather than someone who does not take psychotropics. The results of the model are presented as adjusted odds ratios with corresponding 95% confidence intervals (C.I.s), with a p-value of <0.05 being considered statistically significant.

4.2.6.1. Power

Issues in relation to determining sample size and power in our study have been detailed in *Chapter 3*. In this study, the alpha level (α) was set at 0.05 or $p\leq0.05$ and the power level was set at 0.80 or beta (β) at 0.20 and we employed the following calculation: $N \geq 50 + 8m$ (where m is the number of independent variables) for testing the multiple correlation, or $N \geq 104 + m$ for testing individual predictors(226). For our multivariate regression analysis, our final model contained 7 predictors, and for 653 participants included in the regression analysis, sample size and we were assured of having at least 80% power (106 participants were needed), as discussed in *Chapter 3*. Greater than 80% power was achieved.

4.3. Results

4.3.1. Study Population

Table 4-3 includes details of the demographic and clinical characteristics of the sample with valid medication data by psychotropic status (n=736) (no psychotropic exposure, 1 psychotropic, psychotropic polypharmacy). In the total sample, 5.7% reported cerebral palsy, and less than 1% reported a diagnosis of autism in addition to ID.

Almost half (48.2%) reported a doctor's diagnosis of an emotional / nervous or psychiatric condition. Of those reporting conditions, over half (54%) reported an anxiety condition, 40% reported mood swings, 39% depression, 27.8% emotional problems, 19.1% schizophrenia or psychosis or hallucinations (not mutually exclusive), and 7.9% manic depression. Over 60% of the study population reported some difficulty with sleep (300). 44 people reported a doctor's diagnosis of any dementia.

4.3.2. Psychotropic Medication Use

In total, 436 participants reported use of psychotropics, representing 59.1% of the total sample. Of the sample reporting psychotropic use (436), just over two thirds (66.2%,288) reported concurrent use of two or more psychotropics, and over one-third (38.1%, 166) reported use of three or more psychotropics. Participants who reported psychotropic use had a mean (±SD) of 2.3 (±1.3) psychotropic medicines (maximum concurrent 7 psychotropics).

4.3.3. Profile of those Reporting Psychotropic Use and Psychotropic Polypharmacy

Almost 40% of the eligible study population were exposed to psychotropic polypharmacy, one-fifth reported use of one psychotropic and 40% had no psychotropic exposure *(Table 4-3)*. Almost half (47%) of those over 65 years reported psychotropic polypharmacy exposure, compared to 38.7% of those aged 50-64 and 35.7% of those aged 40-49 years (p=0.09). Almost half (47%) of those with severe/profound ID reported polypharmacy, in contrast to 35.1% of those with moderate ID and 38.7% of those with mild ID (p<0.001). Over half (52.4%) of those living in residential settings reported psychotropic polypharmacy compared to 34% of those living in community group homes and 12.3% of those living

independently($p<0.001$). Eight in ten of those who reported psychotropic use had at least one other chronic condition (they were multimorbid).

Table 4-3: Characteristics of the Population (n=736)

Characteristics	Total 736	No Psychotropic Use 300	1 Psychotropic 148	Psychotropic Polypharmacy 288	p-value
	N (%)	N (%)	N (%)	N (%)	
Gender					
Male	330	136 (41.2)	70 (21.2)	124 (37.6)	0.67
Female	406	164 (40.6)	78(19.0)	164 (40.4)	
Age					
40-49 years	266	121 (45.9)	50(18.4)	95(35.7)	0.09
50 – 64 years	336	137 (40.8)	69(20.5)	130(38.7)	
65+ years	134	42 (31.3)	29(21.6)	63(47.0)	
Level of ID (n=682)					
Mild	163	71(44.2)	29(17.2)	63(38.7)	<0.001
Moderate	316	144(45.6)	61(19.3)	111(35.1)	
Severe / Profound	203	59(29.1)	48(23.6)	96(47.3)	
Residence					
Independent	122	87(71.3)	20(16.4)	15(12.3)	<0.001
Community Group Home	265	115(43.4)	60(22.6)	90(34.0)	
Residential	349	99(28.4)	67(19.2)	183(52.4)	
BMI Category (n=574)					
Underweight	12	4 (33.3)	2(16.7)	6(50.0)	
Normal weight	214	75 (35.0)	48(22.4)	91(42.5)	
Overweight	173	72(41.6)	30(17.3)	72 (41.6)	
Obese	175	73(41.7)	34 (19.4)	68(38.9)	
Emotional/nervous / psychiatric condition (n=731)					
Yes	352	34 (9.7)	87(22.7)	231(65.6)	<0.001
No	352	255 (72.4)	47(13.4)	50(14.2)	
Don't know	27	10(37.0)	11 (40.7)	6(22.2)	
Any sleep difficulty	450	160 (35.6)	98(21.8)	192(42.7)	0.001
Has Epilepsy (n=732)	225	94 (41.8)	54(23.6)	78(34.7)	0.09
Any dementia (n=727)	44	12(27.3)	7(15.9)	25(56.8)	0.05
Self-rated Health (n=730)					
Excellent/good/very good	625	249(39.8)	125(20.0)	251(40.2)	0.31
Fair/poor	105	48(45.7)	23(21.9)	34(32.4)	

4.3.4. Patterns of Psychotropic Use

A wide range of psychotropic medications (57); were reported from five main psychotropic therapeutic classes (antipsychotics; typical and atypical, antidepressants, anxiolytics, sedative/ hypnotics and mood stabilisers (AEDs and lithium) (*Table 4-4).* The three most frequently reported psychotropics were the atypical antipsychotics risperidone, olanzapine and the anxiolytic diazepam; together these three agents accounting for over one quarter (29.4%) of all psychotropic medicines reported. Three different depot antipsychotic preparations were reported (zuclopentixol, flupentixol, and fluphenazine).

Table 4-4: Drugs reported by >5% of those reporting Psychotropic Use (n=436)

Drug	Class	Total psychotropic use
		% (n)
Risperidone	Antipsychotic (atypical)	25.7 (112)
Olanzapine	Antipsychotic (atypical)	23.2 (101)
Diazepam	Anxiolytic (benzodiazepine)	18.9 (82)
Chlorpromazine	Antipsychotic (typical)	16.1 (70)
Lorazepam	Anxiolytic (benzodiazepine)	15.4 (67)
Haloperidol	Antipsychotic (typical)	10.1 (43)
Zopiclone	Hypnotic (benzodiazepine-related)	8.5 (37)
Carbamazepine	Mood stabiliser (antiepileptic)	8.3 (36)
Escitalopram	Antidepressant (SSRI)	8.0 (35)
Valproic Acid	Mood stabiliser (Antiepileptic)	6.4 (28)
Quetiapine	Antipsychotic (atypical)	6.2 (27)
Paroxetine	Antidepressant (SSRI)	5.7 (25)
Citalopram	Antidepressant (SSRI)	5.7 (25)
Fluoxetine	Antidepressant (SSRI)	5.5 (24)
Sertraline	Antidepressant (SSRI)	5.3 (23)
Alprazolam	Anxiolytic (benzodiazepine)	5.1 (22)
Zolpidem	Hypnotic (benzodiazepine-related)	5.1 (22)

All other psychotropics (reported by <5%) in decreasing prevalence : flurazepam, lithium, zuclopentixol, temazepam, 106harmacodyn, venlafaxine, aripiprazole, trimipramine, trazadone, lamotrigine, fluphenazine*, trifluorperazine, pregablin, duloxetine, bromazepam, amitriptyline, flupentixol*, clomipramine, dosulepin, bromazepam, phenobarbital, amisulpride, sulpride, benperidol, lofepramine, chlordiazepoxide, nitrazepam, mianserin, gabapentin, phenytoin, levetiracetam , zisprasidone, periciazine, prazepam, doxepin, buspirone, flunitrazepam, lortemazepam, triazolam, melatonin*

** denotes depot preparations*

In total, 1003 psychotropic medications were reported by 436 participants, constituting almost one quarter (23.2%) of the total of all medicines (4297) reported in the sample. Antipsychotics and antidepressants accounted for over 40% and one-fifth of all psychotropic medications reported, respectively (*Figure 4-3*). The most frequently

reported antipsychotic agents were the atypical antipsychotics risperidone accounting for over one-quarter (27.2%) of antipsychotics reported, olanzapine : 24.5% and the typical antipsychotics chlorpromazine 16.9% and haloperidol (10.7%). The most frequently reported antidepressant agents were: the SSRIs escitalopram, citalopram, paroxetine and fluoxetine. Anxiolytics accounted for almost one-fifth of psychotropics reported with diazepam most frequently reported agent accounting for over 40% of anxiolytics reported, followed by lorazepam and alprazolam. The sedative /hypnotic agents accounted for 10.2%, with zopiclone being most frequently reported, followed by zolpidem and the benzodiazepine agent flurazepam. Mood stabilising agents accounted for almost 10.5% of psychotropics reported, with the antiepileptics carbamazepine and valproic acid being most frequently reported, and 19 people reported lithium.

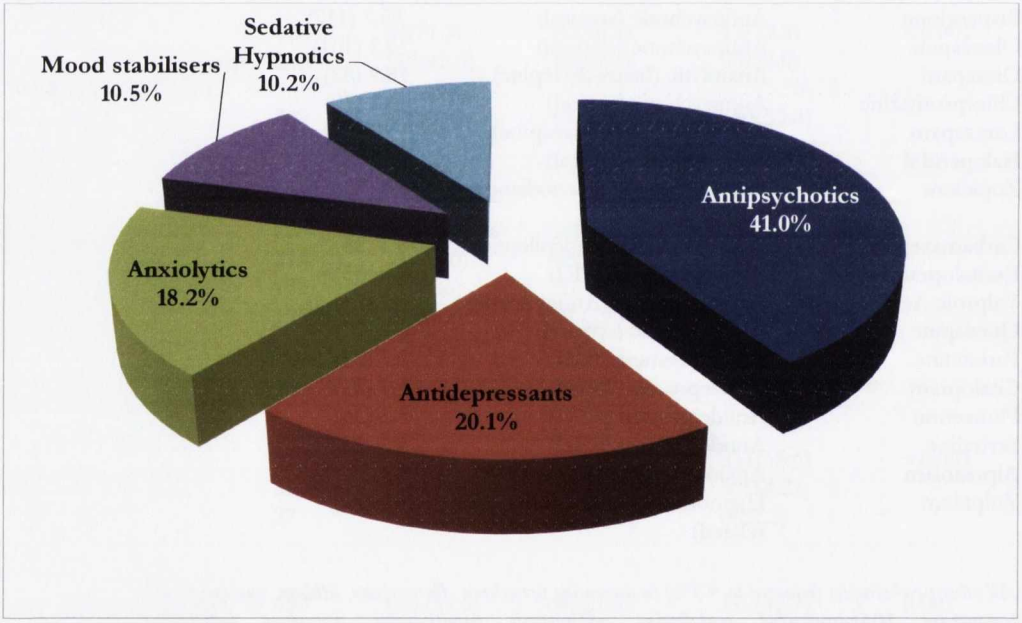

Figure 4-3: Contribution of therapeutic classes to psychotropic medication use

As may be seen in *Table 4-5 (*and *Appendix 8)*, almost half of psychotropic monotherapy regimens consisted of antipsychotics while almost nine out of ten participants who reported psychotropic polypharmacy recorded an antipsychotic agent as part of the regimen. Over half of those who reported polypharmacy reported use of antidepressants and anxiolytics. In total, 30% of the sample used an anxiolytic/hypnotic. Mood stabilisers were mainly used as part of a polypharmacy regimen.

Table 4-5 Psychotropic Class by Monotherapy and Polypharmacy (n=436)

	Regimen		
Psychotropic Class	**1 Psychotropic (n=148)**	**Psychotropic Polypharmacy (n=288)**	**Total (n=436)**
	n(%)	*n(%)*	*n(%)*
Antipsychotics	69 (46.3)	250 (86.8)	319 (73.1)
Antidepressants	34 (23.1)	159 (55.2)	193 (44.4)
Anxiolytics	26 (17.7)	147 (51.0)	173 (39.7)
Hypnotic/sedative	13 (8.8)	87 (30.2)	100 (23.0)
Mood stabiliser	6 (4.1)	82 (28.5)	88 (20.3)

4.3.4.1. Psychotropic Use, Residential Setting

Further analysis of psychotropic use by place of residence are presented in *Table 4-6*. Almost three-quarters (70.1%) of those living in residential settings reported psychotropic use, compared to over half (56.6%) of those living in community group homes and over one –quarter (28.7%) of those living independently or with family (T. There was also a greater prevalence of those reporting two or more mental health diagnoses in residential settings; 37.7% in contrast to 31.4% in community group homes and 8.8% independently. Almost one-fifth of those living in residential settings reported intraclass polypharmacy. With regard to concurrent use of multiple psychotropics, over half (52.4%) of those living in residential settings reported use of 2 or more psychotropics in contrast to 40% of those living in community group homes and 12% of those living independently. Interclass polypharmacy was greatest in residential settings with half (50.7%) reporting interclass polypharmacy, compared to 29.4% in community group homes and 12.3% independently.

Over half (54.1%) of those living in residential settings reported receiving antipsychotics , in contrast to 41.5% of those living in community group homes and 15.6% among those living independently. Use of antidepressants was greatest in residential settings, with one-third (33.5%) reporting use, compared to over one-fifth (21.9%) living in community group homes and 14.8% of those living independently. Use of anxiolytics and hypnotics was markedly higher among those living in residential settings; over one-third reported anxiolytic and over one-fifth reported hypnotics, while in community group homes use was reported at 17.0% and 9.8% respectively, and 6.6% and 5.7% for these agents in independent settings.

Table 4-6: Patterns of Psychotropic Use by Place of Residence (n=736)

	Total (n=736)	Independent (n=122)	Community Group Home (n=265)	Residential (n=349)
	n (%)	n(%)	n (%)	n (%)
Any Psychotropic	436 (59.1)	35 (28.7)	151 (56.6)	250 (71.6)
1 psychotropic	148 (20.0)	20 (16.4)	61(22.6)	67 (19.2)
Psychotropic Polypharmacy	288 (39.1)	15 (12.3)	90 (40.0)	183 (52.4)
Therapeutic Class				
Antipsychotics	319 (43.2)	19 (15.6)	111 (41.5)	189 (54.2)
Antidepressants	193 (26.2)	18 (14.8)	58 (21.9)	117 (33.5)
Anxiolytics	173 (23.5)	8 (6.6)	45 (17.0)	120 (34.4)
Hypnotics	100 (13.6)	7 (5.7)	23 (8.7)	70 (20.1)
Mood stabilisers	88 (12.0)	4 (3.3)	26 (9.8)	58 (16.6)
Interclass Polypharmacy	265(36.0)	15 (12.3)	77(29.3)	173(48.7)
Intraclass Polypharmacy	133 (18.1)	4(3.3)	35(13.2)	94(26.9)
Has emotional / nervous or psychiatric condition (n=731)				
Yes	352 (48.2)	26 (21.5)	119 (45.2)	207 (59.7)
No	352 (48.2)	92 (76.0)	129 (49.0)	131 (37.8)
Don't know	27 (3.7)	3 (2.5)	15 (5.7)	9 (2.6)

4.3.5. Psychotropic Use by Age

Patterns of psychotropic use by age are presented in *Table 4-7*. There was a significant association (p=0.03) between psychotropic use and age, with over two-thirds (68.7%) of those over 65 with psychotropic exposure, compared to 59.2% of those aged 50-64 years and 54.1% of those aged 40-49 years. Use of antidepressants was greater (p=0.05) among those over 65, with almost one third (32.8%) with consumption, compared to 27.1% of those aged 50-64 and 21.8% of those aged 40-49 years.

Table 4-7 Psychotropic Exposure and Therapeutic Classes by Age

Psychotropic Medication	Total (n=736) N (%)	Age 40-49 years (n=266) N (%)	50-64 years (n=336) N (%)	65+ years (n=134) N (%)
Any psychotropic	436 (59.1)	144(54.1)	199 (59.2)	92 (68.7)*
Number psychotropics				
No psychotropic exposure	300(40.7)	122 (45.6)	137(40.8)	42 (31.3)
1psychotropic	148 (20.0)	49 (18.4)	69 (20.5)	29 (21.6)
2 psychotropics	122 (16.6)	40 (15.0)	53 (15.8)	29 (21.6)
3+psychotropics	166 (22.6)	55 (20.7)	77 (22.9)	34 (25.4)
Therapeutic Class				
Antipsychotics	319 (43.2)	108 (40.2)	145 (43.2)	66 (49.3)
Antidepressants	193 (26.2)	58 (21.8)	91 (27.1)	44 (32.8)*
Anxiolytics	173 (23.5)	60 (22.6)	82 (24.4)	31 (23.1)
Hypnotics and sedatives	100 (13.6)	30 (11.3)	48 (14.3)	22 (16.4)
Mood Stabilisers	88 (11.7)	25 (9.4)	41 (12.2)	22 (16.4)
Interclass Polypharmacy	267(36.3)	88 (33.0)	119(35.4)	58 (43.3)
Intraclass Polypharmacy	133(18.1)	35(16.5)	46(18.5)	20(20.1)
Reported Mental Health Condition (n=731)				
Yes	352 (48.2)	111 (42.0)	161 (48.3)	80 (59.7)*
No	352 (48.2)	144 (54.5)	157 (47.1)	51 (38.1)
Don't know	27 (3.7)	11 (4.1)	15 (4.5)	3 (2.2)

**significant at p<0.05*

4.3.6. Patterns of Antipsychotic Use

Antipsychotics were the most frequently reported drug class in our sample with 412 antipsychotic agents reported by almost three quarters (73.1%, 319) of those who reported use of psychotropics. The antipsychotic agents accounted for over 40% of reported psychotropics in the cohort (*Appendix 9*). In total, 15 different antipsychotics (7 atypical, 8 typical) were reported including three depot preparations (zuclopentixol, fluphenazine, flupentixol) and the atypical antipsychotics accounted for almost two thirds (62.9%) of antipsychotics reported. There was no reported use of clozapine. Of those reporting antipsychotics use (319), nine in every ten used one or more of the four most frequently reported agents: risperidone, olanzapine, chlorpromazine and haloperidol. Levels of intraclass polypharmacy was greatest among those reporting antipsychotics, with just over one quarter (25.8%, 82) of those who reported use of

antipsychotics reporting concurrent use of 2 or more antipsychotic agents (maximum 4).

In terms of those reporting use of one antipsychotic (n=237), just over three quarters (75.3%) reported use of an atypical agent as monotherapy while 24.3% reported typical antipsychotic monotherapy, with the atypical antipsychotics risperidone (34.9%) and olanzapine (29.4%) most frequently reported.

Among those reporting antipsychotic polytherapy (n=82), over three-quarters (76.8%) reported a mixed polytherapy regimen consisting of both typical and atypical agents. In terms of specific antipsychotic medications, while most agents were more commonly employed as monotherapy, chlorpromazine and haloperidol were more frequent as an intraclass regimen: half of those reporting intraclass antipsychotic polypharmacy reported chlorpromazine and one-third reported haloperidol.

Interclass polytherapy was also common, with almost three-quarters (73.9%) of those who reported antipsychotic use reporting use of agents from other psychotropic classes. Anxiolytics were the most commonly reported concurrent psychotropic class (37.7%), *(Table 4-8).*

Just over four-fifths (80.3%) of those who reported antipsychotic agents, reported having being diagnosed with an emotional, nervous or psychiatric condition, one-quarter (25.2%) of those reporting antipsychotic use, reported a psychotic diagnosis (schizophrenia, psychosis or hallucinations). Of those reporting dementia (44), 45.5% also reported antipsychotic use.

4.3.7. Profile of Participants who Reported Antipsychotic Polytherapy

The profile of those taking antipsychotics is presented in *Table 4-8*. Of those taking antipsychotics (319), one-quarter (25.8%, 82) reported concurrent use of two or more agents (maximum four reported). Of those reporting antipsychotic polytherapy, 70.7% (58) reported use of multiple oral agents and 29.3% (24) reported use of combinations of depot and oral agents.

Over three-quarters of those reporting antipsychotic polytherapy (76.8%, 63) reported mixed regimens consisting of typical and atypical agents. Combinations of two or more typical agents were reported by 14.6% of those reporting polytherapy and combinations consisting of all atypical agents accounted for 8.5% of polytherapy regimens.

Over four-fifths (81.5%) of these participants reporting antipsychotic polytherapy reported a doctor's diagnosis of an emotional /nervous or psychiatric condition. Almost half (49.4%, 40) reported mood swings. Almost one-third (32.9%, 27) reported depression, and one third (34.1%, 28) reported emotional problems. In terms of psychotic diagnosis, 29.6% (24) of those reporting antipsychotic polytherapy reported one or more of hallucinations / schizophrenia or psychosis, with 8 reporting two or more of these diagnosis. 18.5% (15) reported schizophrenia, 12.3% (10) reported psychosis. 5 participants (6.2%) reported manic depression. Three participants who reported antipsychotic polytherapy reported that they did not know their particular diagnosis or they had none of the mentioned diagnoses. Almost two-thirds (63%) of those reporting multiple antipsychotics lived in residential settings, with almost one-third (32.1%) were living in community group homes and 4.9% living independently.

In terms of concurrent use of other psychotropic classes, over four-fifths (82.7%) of those who used two or more antipsychotics reported use of combinations from other psychotropic classes (interclass polypharmacy). The most common combinations in this group, were use of antipsychotic polytherapy with anxiolytics reported by over half (48%), followed by antidepressants (42.7%).

Table 4-8 : Profile of Antipsychotic Use and reported psychotropic co-medications (n=319)

	Total (n=319)	Monotherapy (n=237)	Intraclass polypharmacy (n=82)
	n (%)	*n (%)*	*n (%)*
Atypical Antipsychotics			
Olanzapine	101 (31.9)	71(30.0)	30(36.6)
Risperidone	112 (34.8)	83 (34.9)	29 (35.4)
Amisulpride	2 (0.6)	2 (0.9)	0 (0)
Sulpride	2 (0.6)	2 (0.9)	0 (0)
Aripripazole	14 (4.4)	6 (2.6)	8 (9.8)
Quetiapine	27 (8.5)	17 (7.2)	10 (12.2)
Ziprasidone	1 (0.3)	0 (0)	1 (1.2)
Typical Antipsychotics			
Benperidol	2 (0.6)	0 (0)	2(2.4)
Chlorpromazine	70(22.0)	29 (12.3)	41 (50.0)
Fluphenazine*	7 (18.9)	2 (0.9)	5 (6.1)
Flupentixol*	4 (1.3)	0 (0)	4 (6.3)
Haloperidol	43 (15.0)	17(39.5)	26(31.7)
Periciazine	1 (0.3)	0 (0)	1 (1.6)
Trifluoroperazine	7 (2.2)	5 (2.1)	2 (3.2)
Zuclopentixol*	18 (5.7)	4 (1.7)	14(17.0)
Interclass polypharmacy			
Any other psychotropic	236 (74.2)	168 (71.1)	68 (82.9)
Antidepressant	129 (40.9)	94 (40.3)	35 (42.7)
Anxiolytic	120 (37.7)	82 (34.7)	38 (46.3)
Hypnotic/sedative	70 (22.1)	42 (17.8)	28 (34.1)
Mood stabiliser	73 (22.9)	47 (19.9)	26 (31.7)
Anticholinergic	112 (35.2)	64 (27.1)	48 (58.5)
Mental health diagnosis			
Yes	254 (80.3)	188 (80.3)	66 (81.5)
No	52 (16.5)	37 (15.8)	15 (18.5)
Don't know	10 (3.1)	9(3.8)	1 (1.2)
Type of condition			
Psychotic diagnosis	81 (25.6)	57 (24.4)	24 (29.6)
Manic Depression	21 (6.6)	16 (6.8)	5 (6.2)
Mood swings	109 (34.5)	69 (21.8)	40 (49.4)
Anxiety	137 (43.4)	101 (32.0)	36 (44.4)
Depression	96 (30.4)	69 (29.2)	27 (32.9)
Emotional Problems	77 (24.4)	49 (20.8)	28 (34.1)

**depot medicines*

4.3.8. Antipsychotic Doses

Mean doses and ranges of the four most frequently reported antipsychotics where participants had dosing data available (risperidone, olanzapine, chlorpromazine and haloperidol) are presented in *Table 4-9.*

Over half (54%) of those reporting risperidone and almost three-fifths (59%) of those reporting olanzapine use had specified dosing data available. Of the 55 people with specified daily doses of risperidone, mean total daily dose was 2.3 mg, with a range of 1-8mg daily. Of the 58 people with specified daily doses, the mean total daily dose was 10mg daily with a dose range of 3-30 mg daily. One participant taking olanzapine was exposed to a dose exceeding the maximum daily dose (30 mg).

Over three-fifths (62.8%) of those who reported chlorpromazine and 65.1% of those who reported haloperidol had specified doses. 'As required' doses were reported; chlorpromazine use (18.5%) and haloperidol (9.3%). The mean total daily dose reported by participants for haloperidol was 10.6 mg. The average total daily dose recorded for those who had specified doses was 107 mg which falls within the recommended dose with the dose range between 5-250 mg daily. The dose range recorded for haloperidol of 1-60mg daily and for chlorpromazine was 5-250 mg daily. There were no records of any exceeding the recommended or exceeding the maximum specified dose in those who reported chlorpromazine. Four of those who reported haloperidol had doses greater than recommended or greater than the maximum specified (20 mg), particularly for older patients.

Table 4-9 Total Daily Doses of people who reported Risperidone, Olanzapine, Chlorpromazine and Haloperidol

	Dose specified n	Mean daily dose	Dose range	As required n	Exceeding recommended doses
Risperidone (n=112)	60	2.3mg	1-8mg	5	-
Olanzapine (n=101)	59	10mg	3-30mg	1	1
Chlopromazine (n=70)	44	107mg	5-250mg	13	-
Haloperidol (n=43)	28	10.6mg	1-60mg	3	4

4.3.9. Intraclass Polypharmacy

Overall, 30.5% (133) of those who reported psychotropic use were exposed to intraclass polypharmacy. The level of intraclass polypharmacy was greatest among those reporting antipsychotics, with just over one quarter (25.6%, 82) of those who reported use of antipsychotics reporting concurrent use of 2 or more antipsychotic agents (maximum 4), and almost one-quarter (23.5%,52) of those who reported anxiolytics/hypnotics reporting two agents, and 11.4% of those using mood-stabilising agents using more than one. 4.7% of those reporting antidepressant uses reported use of two or more agents. Eleven participants reported use of multiple agents in two different classes, for example use of two antipsychotics and two antidepressants concurrently.

4.3.10. Interclass Polypharmacy

Interclass combinations among the four groups (with anxiolytics and hypnotics combined), are presented in *Figure 4-4*. Among those reporting psychotropic medication use (436), almost two-thirds (62.%, 265) reported interclass polypharmacy, with the majority (60%, 161) reporting use of two psychotropic agents from different classes, one-third reported psychotropic agents from three different classes, and 5.9%(15) reported concurrent use of agents from four or more different therapeutic classes.

The most frequently reported interclass combinations were antipsychotics with anxiolytics/hypnotics, by one third (34.9%) of those with psychotropic exposure, and antipsychotics with antidepressants reported by 29.8% (129 of participants who reported psychotropic use.

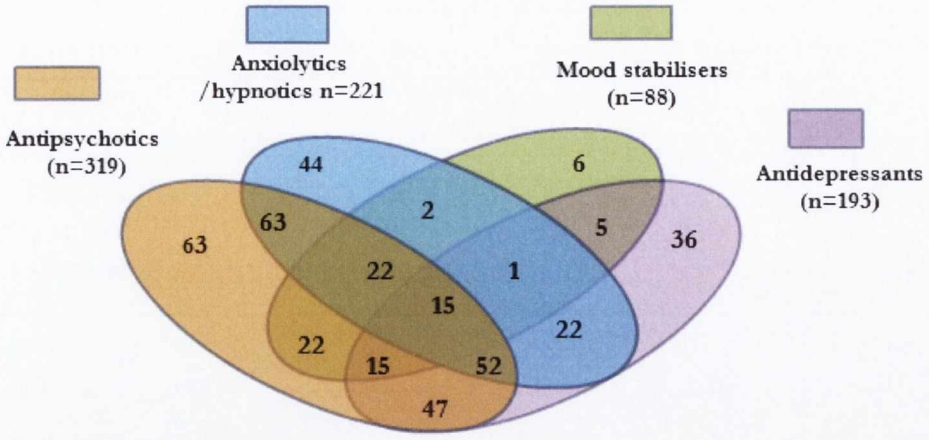

Figure 4-4: Interclass Combinations among four psychotropic classes

Of those reporting psychotropics, 3.6% were exposed to all four psychotropic classes, 11.9% were exposed to antipsychotics, anxiolytics/hypnotics and antidepressants concurrently. Of those with psychotropic exposure, one-quarter (113 participants) were exposed to both inter- and intra-class polypharmacy (e.g. two antipsychotics combined with an antidepressant).

4.3.11. Psychiatric Healthcare Utilization

Utilization of psychiatric and psychological services by psychotropic status is presented in *Table 4-10*. Of those who answered the question in relation to whether they were currently receiving psychiatric treatment (409), almost 80% (79.0%) reported receiving psychiatric treatment; 74% reported use of a psychotropic with psychiatric treatment and 5% reported neither psychotropic nor psychiatric treatment.

Almost 70% reported psychiatric treatment from a psychiatrist (this represents both general adult and ID psychiatrists), over one-quarter (26.9%) reported psychiatric treatment with a combination of psychiatrist and another practitioner (in nearly all cases , this was a general practitioner), 1.2% received treatment from a general practitioner alone and less than 1% reported receiving psychiatric treatment from other sources.

Table 4-10: Psychotropic Use, Psychiatric treatment (n=409), Psychological Treatment (n=338)

	Psychiatric Treatment (n=409)		Psychological Treatment (n=338)	
	Yes (n=323) % (n)	**No (n=86)** % (n)	**Yes (n=191)** % (n)	**No (n=147)** % (n)
Psychotropic Use				
Yes	74 (303)	9 (37)	54 (181)	38 (129)
No	5 (20)	12 (49)	3 (10)	5 (18)

Of those with valid responses for the question in relation to psychological treatment(338) (*Table 4-10)*, over half (56.5%) reported psychological treatment; 54% reported psychological treatment in addition to psychotropic use and 3% reported psychological treatment alone . In terms of the practitioner providing psychological treatment, 65% reported this to be a psychologist, 19.8% a Clinical Nurse Specialist, 6.3% a counsellor, and 25% reported psychological treatment from another practitioner. In terms of those with eligible answers to reported polypharmacy exposure (n=222), 60% reported combined approaches of psychiatric and psychological treatment.

Less than 1% of the total population spent nights in a psychiatric hospital in the previous year. In terms of nights in general hospital, 15.8% of those reporting psychotropic use had been admitted to a general hospital in the previous year, compared to 7.8% of those with no psychotropic exposure.

4.3.12. Factors associated with psychotropic use and psychotropic polypharmacy

Results from the multinomial logistic regression are presented in *Table 4-11*. The model as a whole explained 43.2 %(Cox and Snell R Squared), and 49.2% (Nagelkerke R Squared) of the variance in polypharmacy status. Having a mental health condition and reporting a sleep difficulty was associated with both use of one psychotropic and psychotropic polypharmacy, controlling for all other factors in the model. Living in a residential setting was associated with an increased risk of exposure to psychotropic polypharmacy but not one psychotropic alone. The odds ratio of 0.51 for epilepsy and psychotropic polypharmacy was less than one, indicating that those with epilepsy were significantly less likely to report psychotropic polypharmacy, controlling for other factors in the model. Age, gender or levels of intellectual disability were not significant

factors in predicting use of one psychotropic or psychotropic polypharmacy in the model.

Table 4-11: Results of Multinomial Logistic Model of Factors Associated with Use of 1 psychotropic and psychotropic polypharmacy (n=653)

	Psychotropic Use			
	1 psychotropic		Psychotropic Polypharmacy	
Characteristic	**OR (95% CI)**	**P-Value**	**OR (95% CI)**	**P-Value**
Gender				
Male	1.00		1.00	0.61
Female	0.92(0.56-1.51)	0.74	0.89(0.55-1.42)	
Age				
40-49 years	1.00		1.00	
50-64 years	1.41(0.81-2.44)	0.22	0.98 (0.59-1.65)	0.95
65+ years	1.81(0.87-3.77)	0.11	1.26(0.63-2.50)	0.52
Level of ID				
Mild	1.00	0.032	1.00	0.33
Moderate	1.05(0.53-1.91)		0.75(0.41-1.36)	
Severe/profound	2.26(1.07-4.78)		1.42(0.70-2.87)	
Residence				
Independent/ Community				
Group Home	1.00		1.00	
Residential	0.95(0.54-1.65)	0.85	**2.45(1.45-4.14)**	**<0.001**
Sleep				
No sleep problem	1.00		1.00	0.01
Sleep problem	**1.67 (0.99-2.81)**	**0.06**	**1.92 (1.17-3.15)**	
Mental Health Condition				
No	**1.00**		**1.00**	
Yes	**14.71 (8.52-25.40)**	**<0.001**	**37.56(22.30-63.26)**	**<0.001**
Epilepsy				
No	1.00		**1.00**	
Yes	1.19 (0.70-2.02)	0.53	**0.53(0.31-0.89)**	**0.02**

Reference category = no-polypharmacy, $p<0.05$ is significant, all significant factors in bold
Cox and Snell $r^2 = 0.432$, Nagelkerke $r^2 = 0.49$

4.3.13. Anticholinergic Agents and other Drugs with Central Effects

In the sample (n=736), 16.4% (121) participants reported use of anticholinergic agents (ATC Code N04A). The most commonly reported anticholinergic agent (for 11.5% of the total eligible population) was biperiden. Reported prevalence of Parkinson's was low in the population; <1%. Of those with cerebral palsy (43), 4.7% had anticholinergic use. Over one-quarter (26.9%) of those reporting psychotropic use reported concurrent anticholinergic use in contrast to 1.3% of those who did not report psychotropic use. Of those participants in the sample reporting anticholinergic use (121), 92% (111) reported concurrent use of antipsychotics (*Table 4.3-6).* Use of anticholinergics was greater among those reporting antipsychotic polytherapy, with over one-half (58.5%) reporting a concurrent anticholinergic, compared to just over one quarter (26.8%) of those who reported antipsychotic monotherapy. Use of anticholinergics was greatest (83.3%) among those who reported polytherapy with all typical agents (n=12).

Over one-quarter (28.1%) of those reporting psychotropic use reported use of anti-epileptics for the treatment of epilepsy (had a recorded doctor's diagnosis), while 3% concurrently reported drugs for dementia. Just over 5% (23) of those reporting psychotropic use reported use of opioid analgesics (the majority of these being paracetamol-codeine combinations and tramadol), and 5% reported concurrent use of sedating antihistamines (ATC code R06AB / R06AD). Use of stimulants was negligible, with less than 1% reported use. There were no reports of the use of the opioid antagonists naloxone and naltrexone.

4.4. Discussion

4.4.1. Principal Findings

Psychotropic use was commonplace in this representative sample of ageing people with ID; almost six out of every ten (59.4%) people reported use of at least one psychotropic. Furthermore, psychotropic polypharmacy was prevalent, with 40% of the total sample exposed to psychotropic polypharmacy (this accounted for over two-thirds of those reporting psychotropic use). Psychotropic medicines accounted for almost one-quarter of all medicines reported by cohort and a wide range of psychotropic medicines (almost 60) and a wide range of combinations were reported, with antipsychotics with antidepressants and antipsychotics with anxiolytics/hypnotics being the most common combinations. The antipsychotics represented the most frequently reported psychotropic (and non-psychotropic) class, by over 40% of the total sample and almost three –quarters of those who reported psychotropic use.

We identified a wide variety of combinations, with almost nine out of ten of exposed psychotropic polypharmacy reporting use of at least one antipsychotic agent as part of the regimen. We noted that almost two-thirds of those reporting psychotropic use were exposed to interclass polypharmacy, and three in ten reported intraclass therapy. In addition to reporting a mental health condition, living in a residential setting and experiencing sleep problems were associated with psychotropic polypharmacy in our multivariate analysis, while those with epilepsy were less likely to report psychotropic polypharmacy. The high prevalence of use identified may be accounted for, in part, by the high prevalence of mental health conditions reported; almost half of the population reported at least one mental health condition. Almost three-quarters of those exposed to psychotropic agents reported a doctor's diagnosis of a mental health condition, with anxiety and depression being most common. Furthermore, eight in ten of those with psychotropic use had at least one other chronic condition.

There are wide and varying estimates of prevalence of psychotropic use in the ID population, and some of this variation is accounted for by differences in the definition of psychotropics, sample age and source and whether autism is included in the definition of an intellectual disability. While making direct comparisons is not

possible, our findings of prevalence of psychotropic use are similar to those found in a recent study by Tsiouris et al., (144) of 4069 adults with ID (including ASD) living in New York state, where 58% reported use of psychotropics, but greater than other studies: Van Der Heide identified a prevalence of 46% for psycholeptics among 254 people with severe intellectual disability in residential settings in the Netherlands(95), and another study reported a prevalence rate of 37% for psychotropic medications for 300 community dwelling individuals (147), while Spreat noted a prevalence of 34.3% for 2373 individuals with ID in Oklahoma who were living in a variety of settings(180).

Our findings for psychotropic use are considerably higher than those reported in the general population, the Northern Ireland Study of Health and Stress reported 14.9% (240), while in Ireland, among 6,666 community dwelling adults over 50 years, prevalence of antipsychotic, antidepressant, and anxiolytic use was established as 1.2%, 6.3%, and 5.5% respectively(188).

4.4.2. Antipsychotic Use

Our study found that antipsychotics were the most frequently reported psychotropic class, with 42.3% of the total sample reporting use, and almost three-quarters of those who reported psychotropic exposure reporting antipsychotic use. This finding is consistent with other studies in the ID population, where the antipsychotics were the most frequently employed agent(144, 145, 147, 232, 238, 290). Our findings are similar to a recent study of Tsiouris and colleagues , who reported a prevalence of 45% for antipsychotic use(144), while De Kuiper reported use in 32.2% of 2373 individuals in Norway living in residential settings of three care provisions (238), and Spreat and colleagues reported a prevalence of 20% for antipsychotic use(180). We observed that use of antipsychotics was greatest among those over 65 years, where use confers greatest risk, with almost one half of those aged over 65 years reporting use and over 10% receiving two or more agents. Our study revealed substantially greater prevalence of use, compared to the general Irish population; the Irish Longitudinal Study on Ageing reported a prevalence of 1.2% among 6,666 community dwelling adults over 50 years(188), while the Northern Ireland Study of Health and Stress reported a 12-month prevalence of 2% for 4340 adults between 2004 and 2008(240)

We found that four-fifths of those reporting antipsychotic consumption reported a mental health condition, and one-quarter a psychotic diagnosis (psychosis/schizophrenia/hallucinations). Antipsychotics represent the most

important, yet most controversial drug class for behavioural problems (301). However, determining indication and appropriateness of use was limited in that we did not have information in relation to challenging behaviours, severity of mental health conditions, or length of exposure to psychotropic medicines. However, evidence in the ID literature suggests that they are more often use for behavioural problems, and that many people with ID take antipsychotics for many years (288).

In terms of drug selection, while a wide range of agents were reported (15), we established that 9 in 10 of every person taking antipsychotics reported the use of one or more of the four most frequently reported antipsychotics; risperidone, olanzapine, chlorpromazine and haloperidol. There was also substantial use of the second generation agent quetiapine. These frequently reported medications are similar to that reported by Paton in a UK audit of prescribing of antipsychotics for people with ID, who reported that these same 5 medications accounted for three-quarters of antipsychotics prescribed(11). Our findings of common drug selection were also similar to a Canadian study consisting of 52,404 adults aged 18-64 years with developmental disabilities living in primary care and receiving support from the Ontario Disability Support Group where risperidone, olanzapine and quetiapine were most commonly reported(141). In our study, we observed substantial use of older agents, with over one –quarter of antipsychotics reported being typical agents, the majority being oral preparations. Our findings are in contrast to Tsiouris and colleagues who reported infrequent prescribing of haloperidol and chlorpromazine (144). Furthermore, our findings revealed that over one-fifth of those reporting antipsychotics reported chlorpromazine and 14% reported haloperidol, both agents that carry significant anticholinergic, noradrenergic and antihistamine adverse effects and are no longer recommended in the elderly(29, 302-304). While a limitation of the study is that we did not have information about length of exposure to these agents, these finding may be related to the fact that that high rates of reported use of these agents may be historical, with evidence from other ID studies suggesting that these agents are often utilized for many years by people with ID (288).

Our findings reveal a higher level of antipsychotic polytherapy than previously reported; with one-quarter of those receiving antipsychotics reporting two or more agents, compared to rates of 19%, 15% and 12% reported by Ouellette, Paton and De Kuiper respectively(11, 141, 152, 238). We observed a higher prevalence of polytherapy in residential settings, with three-quarters of those reporting antipsychotic

polytherapy living in residential settings. Reasons for the higher reported prevalence of antipsychotic polytherapy in our study are unclear, but are perhaps partly related to differences in patient characteristics and increasing severity of illness. We did not have information in relation to the severity of the mental health conditions, or of previous response to monotherapy, but previous research in the general population suggests an association between symptom severity and antipsychotic polytherapy (305, 306). While our findings do not permit conclusions to be drawn about rationality or appropriateness of these agents, the extensive evidence demonstrating marginal clinical benefits and the potential for serious adverse drug reactions with these agents, including death (307, 308) must be considered. No one in the study reported clozapine; clozapine is less frequently utilized in the ID population due to issues relating to blood testing and monitoring, consent and side effect reporting(309).

In relation to antipsychotic combinations and regimens, our findings were similar to Paton, where risperidone and olanzapine were most commonly used as monotherapy, while first generation haloperidol and chlorpromazine were more frequently used in combination antipsychotic therapy(11). The high prevalence of use of multiple antipsychotics, especially oral preparations may be a cause for concern, with the only justification for multiple antipsychotic use may be treatment- resistant schizophrenia. ID may be a risk factor for greater psychotropic side effects, for example tardive dystonia (175) and this practice may be considered to be "high risk prescribing. "Antipsychotic polytherapy is only recommended in "exceptional circumstances" , and should generally be avoided due to the known risks of QT prolongation and sudden cardiac death (301, 310). Careful monitoring of potential drug interactions must be exercised when polytherapy is employed, particularly in light of that most psychotropic medications are metabolised by the cytochrome P450 isoenzyme. Research in relation to use of combined antipsychotics is sparse in this population, therefore risks and benefits in relation to their use if often empirical based (experience based), and less evidence based (114).

A recent study of the people with ID receiving antipsychotics, participants had little knowledge about their medicines beyond dosing, and were generally accepting of the side effects they were experiencing (311),with reliance on carers for knowledge.

Reassuringly, the vast majority of recorded antipsychotic doses for both typical and atypical agents fell within the recommended range. Only 5 cases out of 191 exceeded the recommended dose range, and 4 of those were for haloperidol. There

were also 12% of cases in which the dose was recorded "as required". More comprehensive capture of dose information is needed for an evaluation of the potential risks posed by this important group of drugs. The longitudinal nature of our study will allow us to identify if older agents continue to be used and monitor incidence and length of antipsychotic use in our sample. Researchers have demonstrated that chronic exposure may result in irreversible central nervous system and neurochemical changes (167),which may result in negative effects on prosocial behaviours such as learning , alertness, and social and adaptive functions.

4.4.3. Interclass Polypharmacy

According to our findings, there was a high prevalence of concurrent use of psychotropic agents from different classes and complex pharmacologic regimens; two thirds of those who reported psychotropic use reported inter-class polypharmacy with antipsychotics with anxiolytics/hypnotics were reported by one third of those with psychotropic consumption, and antipsychotics with antidepressants (29%) being the most commonly reported combinations. Of those reporting psychotropic use, 3.6% reported medicines from four different psychotropic classes. There is less evidence relating to psychotropic combinations practices and safety in the ID literature (114). McGillivray and McCabe (2006) described the management of 873 people with ID and challenging behaviours and found interclass polypharmacy in 53% of treatment regimens, with antipsychotics and mood stabilizers being most common(152). Our findings are similar to those found by De Kujiper 2010, who reported that 17% of those reporting antipsychotic use reported combinations with antidepressants and 20% with benzodiazepines, while in the UK Paton reported that 33% of those reporting antipsychotics also used antidepressants and 15% benzodiazepines(11, 238).

In the general population, some benefits of combining antipsychotics with antidepressants in treatment-resistant depression have been reported(312). In the ID population, Verhoeven used combinations of citalopram with different psychotropic medication classes in 64 people, and found that citalopram combined with antipsychotics was associated with an increased incidence of self-harming and stereotyped behaviours(313). One small study by Mahan et al., found a greater prevalence of side effects including general effects on the CNS, gastrointestinal side effects and behavioural / akathisia on the CNS in people with ID taking two or more psychotropics compared to those who reported taking one(175). In addition,

antipsychotic-antidepressant combinations may be especially prone to adverse drug reactions, due to the effect of some antidepressants of the cytochrome P450 system. For example, inhibition of risperidone metabolism in patients with schizophrenia who were co-administered fluoxetine has been reported (314),and other clinically relevant antidepressant-antipsychotic interactions between these combinations have been reported (315, 316).

The International Consensus guidance on psychopharmacology and intellectual disability recommends that "interclass polypharmacy" should be minimised"(289). Given the evidence for interactions and augmentation of side effects with combination therapy, the use of combinations should be approached with caution, particularly given that people with ID may not be able to self-report side effects or adverse drug reactions. It is not known from our study how frequently patients receiving multiple combinations were re-evaluated to assess the benefits and risks of combination therapy, or how often serum blood testing took place.

4.4.4. Factors associated with Pyschotropic Use and Pyschotropic Polypharmacy

Our study revealed no significant difference in the prevalence of psychotropic use or polypharmacy between men and women, these findings being consistent with one previous study in the ID population, which found no significant gender difference in the prevalence of psychotropic polypharmacy(233). Among 1023 people with ID 16-63 years, Cooper and colleagues identified that mental ill health was associated with female gender (58). However, these findings are in contrast to the general elderly population, where women have been consistently shown to use psychotropics more frequently, even after adjustment for confounders(240, 317-319).

In the multivariate model, after adjustment we found no significant difference in ID severity and psychotropic use. Again, these findings are similar to a previous study investigating psychotropic polypharmacy and cognitive function in people with ID (181).

While age was not significant in our multivariate analysis after adjustment for relevant confounders, however, at bivariate level there was a significant association between age and antidepressants, with almost one third of those over 65 reporting consumption. We also noted a corresponding higher prevalence of mental health conditions in those oldest; 59% reported a mental health condition. Among 1023

people with ID 16-63 years, Cooper identified no association between mental ill health and advancing age, after adjusting for relevant confounders(58) While treatment of mental health is particularly important to improve quality of life in older age, and has been shown to also improve prognosis for other conditions a person is suffering from, given the increased risk profile of use of these agents in older people, and the lack of research in older people with ID, this warrants further study.

Unsurprisingly, those reporting mental health conditions were significantly more likely to report psychotropic use, however the wide confidence intervals mean the results of the model should be interpreted with some caution.

Despite the evidence that psychopathology is more common in both patients with epilepsy and those with ID (179), our multivariate regression revealed that those with epilepsy were significantly less likely to report psychotropic polypharmacy. There are several potential reasons for this. Perhaps, prescribers are more cautious in prescribing combinations, given the potential for interactions in with antiepileptic agents. It also may be possible, that in some cases, AEDs properties are prescribed primarily to control seizures, and also for a secondary mood stabilising indication. In the Netherlands, Leunissen carried out a retrospective cohort study with 246 adults with ID and epilepsy in a long stay institution, and found that patients with epilepsy taking lamotrigine used significant less antidepressants, while those taking carbamazepine, valproic acid and lamotrigine used less anxiolytics(179).

We identified no association between fair or poor self-rated heath, and psychotropic use in our bivariate analysis, thus this factor was not included in our regression model. To our knowledge, no studies in the ID population have examined the relationship between psychotropic utilization and health perception. In the general population, health perception (one's self-evaluation of one's own health) has been demonstrated to be a stronger predictor of psychotropic drug use, than diagnosis or disease(320). It has been hypothesised that poorer health perception, may cause a negative effect on a person's health status, which may lead to a request for psychotropic agents (320-322). Our contrasting results could be for a number of reasons; they could reflect successful treatment of mental health conditions, and thus an improved perception of health for those with psychotropic use. However, this question was more subjective, and was answered by both respondents, and proxy as appropriate. The validity of proxy response on more subjective questions has been called into question (270).

In the general population, social determinants of health including socioeconomic status, educational attainment, employment and marital status have been identified as key predictors of psychotropic use (133). For the purposes of our study, it was not possible to examine the influences of these factors in detail, as our sample was homogeneous with respect to many of these characteristics; almost all were unmarried, there was a very low level of paid employment (22, 220) and level of educational attainment was low. A recent study by Haider and colleagues examining rates of polypharmacy (five or more prescribed medicines) in 897 adults with ID living in a variety of settings in Victoria, Australia found an association with unemployment, but no relationship with education(140). Future research is needed to examine the influence of discrimination, and social connections on mental health and psychotropic use.

4.4.5. Place of Residence

Consistent with previous findings in the ID literature (145, 180), we observed that psychotropic use and psychotropic polypharmacy was greatest for those in residential settings, with almost three-quarters (71.6%) of those living in residential settings reporting psychotropic use, compared to over half of those living in community group homes (56.6%) and over one-quarter(28.7%) living independently. While the greatest proportion of those in our study lived in institutional settings, notably, over half of those living in residential settings reported psychotropic polypharmacy compared to 40% living in community group homes and 12.3% of those who lived at home. Our multivariate model revealed that even after adjusting for confounding variables, those living in residential settings were significantly more likely to be exposed to polypharmacy. These trends had previously been confirmed by Spreat, and Robertson who found higher rates of psychotropic use among institutional settings(145, 180), while Tsiourus found no difference in the prevalence of psychotropic use between those living in developmental centres or community group homes, but lower rates for adults living with family(144). The higher use of psychotropic medication in residential settings is also an acknowledged fact in elderly populations (323).

Our findings demonstrated that over half (54%)of those living in residential settings reported antipsychotic use, a similar finding to Robertson, who found that 56% reported antipsychotic use (145), while Spreat reported a rate of 31.7% in nursing homes(180). These findings may be in part explained by the fact that there was a higher

prevalence of mental health conditions found in our study for those living in residential settings (59.7%) compared to 45% of those living in group homes and one fifth of those living independently, and it is that those living in institutional settings had more severe ID and more severe mental health diagnoses that may require further treatment. Due to small numbers living independently that reported psychotropic polypharmacy, we collapsed those living independently and in community group homes into a single variable in our regression, so we could not differentiate in differing patterns of use between these two settings types at multivariate level.

These findings are of particular importance in the current context, with the continued transition of people from residential settings to community placements in Ireland. To date, findings in relation to the influence of place and change of setting on medication use remain inconclusive, with early research suggesting that medication use may increase for people with ID after community placement (324, 325). In contrast, Thinn (1996) found no significant difference in rates of use of antipsychotics for people with ID moved from long stay hospitals into community placements (326), and Nottestad (2003) found no significant difference in psychotropic or antipsychotic use before or after deinstitutionalisation(327). Spreat reported that medication use increased slightly for people who lived in congregated settings in 1995 and had transitioned to the community in 2000(180), with an increase in antidepressants, and a slight decrease in antipsychotic use. Given that people with ID display increased vulnerability to environmental factors that influence mental health, and are less well able to adapt and respond to features and changes of environment, services and transitional changes need to be sensitive to this (55). As people with ID continue to transition from residential settings in Ireland into community placements and access primary care, the longitudinal nature of the study will enable us to address the questions in relation to the influence of place of residence and the effect of transitions of environment on mental health, and consequently on psychotropic medication use patterns.

4.4.6. Benzodiazepine and Hypnotic Use

A new finding from our study was the higher rate of use of anxiolytics and hypnotic agents than previously reported; almost one quarter (23.5%) of our study population reported benzodiazepine anxiolytics, and 13% reported use of hypnotics, with 30% using either. Furthermore one quarter of those using an anxiolytic/hypnotic used two

or more of these agents concurrently. This prevalence is higher than a recent study of over 4,000 individuals with ID (including those with ASD) in New York state, which reported a prevalence of 16% for anti-anxiety agents and 1% for hypnotics (144), while Spreat reported a prescription rate of 11.2% for anxiolytics and 2% for sedative/hypnotics, while Molyneaux 1999 reported 10% receiving anxiolytics or hypnotics(180, 232), Robertson and colleagues reported rates of anxiolytics use of 4-6% depending on setting and hypnotic of 2-5%(145). Some of this variation may be accounted for in variations of anxiolytic and hypnotic definitions, and exposure measures (i.e. point prevalence) across studies and countries. In our study, we observed differences in prevalence of use of these agents by place of residence, use of these agents was greatest for those living in residential settings, with over one-third receiving anxiolytics and one fifth receiving hypnotics. However, anxiety conditions was the most commonly reported mental health condition in our study with over one quarter of the study population reporting a doctor's diagnosis of an anxiety condition. Spreat also noted a higher rate of anxiolytic use in nursing homes (18.5%) compared to 11.2% overall(180).

We also observed a higher prevalence of hypnotic use among those oldest, with 16% of those over 65 reporting hypnotic use, compared to 11% of those aged 40-49 years, however this trend did not extend to anxiolytic use where there was a similar spread across age ranges. It is possible that our findings may reflect broader trends in relation to prescribing of benzodiazepine and hypnotic use in the general Irish elderly population: Byrne et al 2011 reported that the most commonly reported instance of potentially inappropriate prescribing in Irish older long term care residents related to use of benzodiazepine agents; they accounted for 38% all of potentially inappropriate prescriptions among older residents in Irish nursing homes in the study and half of all instances in Northern Ireland(328). Byrne and colleagues also raised concerns in relation to risks associated with the high prevalence of long term use of hypnotic agents by long term residents. Richardson and colleagues reported that 5.5% of 6,666 community dwelling Irish adults used anxiolytics/hypnotics(188). The Benzodiazepine Committee (2002) reported that 11.8% of the adult GMS population were using benzodiazepines (including z drugs), with alprazolam most frequently reported(329).

Benzodiazepines offer the clinical advantage in that they work quickly, are very effective at reducing anxiety, and in low doses and short courses have few unwanted

side effects (330). However, the concerns relating to the use of benzodiazepines in the elderly are well recognised and include the risk of abuse, dependence, withdrawal adverse effects after long-term use, tolerance and effects on cognitions, increased risks of falls and fractures and increased mortality (281, 331-334). For people with intellectual disabilities, use of these agents confers an additional risk , as benzodiazepine-related behavioural side effects, or "paradoxical reactions" such as hyperactivity, aggression and disinhibition , which may be under-recognised, are more common for people with ID , with up to 13% of people with ID who take benzodiazepines exhibiting behavioural side effects (168). These paradoxical reactions may be more common in the young, the old and those with brain damage. While higher prevalence of sleep disorders among those oldest, these agents confer greater risk.

4.4.7. Mood stabilisers

Our findings established that over 10% of our sample were exposed to mood stabilising agents, and did not have an epilepsy diagnosis, with valproic acid being the most frequently reported agent. Mood stabilisers were rarely utilized on their own; over nine in ten of those who used a mood stabiliser was exposed to psychotropic polypharmacy with antipsychotics and antidepressants being the most common co-medications and some uncontrolled studies have supported the use of valproic acid in the population with ID(335).

4.4.8. Antidepressants

Our findings reveal that one-quarter of the population reported use of antidepressants, with the majority of prescriptions (70%) being for SSRI agents but only one-fifth reported a doctor's diagnosis of depression. In total, 16 different antidepressant agents were reported, with escitalopram and paroxetine being most frequently used. Our findings reflect the trend of increasing use of antidepressant agents in people with ID; reported use of antidepressant agents in people with ID was infrequent before 1995, and prevalence rates of 8-10% for these agents were reported between 1995 and 2000 (145, 232). This higher prevalence rate of antidepressant use is similar to that reported by Tsiourus 2014, who reported a rate of 23% (144),while De Kuijper 2010 and Spreat 2004 reported rates of 17% and 15% respectively(180, 238). In addition, the pattern of class use is similar to that reported by Spreat , where SSRIs accounted for 74% of

antidepressants used(180). Depression was prevalent in our population, with almost 40% of those who reported mental health conditions reporting a doctor's diagnosis of depression. Our findings of a high rate of use of antidepressants to some extent corroborates with the high prevalence of antidepressant use reported in the Irish general population; the National Advisory Committee on Drugs reported a prevalence of 12% for Northern Ireland and Ireland in 2010/2011, and the Northern Ireland Study of Health and Stress a 12-month prevalence of 9.4% for 4340 adults between 2004 and 2008, both of which are among the highest rate of consumptions for countries contributing the World Mental Health survey initiative(240). In the Irish community dwelling population over 50 years, a prevalence of 6.5% for antidepressant use has been reported (188).

Our study found a higher rate of use of antidepressants in residential settings; one-third reported use, compared to one-fifth of those in community group homes and 14.8% in independent settings. Higher rates of antidepressant use in NHS residential campuses compared to dispersed housing or village homes were also reported by Robertson (145). In contrast, Spreat et al (2004) reported a more consistent similarity of rates of antidepressant use across settings, as did Tsiourus et al 2014(144, 180). Higher rates of use of antidepressants may reflect an increasing recognition and diagnosis of depression in people with ID, and may reflect a growing recognition that depression may have been previously underdiagnosed in this population(30). Reported consumption was also greatest for those over 65 years, where almost one-third reported use. The treatment of depression in older people is of particular importance, as it can result in improved quality of life and improvement of other co-morbid physical conditions. While the SSRIs have fewer drug interactions and serious adverse effects when compared with the Tricyclic Antidepressants, monitoring in the elderly is required for sodium and low blood pressure. It is important to note that in our study, over 80% who reported antidepressants reported other concurrent psychotropics. Given the fact that some antidepressants such as fluoxetine, paroxetine and sertraline are potent inhibitors of the cytochrome P450 enzymes(28) and thus impact metabolism of other psychotropics, caution and regular review and monitored is required when these agents are used in combination regimens. We also identified that almost 5% of those using antidepressants had concurrent use of two agents, further increasing the potential for interactions and adverse effects. In the general Irish

population over 65 years, prevalence of concurrent antidepressant use was established at 0.06%(336).

4.4.9. Health Care Utilization

We noted that utilisation of health professionals to treat psychiatric conditions was high in our study; our findings indicated that three-quarters reported that treatment was received from a psychiatrist. The data gathered in our study do not clearly distinguish between the training of the treating psychiatrist, or if they were supported by a multidisciplinary team, so it is not possible to report if there are differing prescription practices between the groups. Ramsey et al., 2014 examined access to mental health services in this study population, and noted that individuals with ID in rural areas were more likely to be prescribed antipsychotics without a supervising psychiatrist (112).

Our findings in relation to levels of engagement with psychological treatment were also encouraging; of those who answered the question as to whether they were receiving psychological treatment, over half reported psychological treatment in addition to psychotropic use, with almost two-thirds reporting that they were receiving this from a psychologist. Over 60% of those reporting polypharmacy exposure reported combined approaches with psychiatry and psychological therapy. Notably, very few (3%) received psychological therapy alone. These findings would be in accordance with the World Health Organisation recommendations that "a combined psychosocial and pharmacological approach is likely to yield best results" for treating mental health disease (276), and the benefits of psychological approaches are increasingly recognised (337).

Few studies to date have examined prevalence of psychological therapy in combination with psychotropic medications in people with ID(114). Combining medications with psychotherapy or other psychosocial approaches may be also a better approach than polypharmacy (172, 338). It is not possible from our study, to determine whether psychological therapy preceded psychotropic medications or was added in to existing medication therapy, but it appears that this form of therapy may be being used to supplement medications.

We noted that despite the high prevalence of mental health conditions in our study, use of tertiary healthcare was negligible, with only 1% of the population reporting spending nights in a psychiatric hospital in the previous year. While we do

not have information as to whether individuals/services attempted to access acute hospital care, these findings may reflect concerns highlighted by the Royal College of Psychiatry in 2011 in relation to lack of availability of dedicated inpatient beds for people with ID and acute mental health disturbances(113). Recommendations were made to develop a forensic ten bed national forensic unit for those with ID, but no progress was made. Furthermore, it has been acknowledged that a significant number of people are placed out of state because there are inadequate therapeutic residential services in Ireland (113, 339). Irish psychiatrists participating in the Royal College of Psychiatry survey of specialist service requirements in ID in 2010 estimated that 137 people with ID who require specialist services are unable to avail of them, either in Ireland and abroad(339). Considering the response rate to the survey was low at 36%, this is likely to be an underestimate for unmet need of specialist services(113). Findings in relation to place and type of mental health service provision will require further examination in future waves of the study, particularly in the context of deinstitutionalisation, and current debate in relation to where, who and how best to treat complex mental health conditions for people with ID(158).

Our findings in relation to patterns of healthcare utilization are in contrast to reported to that of the general Irish population; The Health Research Board National Psychological Wellbeing and Distress Survey reported that 40% of the Irish population who reported mental health problems in the previous year did not seek health from a GP for their problems, and when they did, the majority received treatment in by GPs in primary care, with only 10% of mental health problems being treated by specialised mental health services (55, 340).

4.4.10. Study Strengths

Our study has a number of strengths. To our knowledge, this is the first nationally representative study in Ireland examining prevalence, patterns and predictors of psychotropic use and polypharmacy in a representative population ageing with ID. The use of a large, randomly sampled population-representative sample enabled us to have sufficient power for our multivariate analysis, and means our findings may be 134harmacodynam to the Irish ID population, and ID populations in other countries. For our definition of psychotropic use and polypharmacy, we employed a literature review and adopted a consensus approach (two pharmacists, and an ID psychiatrist) in deciding on classification of psychotropics, which adds validity. Our dataset

included information on mental health morbidity and psychiatric and psychological care, which enabled us to examine the use of medication in the context of illness and associated healthcare utilization. Few studies in the ID population have gathered information as to whether psychological therapy was used in addition to medications. Few studies in ID population contain older age group and look at combinations of psychotropics employed (114). We also were able to include mood stabilizing AEDs, and to separate them from AEDs used for epilepsy. Furthermore, for our study, participants and/or proxy respondents underwent a detailed assessment of health characteristics, socioeconomic circumstances, health care utilization, self-rated health, allowing us to examine potential confounders on our regression model, that are usually unavailable to many pharmacoepidemiological studies. Moreover, we examined concurrent and other agents affecting the CNS, giving a comprehensive picture of CNS influencing drug use in the ID population. The longitudinal nature of our study offers a substantial advantage, as we have the ability to monitor patterns of psychotropic use, as people age, move settings, and as further evidence in relation to risks and benefits of psychotropic therapies emerge.

4.4.11. Study Limitations

Our study had a number of limitations. First, the medication information and that of mental health conditions was based on self-report or proxy report, or combinations of reporting styles. Respondents stated the diagnosis, which may not be a fully accurate report, as it is not based on medical notes, or diagnostic criteria. The question and categories have their limitations diagnostically, but were similar to questions asked in the English Longitudinal Study on Ageing (and so permitted comparability to other longitudinal studies). In addition, mental health conditions prevalence reported were lifetime, not point prevalence. However, both medication information and mental health questions were included as part of the pre-interview questionnaire, which was sent to participants at least one week in advance of the face-to-face interview, thus giving time to review case notes and medication information and gather the information. In addition, to further increase reliability and accuracy, all information was cross-checked by the interviewer at the time of interview. Furthermore, the majority of those who reported mental health conditions or psychotropic use reported currently receiving psychiatric treatment which adds confidence to the accuracy of the data.

Secondly, we do not know the extent to which answers in the face to face interview, for example in relation to sleep problems, were influenced by the combination of responses styles; some interview directly with participants, some with proxy only and some adopted a hybrid approach. In keeping with the goals of inclusion of our study, of including all people with ID in the research regardless of level of ID is very important. Those with severe or profound ID were more likely to have a proxy only interview or a mixed answer style. The validity of proxy responses on more subjective items has been called into question (270). Further research is warranted to determine the effect of the differing response styles and inclusive research.

Thirdly, we did not collect information about the length of time of exposure to psychotropic medications, thus there is the possibility that someone may be in an interim period discontinuing one psychotropic and starting another, or that an agent could have been indicated for short term use in an appropriate manner. We have addressed this limitation in Wave 2 of the study and added in a question relating to length of time of exposure to medicines. We also did not have full information in relation to medicine doses, which limits comments about appropriateness of use of agents. We have adjusted our medication data form for Wave 2 to improve the proportion and quality of dosing information available.

Fourthly, we did not have information about the severity of mental health conditions. We also did not have definitive information about challenging behaviours, so it was not possible to establish the number of people receiving medications for these indications.

Fifthly, we did not collect information as to whether people experienced side effects from psychotropic medications, and whether they were monitored for efficacy and side effects. In response to this limitation, further questions were added to the w Wave two questionnaire addressing these issues, which will provide a more holistic profile of the medication use process for people with ID and monitoring.

Sixthly, the cross-sectional multivariate analysis examined associations between factors and psychotropic use, but does not address cause and effect. It is possible that there were other confounding factors contributing to psychotropic use. The wide confidence intervals associated with the mental health variable suggests that the results should be interpreted with caution; this variation is likely to be related to the self-report nature of the mental health questions. With subsequent waves of the study, we will have further information in relation to these issues.

4.5. Conclusions

Our findings indicate that use of psychotropic agents in commonplace in this population, with almost six in ten reporting use, reflecting the high prevalence of mental health conditions, with the high use of complex multiclass regimens and older, typical antipsychotics being a potential cause for concern. Our findings revealed higher levels of antipsychotics, anxiolytics, antidepressants and interclass regimens, but interpretation of appropriateness of use of these agents was limited by our lack of detailed information in relation to severity of mental health diagnoses and length of exposure to agents. Our multivariate model revealed that, after adjusting for relevant confounders, those reporting mental health conditions, sleep difficulties and those living in residential settings were more likely to be exposed to psychotropic polypharmacy, those with epilepsy were significant less likely to report polypharmacy, but age and gender had no significant effect. The high level of access and engagement with both psychiatric and psychological services to treat mental illness reported was encouraging, but we did not have information on quality or nature of these services.

The importance of identifying and managing mental health conditions in this population must be balanced against the ever increasing evidence base for adverse effects associated with psychotropic drug use (275, 281, 307, 341). As there is a paucity of data in the ID population supporting the efficacy and safety of most commonly employed psychotropic combinations, such as multiple antipsychotics, or antipsychotics combined with antidepressants, renewed efforts are needed to limit use of these combinations to clearly documented and justified clinical circumstances, and regular review and monitoring of efficacy and side effects associated with these therapies should take place at regular intervals. If use of antipsychotics is indicated and appropriate, the lowest possible dose should be used to minimise adverse drug reactions, impairment in new learning and movement disorders(89). At the same time, more research is needed in this population to assess the benefits, including adverse effects on prosocial behaviours, and safety of common psychotropic combinations, particularly as this population continues to age and present with complex mental health morbidity.

What is already known about this topic:

- People with ID are at increased risk of exposure to psychotropic drugs, and psychotropic polypharmacy due to the higher prevalence of mental health conditions present in this population and more controversially, the use of these agents to treat challenging behaviours.
- Psychotropic agents improve function and quality of life for many people diagnosed with psychiatric disorders, but there are also concerns with these agents including the potential for sedation, falls, and other adverse effects, particularly in the elderly.
- Challenges associated with communication difficulties, correct assessment and diagnosis, communication of side effects, and the limited evidence base means use of these agents may carry extra risk in older people with ID.
- Despite the fact that many adults with ID are exposed to psychotropic use, and psychotropic polypharmacy, few studies to date have focused on the patterns of use of multiple psychotropics, or factors associated with psychotropic polypharmacy, particularly in the older population.

What this study adds:

- Our study revealed that use of psychotropic agents was commonplace; four in ten were exposed to psychotropic polypharmacy, and a further two in ten used one psychotropic.
- Our multivariate regression revealed that those reporting mental health conditions, sleep problems, and those living in residential settings were likely to be exposed to psychotropic polypharmacy, while those with a diagnosis of epilepsy were significantly less likely, and age and gender had no significant effect.
- Our findings revealed high levels of antipsychotics, anxiolytics, antidepressants, and complex interclass regimens.
- Psychotropic use, particularly the use of psychotropic combinations needs to be regularly reviewed for safety, efficacy and adverse effects, and rationale for use of multiple agents needs to be clear and documented.

Chapter 5. Anticholinergic Burden in Ageing People with Intellectual Disability

5.1. Introduction

Many commonly prescribed medications possess anticholinergic activity and are used to treat a variety of conditions such as depression, hypertension, Parkinson's disease, psychotic symptoms and behavioural problems (342, 343). Medications with anticholinergic effects may be associated with both central and peripheral anticholinergic side effects, such as dizziness, sedation, confusion, dry mouth and adverse dental outcomes, blurred vision and constipation; the risk of adverse outcomes increasing with increasing anticholinergic exposure (342, 344-347), including hospitalisation and falls. Frail, elderly patients are particularly vulnerable to anticholinergic- related adverse effects due to a high probability of exposure to these agents to treat multiple age-related morbidities, in addition to their increased age-related sensitivity to anticholinergic-related cognitive adverse effects (342, 345, 348-350). Furthermore, medical problems prevalent in the elderly such as urinary dysfunction, falls, constipation, sleep difficulties and dementia may be worsened by the use of anticholinergics (351, 352).

In the general elderly population, it has been estimated that 20-50% have been prescribed one or more of these medications (28, 345), and a greater prevalence has been reported in those living in nursing homes or institutional settings(353) . Those with mental illness are also at higher risk of exposure, as medicines indicated for psychiatric conditions (depression, schizophrenia) have some anticholinergic activity, such as antipsychotics and tricyclic antidepressants. Furthermore, they may be additionally susceptible to adverse neuropsychiatric effects of medicines, as individuals in this group may already have evidence of cognitive impairment(354).Anticholinergic medications have been highlighted as being potentially inappropriate in older and frail adults(200, 355). A systematic review carried out by Fox et al (2014) assessing the effects of medications with anticholinergic properties on health outcomes found the strongest evidence for association between increasing anticholinergic load and adverse cognitive outcomes, and a potential association with a deterioration in physical function , but no significant association between anticholinergic load and 141harmaco or mortality, despite some studies which have supported these associations (356).

Drug-induced anticholinergic activity is thought to be additive, and the overall burden of anticholinergic drugs determines the risk of adverse effects in an individual (357-359). It is possible that anticholinergic toxicity may result from a medication

regimen in which some or all of implicated medicines have modest anticholinergic effects even if a patient receives no readily identifiable anticholinergic drug (360). In many incidences it is the accumulation of multiple medicines that may result in anticholinergic toxicity (361). Whether a patient experiences anticholinergic adverse effects depends on multiple factors including the degree to which the drug penetrates the blood-brain barrier, the anticholinergic load of an individual from multiple anticholinergic (AC) drugs, baseline cognitive status and individual pharmacokinetic and 142harmacodynamics variability (related to renal and hepatic function) (351, 352). In clinical practice, adverse effects associated with anticholinergic drugs are frequently treated with additional medicines (e.g. laxatives), as opposed to withdrawal or dose reduction of the particular drug (362, 363). In addition, anticholinergic side effects may be misattributed to a consequence of the normal ageing process and drugs with AC properties may be a cause of unrecognised ADRs (304). Recommendations have advocated the avoidance of inappropriate prescribing of anticholinergic drugs (364). Anticholinergic medications have been considered to be potentially inappropriate in older populations (249, 365), including vulnerable elders and those with dementia(90, 366).

Use of psychotropics in people with ID may confer additional risk due to the presence of organic brain dysfunction, which may lead to differences in symptomology and response to drugs of an idiosyncratic nature (115, 197, 206-209) as discussed in *Chapter 2*. People with ID are therefore at additional risk of experiencing the "prescribing cascade", where the side effects of drugs are misdiagnosed as symptoms of another problem or symptoms are misattributed to the underlying intellectual disability resulting in further medications prescribed and further risk of side effects and interactions (125). One such example is the prescribing of anticholinergic medications to treat extrapyridimal symptoms associated with antipsychotic agents, a practice no longer recommended in the elderly(355).

Assessment of exposure to anticholinergic drugs was traditionally based on use of anticholinergic drugs and the total number of anticholinergic drugs taken by a patient (367). The risk of adverse anticholinergic effects may also be dependent on other characteristics of a drug and/or its metabolite including dose of the drug, bioavailability , metabolism, blood brain barrier (BBB) permeability and serum and tissue concentrations (368). In response to this, since 2001 many medication scales have been developed to capture the cumulative burden and to address these issues

and improve the evidence base and stratification of risk (346). These scales compute a total score of drugs to determine an anticholinergic burden of an individual (369, 370). The Anticholinergic Cognitive Burden (ACB) scale is a tool that identifies the severity of anticholinergic negative effects on cognition of medications (prescribed and over-the-counter) ; drugs with possible anticholinergic effects were given a score of 1, drugs with established and clinically relevant cognitive anticholinergic effects were given a score of 2 or 3 (342). Drugs with no AC effects were given a score of 0 (342). It has been demonstrated that each additional anticholinergic may increase the risk of cognitive impairment by 46% over six years (371) . In another study, for each point increase in total ACB score, there was a correlation of a 26% increase in risk of death (353).

Older people with ID may experience "ageing in", due to age – related changes in metabolic capacity resulting in a reduced ability to metabolise medicines. Medications which people with ID may have been taking for many years may start to produce anticholinergic adverse drug reactions that may go unrecognized because they had not previously presented a problem. (29, 90, 203, 372). Loss of physical and cognitive function associated with ageing significantly threatens the quality of life of the elderly. (373). Therefore, identifying strategies to maintain and prevent functional decline in this population, particularly in vulnerable populations is of importance. Fox and colleagues recommended that "the assessment of medicines with anticholinergic properties should be further evaluated in people at risk of poor outcome" (356) . The National Task Force on Intellectual Disability and Dementia Practice Consensus Recommendations for Evaluation and Management of Dementia in Adults with Intellectual Disability recommends reviewing the medication list "thoroughly" paying special attention to medications that are "psychoactive, antiepileptic or anticholinergic or those with sedating properties (90), but does not give specific focused guidance. Given the evidence that exists in the general elderly population of risks associated with exposure to anticholinergic medications in older people (353, 356, 373) and the unique risks of frailty, cognitive decline and adverse drug reactions in people with ID (122, 203, 374, 375) coupled with the high prevalence of mental health conditions and the extent of psychotropic polypharmacy in many people with ID, we decided to determine the anticholinergic exposure of a representative ageing population with ID., We hypothesised that those with ID who were older or had co-morbid mental health concerns were likely to be at risk of exposure to a higher anticholinergic load. To our

knowledge, no studies to date have assessed the anticholinergic burden of drug use in an ageing population with ID. Our aims were therefore: to determine the prevalence, patterns and factors associated with anticholinergic drug burden in an ageing population with ID.

Our primary objectives were:

1) to determine each individual's cumulative exposure to anticholinergic medications by using the Anticholinergic Cognitive Burden Scale (ACB);

2) to provide a description of the pattern of anticholinergic medication use in relation to demographic and clinical characteristics and the most frequently reported therapeutic classes which were contributing to total anticholinergic burden;

3) to examine the factors associated with higher anticholinergic burden exposure;

4) to explore the relationship between anticholinergic burden scores and indicators of peripheral and central anticholinergic adverse effects.

5.2. Methods

5.2.1. Study Design

More detail on the study and the specifics of medication data collection, analysis and coding is outlined in *Chapter 3*.

5.2.2. Study Participants, Flow Chart

Analysis and variables considered for this study are presented in *Figure 5-1*.

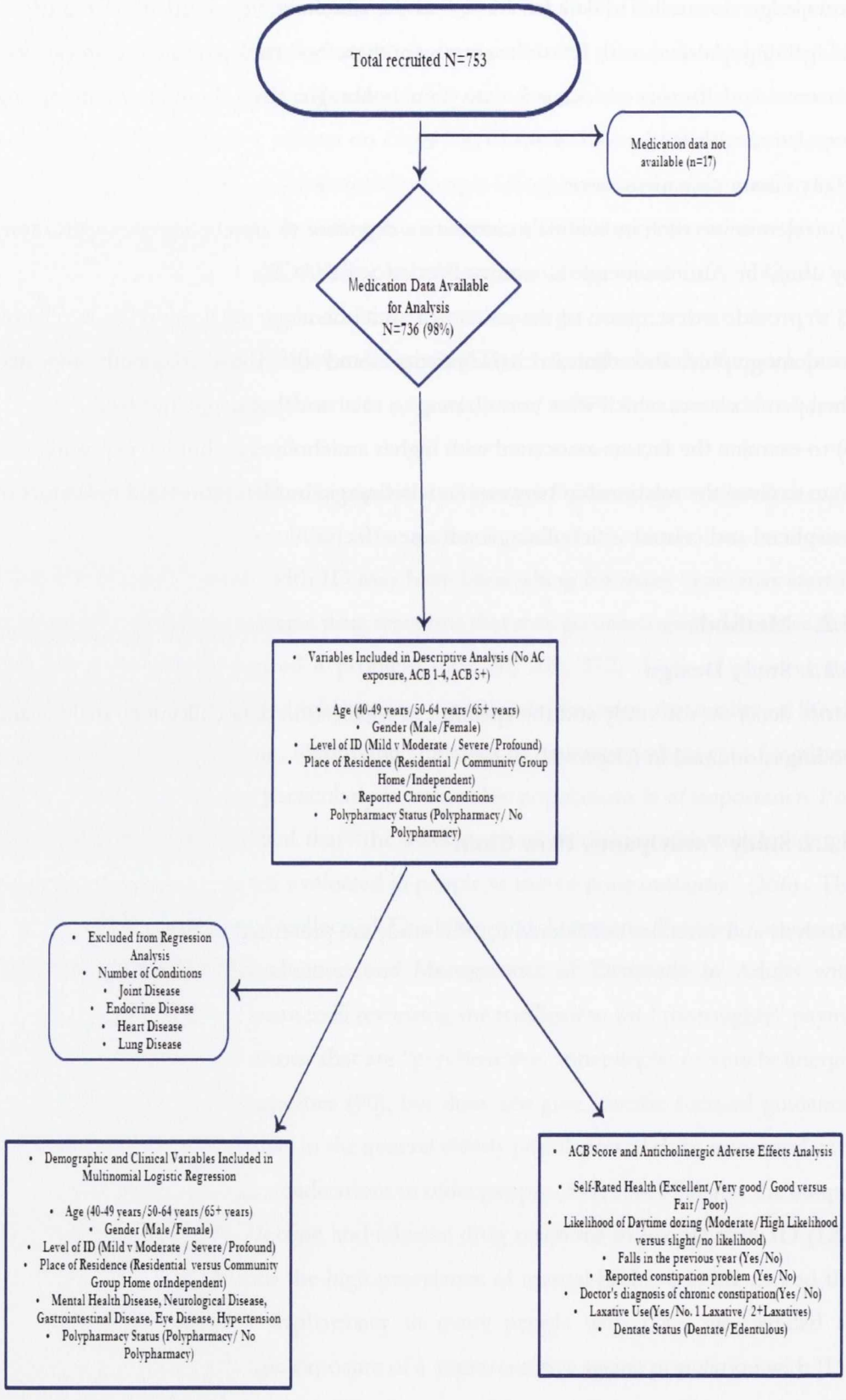

Figure 5-1: Flow Chart for the study

5.2.2.1. Measuring Exposure to Anticholinergic Medications

Our primary outcome of interest (the dependent variable) for the purposes of this study was participants' Anticholinergic Burden Score. The anticholinergic burden of each participant was calculated using the updated 2012 Anticholinergic Cognitive Burden (ACB) Scale(376).

Medications were defined as having absent (ACB Score 0), possible (ACB score 1) or definite anticholinergic properties (ACB score 2 or 3) based on the ACB scale.

In addition, in our study, the ACB list was assessed and modified to include drugs with anticholinergic properties taken by participants but not included in the ACB scale. Two pharmacists (MO'D, IM) independently consulted standard reference sources, the product characteristics (SmPC) information, and the other validated anticholinergic rating scales, to assign a score to other drugs with anticholinergic properties that were not included in the ACB list. The amended list included drugs and corresponding scores were reviewed by another pharmacist (MH). Based on this, the ACB was modified to include medications with anticholinergic properties that are available in Ireland. Any disagreements were resolved by consensus. Drugs included in our analysis with respective scoring are listed in *Table 5-1*. Medications with anticholinergic properties which were not available in Ireland and/or not present in the dataset were excluded (42 medications). *Table 5-1* details all medications in the final list that were recorded in our dataset, with corresponding ACB scores.

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

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

ACB Category 3		*ACB Category 2*		*ACB Category 1*	
Anticholinergics	***Urologicals/antispasmodics***	**Muscle Relaxants**		**Analgesics**	**Antihistamines**
*Biperidin**	*Tolterodine*	Tizinadine*		Codeine	Cetirizine
*Procyclidine**	*Solifenacin*				Desloratidine
Benzatropine	*Oxybutynin*				Loratidine
	Festoteridine				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, Fluvoxamine, Hydralazine, Iloperidone, Paliperidone, Quinidine, Triamterine

ACB 2: Amantadine, Belladonna, Cyclobenapine, Cyproheptadine, Loxapine, Meperidine, Methotrimeprazine, Molindone, Oxcarbamazepine, Pimozide

ACB 3: Amoxapine, Brompheniramine, Carbinoxamine, Clemastine, Clozapine, Darifenacin, Desipramine, Dicylomine, Dimenhydrinate, Diphenhydramine, Fluvoxate, Meclizine, Methocarbamol, Nortriptyline, Orphenadrine, Perphenazine, Propantheline, Propiverine, Trihexyphenidyl, Trosopium

We then categorised participants' exposure to anticholinergic medicines in three ways;

1. A continuous variable was created to capture the total Anticholinergic Cognitive Burden (ACB) score of each participant, by adding up the score of each possible or definite anticholinergic together (range 0-16),

2. A binary variable was then created; those exposed to any anticholinergic medicine; anticholinergic exposure (ACB score ≥1) (n=522), and those with no anticholinergic exposure (ACB 0) (n=214) (*Table 5.3-1*),

3. For the purpose of our analysis of clinical conditions and anticholinergic adverse effects, another derived categorical variable was created which grouped the population into three groups; those with no exposure to anticholinergic medications (ACB 0) (n=214), those with ACB score of 1-4 (n=307), and those with an ACB score of ≥5 (n=215). The use of a threshold of greater than 5 has been used previously in a study of older adults, and demonstrated a significant association with lower Mini Mental State Examination scores (MMSE)(353).

5.2.2.2. Covariates

Covariates investigated from the study were: gender, age, level of intellectual disability, residential setting (independent, community group home or residential setting),) (377), any dementia (doctor's diagnosis of dementia, organic brain dysfunction, senility or serious memory impairment), (*Appendix 6*) . Prevalence of any dementia was low in our population; 6%, so it was not possible to include this in further multivariate analysis. Each participant / caregiver respondent reported if the individual with ID had ever been diagnosed by a doctor or other relevant health professional with one or more of 12 chronic health conditions *(Appendix 6)*(53). Lung disease, stroke and cancer had insufficient numbers at univariate level and were excluded from analysis beyond univariate level. We examined a number of chronic conditions reported, but this was not included beyond univariate analysis, due to correlation with types of chronic conditions. In relation to use of multiple medicines, for the purposes of our analysis we used commonly used definitions: polypharmacy (the concurrent use of 5 or more medicines) (230, 235).

In addition, we examined the relationship between anticholinergic exposure and self- rated health (proxy or self-report), and potential anticholinergic adverse effects; if the participant had reported fall(s) in the previous year, their likelihood of day-time

dozing, if participants reported constipation as a problem in addition to reported physician diagnosis of chronic constipation. Participants were divided into those who were dentate (reported having some or all of their original teeth), and edentulous (no original teeth)*(Appendix 7)*(378).

5.2.3. Statistical Analyses

Statistical Analyses were carried out using the Statistical Package for Social Sciences, Version 20 (SPSS Inc.). Descriptive statistics were generated to describe the characteristics of the eligible study population (n=736). The characteristics of the sample were expressed as percentages, means with standard deviations (±SD), and 95% confidence intervals (C.I.s) as appropriate to the variable.

Bivariate analysis was initially used to examine associations between the dependent (anticholinergic exposure (ACB ≥1) versus no exposure), and explanatory variables, with a p-value of <0.05 being considered statistically significant.

The overall prevalence of anticholinergic exposure was calculated as a proportion of the total population (n=736). The prevalence of specific therapeutic classes and anticholinergic drugs were then calculated as a proportion of those who reported anticholinergic exposure (n=522).

Multinomial logistic regression was then used to identify the factors associated with having no AC exposure, an ACB score of 1-4 and an ACB score of 5+. In this model, the outcome variable had three potential outcomes and the individuals who reported no AC exposure (ACB score of 0) were the reference category *(Figure 5-2).*

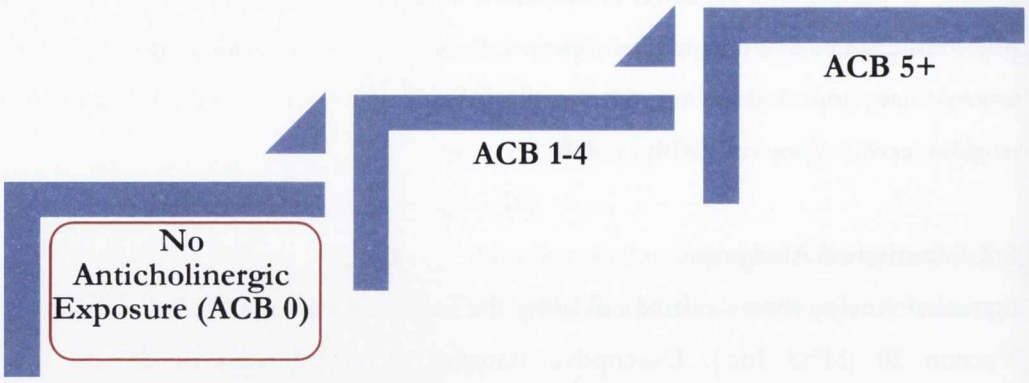

Figure 5-2 Levels of Anticholinergic Burden (ACB) Exposure for Multinomial Logistic Regression (reference category: no Anticholinergic exposure)

All demographic variables were included in the model (age, gender, level of ID). Those with unverified ID (N=54) were excluded from the model. Factors that had a p value of <0.10 at univariate level were included in the multivariate model. The following conditions were insignificant (p>0.10) at univariate analysis, and so were excluded from potential inclusion in the multivariate model; endocrine, heart disease. Those who lived independently or in community group homes were included as a single variable for the purposes of the regression analyses, as the subpopulation of those with an ACB score of 5+ in the independent setting was small (n=11).

Multicollinearity between independent variables was examined using a *Variance Inflation Factor (VIF)* >2 being considered as the cut-off, and a *Spearman's correlation coefficient,* where correlations of >0.4 were considered to be significant. This has been described in more detail in *Chapter 3*. All fell below the specified thresholds, indicating no concerns. All factors were entered into the model simultaneously.

The full model containing all predictors was statistically significant, χ^2 (24, N=658) = 412.1, P<0.001, indicating that the model was able to distinguish between those who reported an ACB score of 1-4, ACB 5+ and no Anticholinergic Exposure. The model presented is adjusted for polypharmacy status (polypharmacy exposure versus no polypharmacy exposure). The R^2 (the percentage of variance explained by the model) is presented in *Table 5.3-5*. The Cox and Snell R^2 and Nagelkerke R^2 for the model is presented in *Table 5.3-5*. The results are presented as adjusted Odds Ratios with corresponding 95% Confidence Intervals (C.I.s), and a p-value of <0.05 being

considered statistically significant. All p-values reported are two-sided. Interpretation of the results for a specific risk factor is based on the odds of being, for example, exposed to an ACB score of 5+ rather than being exposed to no AC exposure (ACB 0).

The relationship between ACB score and potential AC adverse effects was also examined at a bivariate level, a chi-squared (χ^2) test for independence was used to test for a significant association between the three anticholinergic groupings (*Table 5.3-6*). To control for problems associated with multiple comparisons (which increases the likelihood of rejecting the null hypothesis when it is true; Type I error), and the False Discovery Rate (FRD) we adopted the Bonferroni correction procedure to maintain the Family wise Error Rate (FWER) (379). In relation to adverse effects, we tested 6 hypotheses, with a desired α of 0.05, the 152harmacody correction tested each individual hypothesis at $\alpha=0.05/6 =0.008$.

5.2.4. Sample Size and Power

In addition to the issues addressed above, sample size and power was a critical consideration for the present study, with particular attention required for using multinomial logistic regression as our analysis method. Sample size and power has been discussed in more detail in *Chapter 3*. We employed the following equation described by Tabachnick and Fidell,; $N \geq 50 + 8m$ (where m is the number of Ivs) for testing the multiple correlation or $N \geq 104 + m$ for testing individual predictors(226) Our final model contained 10 predictors, and for 658 participants in the regression analyses, sample size was adequate for 80% power (130 participants would be required) for the number of variables considered.

5.3. Results

5.3.1. Demographics and Medication Use

Of the 753 participants, 736 (98%) provided data on medication use. The baseline characteristics of these 736 participants are presented in *Table 5-2,* and in *Chapter 3.*

5.3.2. Anticholinergic Exposure

Of the eligible population (n=736), 70.9% (522) of participants reported taking any medications with possible or definite anticholinergic properties (ACB $\geq$1), with half of

the population (50.0%, 368) reporting medicines with definite anticholinergic properties (medications with an ACB score of 2 or 3).

In total, 1236 AC medicines were reported, accounting for almost 30% of total medicines reported by the population. Of the medications with AC properties reported, ACB 3 medications accounted for over half (53.1%), 11% were ACB 2 medications and over one-third (34.8%) were ACB 1 medications.

Of the 522 participants who reported exposure to anticholinergic medications, the mean (±S.D) total ACB score was 4.5 (±3.0) (range 1-16), and 41.2% reported an ACB score of ≥5.

5.3.3. Characteristics of those with AC exposure

A greater proportion of females reported anticholinergic exposure (an ACB score of ≥1), with almost three – quarters of females reporting anticholinergic use (73.2%) versus 68.2% of males, however this difference was not significant (p=0.08) (*Table 5-2*). There was a significantly higher prevalence (p<0.001) of those exposed to medications with anticholinergic properties in those over 65 years with 87.3% of those over 65 reporting use compared to 69.6% of those aged 50-64 years and 64.3% of those aged 40-49 years. There was a significant association between level of ID and AC exposure, as 85.2% of those with severe/ profound ID were exposed to anticholinergics, compared to 66.5% of those with moderate ID and 65.6% of those with mild ID (n=682, p<0.001). A greater proportion of those in residential settings reported AC use (83.7%), compared to 69.1% of those living in community group homes and 38.5% of those living independently, this difference was significant (p<0.001). There was a significant association between number of reported morbidities and anticholinergic exposure, with 83% of those reporting 3 or more conditions reporting AC exposure (p<0.001).

Table 5-2 Characteristics of those reporting anticholinergics (N=522) compared to those not reporting use (n=214)

	Total Population (n=736)	Anticholinergic Use (n=522)	No anticholinergic use (n=214)	p-value
	N (%)	N (%)	N (%)	
Sex				
Male	330	225 (68.2)	105 (31.8)	0.08
Female	406	297 (73.2)	109 (26.8)	
Age				
40-49 years	266	171 (64.3)	95 (35.7)	<0.001
50-64 years	336	234 (69.6)	102 (30.4)	
65+ years	134	117 (87.3)	17 (12.7)	
Level of ID (n=682)				
Mild	163	107 (65.6)	56 (34.4)	
Moderate	316	207 (65.5)	106 (34.5)	<0.001
Severe/ profound	203	173 (85.2)	30 (14.8)	
Residential Setting				
Independent	122	47 (38.5)	75 (61.5)	<0.001
Community Group Home	265	183 (69.1)	82 (30.9)	
Residential	349	292 (83.7)	57 (16.3)	
Number of co-morbidities				
0	51	27 (52.9)	24 (47.1)	<0.001
1	157	84 (53.5)	73 (46.5)	
2	192	137 (71.4)	55 (28.6)	
3+	336	279 (83.0)	57 (17.0)	

5.3.4. Frequently Reported Anticholinergic Medications

In the population, 71 different medications with possible or definite anticholinergic effects were reported (45 *ACB 1* medicines, 4 *ACB 2* medicines, 22 ACB 3 medicines) (*Table 5-1*). Frequently reported agents, with their corresponding ACB scores are presented in *Table 5-3*. The most frequently reported anticholinergic medications were carbamazepine, reported by almost one quarter (24.3%, 127) of those who reported anticholinergic exposure, followed by risperidone which was reported by over one fifth of those reporting AC exposure (21.4%, 112) , olanzapine

(19.3%, 101) and biperiden (16.2, n=85, ACB-3). The four most frequently reported anticholinergic medications accounted for one third (33.7%) of all anticholinergic medications reported in the sample.

Table 5-3 Frequently reported ACB Medicines (n=522)

ATC Code	ACB 3 Medicine	Rank	N (%)	ATC Code	ACB 1 Medicine	Rank	N (%)
N05AH03	Olanzapine	3	101(19.3)	N05AX08	Risperidone	2	112 (21.4)
N04AA02	Biperiden	4	85 (16.3)	N05BA01	Diazepam	5	82 (15.7)
N05AA01	Chlorpromazine	6	70 (13.4)	A07DA03	Loperamide	7	56(10.7)
N05AD01	Haloperidol	8	44 (8.4)	N06AB10	Escitalopram	9	35(6.8)
N04AA04	Procyclidine	9	37 (7.0)	R03BB01	Ipratropium	10	31(5.9)
N05AH04	Qeutiapine	11	27 (5.1)	N06AB04	Citalopram	12	25(4.8)
N06AB05	Paroxetine	13	25(4.8)	C03CA01	Furosemide	14	23(4.4)
	ACB 2			N05BA12	Alprazolam	15	22(4.2)
N03AF01	Carbamazepine	1	127 (24.3)				

All other anticholinergic drugs reported in decreasing prevalence : ACB (3) *: chlopheniramine, scopolamine, tolteridine, trimipramine, oxybutynin, promethazine, solifenacin, clomipramine, amitriptyline, festoteridine, atropine, benzatropine, hydroxyzine, doxepin*

ACB 2:*Nefopam , tizanidine*

ACB 1*: cetirizine, codeine, prochlorperazine, 156harmacodyn, atenolol, aripiprazole, venlafaxine, 156harmacodyna, desloratidine, trazadone, fluphenazine, ranitidine, mebeverine, tiotropium, baclofen, prednisolone, flupentixol, levocetirizine, nifedipine, warfarin, digoxin, bendroflumethiazide, loratidine, sulpride, alverine, amisulpride, dipyrimadole, metoprolol, captopril, benperidol, isosorbide, colchicine, hydrochlorthiazide, alimemazine, cinnarizine*

5.3.5. Contribution of Drug Classes to Total ACB Score

In total, 1236 medicines with definite or possible anticholinergic properties were reported Contribution of therapeutic classes to total ACB score in the sample are presented in *Figure 5-3*. The antipsychotics accounted for over one-third (36%) of the total cumulative ACB score for the cohort, followed by the anticholinergics (16%) and the antidepressants (11%).

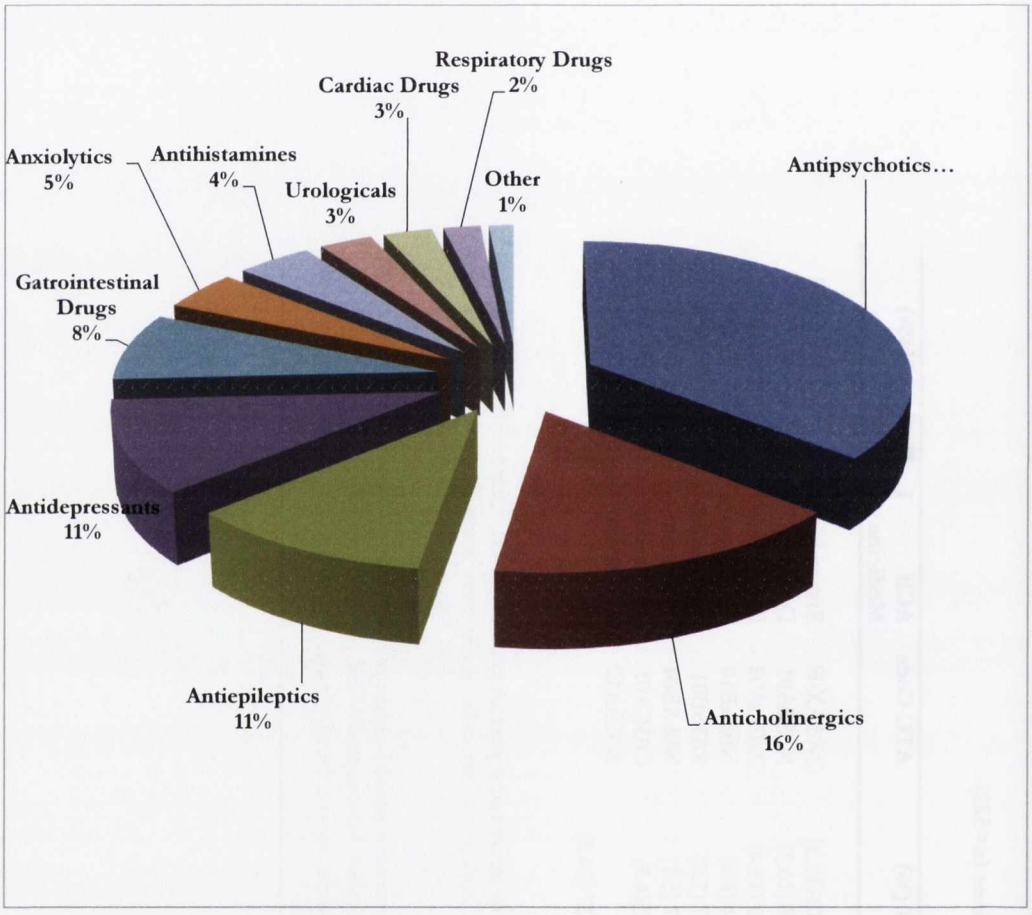

Figure 5-3: Contribution of Drug Classes to Total ACB score (n=736)

** The Contribution of Each Medication Class was Estimated from the Number of People Reporting Use of Medications of that Class Multiplied by its score (1-3) on the Anticholinergic Cognitive Burden (ACB) Scale ,Divided by the Population Cumulative ACB Score*
(Figure adapted from Lancot et al. (380))

5.3.6. Medications with Definite Anticholinergic Activity

Medications with moderate AC effects (ACB score 2) were reported by over one-quarter (26.6%) of those reporting anticholinergic exposure, and accounted for 11.6%

of all reported AC Medicines, with the most frequently reported medicine with moderate activity (ACB-2) being carbamazepine (n=127). ACB score 3 medicines were reported by 58.2% of those reporting anticholinergic exposure, and accounted for over half of all reported AC medicines, with the most frequently reported medicine with severe anticholinergic activity (ACB- 3) being olanzapine (n=101). Of those who reported use of ACB 3 medicines (n=306), 37.6% (115) reported concurrent use of two or more agents with severe AC activity with a maximum exposed to four concurrent medications with severe anticholinergic properties. Antipsychotics accounted for the greatest proportion of ACB 3 medicines reported; 46% followed by the anticholinergics (27.6%) and antidepressants (9.6%) (*Table 5-4*). Risperidone was the most commonly reported drug with an ACB score of 1 by 112 participants.

Table 5-4: Therapeutic Class contribution to ACB 3 Medicines Reported

ACB 3 Therapeutic Classes	ATC Code	Number Medicines (450)
		%
Antipsychotics	N05A	46
Anticholinergics	N04A	27.6
Antidepressants	N06A	9.6
Antihistamines	R06A	5.3
Urologicals	G04B	5.1

5.3.7. Antipsychotics and Psychotropics with Anticholinergic Properties

The antipsychotics represented the most frequently reported ACB contributing medication class, with 60.3% (318) of participants who reported anticholinergic exposure reporting use of an ACB antipsychotic. Of the 15 antipsychotics reported by participants, 14 were represented in the ACB Scale (all except zisprasidone). Of the 319 participants reporting use of an antipsychotic, 318 reporting an antipsychotic listed in the ACB scale and one-quarter of these (25.9%), reported concurrent use of ≥2 antipsychotics listed in the scale. Of the 319 participants who reported use of antipsychotics, 187 (58.8%) participants reported use of an antipsychotic with severe anticholinergic properties, 18 (17.7%) reported use of an antipsychotic with moderate

anticholinergic properties, and 165 (51.9%) participants reported use of an antipsychotic with possible anticholinergic properties. Anticholinergics (ATC N04A) accounted for over one-quarter of all ACB 3 medicines reported, with biperiden being most frequently reported by 85 participants.

5.3.8. Concurrent Anticholinergics and Antipsychotics

Anticholinergic agents (ATC N04A) accounted for the second most frequently reported therapeutic class with severe anticholinergic activity in the cohort, reported by over one-quarter (27.2%) of those who reported medications with severe AC properties. Anticholinergic medicines also accounted for 16% of the total cumulative anticholinergic burden in the cohort. There was a low reported prevalence of Parkinson's disease in the cohort; less than 1%. Of those who reported anticholinergic medications (121), 91.7% (112) reported concurrent use of antipsychotics with anticholinergic properties. Use of anticholinergic agents was greater for those reporting antipsychotic polytherapy; over half (58.5%) reported use, with over one-quarter of those reporting antipsychotic monotherapy received a concurrent anticholinergic.

5.3.9. Anticholinergic Burden Score

In the sample, 29.2% reported an ACB score of 5+, 41.7% reported an ACB score of 1-4 and 29% reported no AC exposure (an ACB score of 0) (*Table 5-5*). At bivariate level, there was a significant association ($p<0.001$) between age and ACB score category, with 41.4% of those over 65 with a score of 5+, compared to 27.1% of the group with a score of 1-4 and 25.6% of those with no AC exposure. Those with severe/profound ID had greater ACB scores , 36.5% had a score of 5+, compared to 28.2% of those with moderate ID, and 19.9% of those with mild ID, this difference was significant ($n= 682$, $p<0.001$). A greater proportion of those living in residential settings had a score of 5+; 41.3%, compared to 28.2% of those in community group homes, and 9% of those who lived independently ($p<0.001$). Almost half (48.6%) of those with polypharmacy exposure had a score of 5+. Of those with mental health conditions, 46.7% had ACB 5+, and a further 46.7% had a score 1-4 ($p<0.001$). There was a significant association between ACB score and number of chronic conditions reported; over one-third (35.7%) of those reporting three or more conditions had an ACB of 5+, compared to 31.8% of those with two conditions, 17.2% of those with one condition and 3.2% of those with no chronic conditions ($p<0.001$).

Table 5-5: Demographic and Clinical Characteristics by ACB Score Categories (n=736)

Characteristic	Total Population	No-anticholinergic exposure	ACB 1-4	ACB 5+	p-value
	736	**214**	**308**	**215**	
Demographics					
Gender (n,%)					
Male	330	105(31.8)	119(36.1)	106(32.1)	0.013
Female	406	109(26.8)	189(46.6)	108(26.6)	
Age group (n,%)					
40-49 years	266	95(35.7)	103(38.7)	65(25.6)	<0.001
50-64 years	336	102(30.4)	143(42.6)	91(27.1)	
65+ years	134	17(12.7)	61(45.5)	56(41.8)	
Level of ID (n=682)					
Mild	163	56(34.4)	66(23.2)	41(19.9)	<0.001
Moderate	316	109(34.5)	118(37.3)	89(28.2)	
Severe/profound	203	30(14.8)	99(48.8)	74(36.5)	
Residential setting					
Independent	122	75(61.5)	36(29.5)	11(9.0)	<0.001
Community	265		124(46.4)	60(22.6	
Group Home		82(30.9)			
Residential	349	57(16.3)	148(42.4)	144(41.3)	
Drug Use (mean ±S.D.)	5.8(±4.4)	2.2(±4.4)	5.8(±3.6)	9.4(±3.9)	<0.001
Polypharmacy Status					
No-polypharmacy	341	181(53.1)	130(38.1)	23(6.7)	<0.001
Polypharmacy (5+ medicines)	395	33(8.4)	170(43.0)	192(48.6)	
No chronic conditions (mean±s.d)	2.5(±1.5)	18.(±1.3)	2.7(±1.5)	2.9(±1.5)	<0.001
0 conditions	51	73(46.5)	17(5.7)	7(3.2)	<0.001
1 condition	157	73(46.5)	57(36.3)	27(17.2)	
2 conditions	192	55(28.6)	76(39.6)	61(31.8)	
3+ conditions	336	58(17.3)	157(46.7)	120(35.7)	
Eye disease	380	128(33.7)	157(41.3)	95(25.0)	<0.001
Mental Health	356	22(6.2)	167(46.9)	167(46.9)	<0.001
Neurological	268	53(19.8)	132(49.3)	83(31.0)	<0.001
Gastrointestinal	198	32(16.2)	88(44.4)	78(39.4)	<0.001
Endocrine	162	49(30.3)	66(40.7)	78(39.4)	0.94
Joint Disease	153	36(23.5)	71(46.4)	47(29.0)	0.21
Hypertension	112	26(12.4)	43(38.4)	46(30.1)	0.06
Heart Disease	89	22(24.7)	42(47.2)	21(38.9)	0.49

5.3.10. Factors associated with High Anticholinergic Burden

Results from the multinomial logistic regression are presented in *Table 5-6*. The model as a whole explained 46.5 %(Cox and Snell R Squared), and 52.5% (Nagelkerke R Squared) of the variance in anticholinergic burden. Those aged over 65 years , and those reporting mental health conditions were likely to report an ACB score of 1-4 and ACB of 5+, compared to those with no anticholinergic exposure, controlling for other factors in the model. Gender, level of ID or place of residence were not significant with either level of AC exposure, nor were the other clinical conditions.

Table 5-6: Results of the Multinomial Logistic Regression of ACB 0-4 and ACB5+ (n=658)

	ACB Categories			
	ACB 1-4		**ACB 5+**	
Characteristic	**OR (95% CI)**	**P-Value**	**OR (95% CI)**	**P-Value**
Gender				
Male	1.00	0.22	1.00	0.28
Female	1.34 (0.84-2.15)		0.73 (0.41-1.29)	
Age				
40-49 years	1.00		1.00	
50-64 years	1.13 (0.69-1.86)	0.63	0.97 (0.52-1.79)	0.92
65+ years	**3.25 (1.47-7.17)**	**0.004**	**3.21 (1.30-7.95)**	**0.012**
Level of ID				
Mild	1.00		1.00	
Moderate	0.76(0.53-1.58)	0.37	0.68 (0.33-1.39)	0.29
Severe/ profound	1.42 (0.66-3.08)	0.36	0.85 (0.34-2.13)	0.72
Residence				
Independent/Community	1.0		1.0	
Group Home				
Residential	0.92 (0.53-1.58)	0.76	1.52 (0.80-2.90)	0.20
Conditions				
Mental Health				
No	**1**		**1**	
Yes	**9.71 (5.58-16.90)**	**<0.001**	**23.96 (12.42-46.21)**	**<0.001**
Neurological				
No	1		1	
Yes	1.29 (0.77-2.21)	0.33	0.73 (0.39-1.37)	0.33
Gastrointestinal				
No	1		1	
Yes	1.21 (0.66-2.22)	0.54	1.25 (0.63-2.50)	0.52
Eye				
No	1		1	
Yes	0.81 (0.50-1.32)	0.40	0.69 (0.38-1.27)	0.23
Hypertension				
No	1		1	
Yes	0.66 (0.32-1.35)	0.25	0.74 (0.32-1.67)	0.46

Reference category = ACB 0, p<0.05 is significant, all significant factors in bold
Cox and Snell R^2 = 0.465 Nagelkirke R^2 = 0.53
Reference categories : male, 40-49 years, mild ID, independent setting, polypharmacy (5-9 medicines), no eye condition, no mental health condition, no hypertension, no gastrointestinal disease, no neurological condition. Model adjusted for polypharmacy status

5.3.11. Anticholinergic Adverse Effects

Table 5-7 examines the association between central and peripheral anticholinergic adverse effects in relation to ACB Category score.

There was a significant association (p<0.001) between day time drowsiness and ACB score, with 43.3% of those with an ACB score of 5+ reporting a moderate / high likelihood of daytime drowsiness, compared to 38.3% of those with an ACB Score of 1-4 and 23.4% of those with no anticholinergic exposure. There was a higher prevalence of falls among those with anticholinergic exposure, but this was not

significant (p=0.02), with 29.1% of those with an ACB score of 5+ reporting falling in the previous year compared to 31% of those with an ACB score of 1-4 and 20.3% of those who were not exposed to anticholinergics. A greater proportion of those exposed to anticholinergics reported a doctor's diagnosis of chronic constipation: 26.6% of those with an ACB score of 5+ compared to 17.9% of those with an ACB score of 1-4 and 7.9% of those with no AC exposure, this difference was significant (p<0.001). Neither dentate status, nor self-rated health were significantly associated with ACB score.

Table 5-7: ACB Score and AC Adverse Effects

Characteristic	**Total Population 736**	**No AC Exposure 214**	**ACB 1-4 308**	**ACB 5+ 215**	**p-value**
	n(%)	n(%)	n(%)	n(%)	n(%)
Self-rated Health (n=730)					
Excellent/very good/good	625(85.6)	179(84.8)	259(84.4)	187(88.3)	0.4
Fair/poor	105(14.4)	32(15.5)	48(15.5)	25(11.7)	
Central Anticholinergic Adverse Effects					
Likelihood of Daytime Dozing					
High/ Moderate Likelihood	267(35.7)	50(23.4)	118(38.3)	99(43.3)	**<0.001**
Slight/ Would never doze	473(64.3)	164(76.6)	190(61.7)	115(53.7)	
Have fallen in previous year (n=731)	200(27.4)	43(20.3)	95(31.0)	62(29.1)	0.02
Peripheral Adverse Effects					
"Is constipation a problem for you?" (n=725)	316(43.6)	60(28.0)	139(45.7)	117(55.2)	**<0.001**
Doctor's Diagnosis of Chronic Constipation	128(17.4)	16(7.5)	55(17.9)	57(26.6)	**<0.001**
Any Laxative Use	276(37.5)	41(19.2)	119(38.8)	116(53.5)	**<0.001**
1 Laxative	146(19.8)	62(29.5)	62(38.7)	54(24.9)	
2+ Laxatives	130(17.7)	3(1.4)	58(18.7)	62(28.5)	
Dentate Status(n=734)					
Dentate	547(74.5)	169(80.5)	228(74.0)	150(69.4)	0.03
Edentulous	187(25.5)	41(18.5)	80(26.0)	66(30.6)	

5.4. Discussion

5.4.1. Principal Findings

Our study investigated total anticholinergic exposure in an older population with ID through use of the Anticholinergic Cognitive Burden Scale, modified by consensus. We found that the anticholinergic burden was high, with seven in ten participants exposed to anticholinergic medications, and over one quarter of the sample reporting an ACB score of ≥5. We identified 71 different medications in our cohort with possible or definite AC properties; medications with anticholinergic properties accounted for over one-quarter of all medicines reported in the study, with the majority of the anticholinergic burden being attributed to agents to treat mental health and neurological conditions. Our findings demonstrated that half of our sample was exposed to medicines with definite anticholinergic activity. Consistent with our primary hypothesis, our multivariate model identified that older age and reporting a mental health condition were independently associated with higher anticholinergic burden, after adjusting for confounding variables. A substantial proportion of participants were taking multiple anticholinergic agents which were contributing to cumulative high ACB scores.

5.4.2. Comparisons to other cohorts

Comparisons with other ID cohorts are limited, as to our knowledge no other study has examined cumulative anticholinergic exposure in an ID sample. Furthermore, comparability to general population studies are limited, due to differences in anticholinergic scales employed, sample characteristics, and the established higher prevalence of mental health and neurological morbidity in older people with ID. Nevertheless, our findings of anticholinergic burden are higher than previously reported studies in the general population. In the Irish community dwelling population over 50 years Richardson and colleagues reported that among 6,666 individuals, 4% had regular use of an agent with definite anticholinergic activity and 26% reported agents with possible anticholinergic activity (381). As part of a longitudinal study examining the effect of anticholinergic medication use on cognitive impairment in 12,423 community dwelling and institutionalised people over 65 years in England and Wales, Fox and colleagues reported that 48% reported any medication with possible or definite anticholinergic properties, 4% had a medication with definite anticholinergic properties, and 2% an ACB score over 5(353). Among those with

anticholinergic exposure, Fox reported a mean ACB score of 1.8±1.1, lower than mean ACB score of 4.5±3.0 noted in our study. Myint and colleagues examined AC exposure among 21,636 adults aged 40-79 years from general practice registers from 1993-1997 as part of the EPIC-Norfolk study, and identified that 80% had no AC exposure, 12.5% had an ACB score of 1, 6.1% a score of 2-3, and 1.3% an ACB score of >3 (382). In a study of 1168 hospital inpatients over a number of hospitals in Italy, 58.8% were exposed to medicines with anticholinergic properties, and 1.2% had an ACB score of 5+(383). Ness reported a prevalence of 27% of community dwelling veterans over 65 years reporting AC exposure (364). In Scotland, Sumukadas and colleagues reported that among all the population over 65 years dispensed medicines in 2010 (n=73,645), 23.7% were exposed to anticholinergics (as determined by an updated version of the Anticholinergic Risk Scale), and 9.9% had a score of 3+(344).

5.4.3. Frequently reported medicines.

We identified 71 different drugs in 15 different therapeutic classes that contributed to anticholinergic exposure in our sample. The most frequently reported anticholinergic agents in our population were agents to treat neurological and mental health morbidities; carbamazepine, risperidone, olanzapine, and biperiden; three of which are medicines with definite anticholinergic properties. These findings are in contrast to patterns of prevalent anticholinergic agents used in the general population; Fox noted that most frequently used agents in 12,243 community dwelling and institutionalized participants over 65 years were agents with possible anticholinergic properties: furosemide, dextroproxyphene, atenolol and nifedipine (353). In the Irish community dwelling population over 50, Richardson also indicated that the most prevalent anticholinergic agents in the sample were cardiac agents with a corresponding ACB score of 1; hydrochlorothiazide, atenolol and bendroflumethiazide(381). In the Scottish study, amitriptyline was the most common anticholinergic agents, followed by rantidine and tiotropium(344), while in Italy, Pasina noted that furosemide, warfarin and digoxin were most frequently used (383).

We identified that antipsychotics accounted for over one-third (36%) of the cumulative burden for the cohort. These patterns of use are in contrast to the general elderly population, where agents to treat cardiac conditions, gastrointestinal conditions, allergies and urinary incontinence make a more frequent contribution to burden (344, 381, 383). Our finding are consistent with other studies in the ID

population, where antipsychotics represent the most widely used psychotropic drugs (145, 167). Indeed, a high prevalence of first generation antipsychotics with high anticholinergic burden were identified in our study. These older antipsychotics, in particular the phenothiazines are not recommended in the elderly due to their anticholinergic, noradrenergic and antihistamine effects (29), and the risk of development of tardive dyskinesia. In particular, the high frequency of reported use of chlorpromazine (70 participants; 9.4% of the population) is of concern. While we were limited in commenting on the rationale or appropriateness of use of these agents due to a lack of information on risk benefit assessments and length of exposure, is these agents were used from a younger age, studies have examined the cognitive effects of antidepressants and antipsychotics with known anticholinergic effects, and found that cognitive deficits may persist, despite an improvement in psychosis or mood(384, 385).

We identified that antidepressant agents accounted for over 10% of the cumulative anticholinergic burden, with the SSRIs paroxetine (ACB score of 3), citalopram and escitalopram (ACB score of 1) being most the frequently reported. We identified that use of Tricyclic Antidepressants, which are associated with cardoiotoxic and substantial anticholinergic adverse effects was low in our study, reflecting the move to SSRIs, which have an improved safety profile(28). However, paroxetine was most commonly reported, and it is the most anticholinergic of the newer antidepressants(28).

5.4.4. Factors associated With High Anticholinergic Burden

In support of our primary hypothesis, our multinomial logistic regression identified that those over 65 years of age were likely to be exposed to both higher levels of anticholinergic burden, compared to those with no anticholinergic burden, after adjusting for confounding variables. While the majority of the population in our study were aged between 50 and 64 years, anticholinergic burden was greatest among those over 65 years; nine in ten were exposed to anticholinergics, and almost half of those over 65 years had an ACB score of 5+. Our findings in relation to higher burden in older age are consistent studies in the general elderly population(344, 356).

Our multivariate analyses also identified that reporting a mental health condition was also associated with higher burden; over half of those with a mental health condition had an ACB score of 5+. However, the wide confidence intervals associated with mental health conditions, mean our results should be interpreted with

some caution, and may reflect variability in the reporting of mental health conditions, or perhaps that some of the anticholinergic burden could be attributed to use of medicines in challenging behaviours where there was no mental health diagnosis. In a study examining anticholinergic load of psychiatric inpatients aged over 65 years, 83 patients had an average ACB score of 3.28(386), and the study also identified that patients with psychiatric disorders were at special risk of high burden. Wawruch also identified hospitalised elderly patients with depression as being at risk of use of medications with anticholinergic properties(363). These findings of greater likelihood of very high anticholinergic burden in the old, and those with mental health morbidity may be a cause for concern, given the evidence that those who are older , or with psychiatric morbidity are at increased vulnerability to the adverse neuropsychiatric effects associated with anticholinergic drugs, as these individuals may already have some evidence of cognitive impairment (e.g. depression, schizophrenia, dementia) (354, 387-390). Furthermore, detection of adverse effects on cognition may be difficult, as changes in memory and attention may be subtle, and occur in the absence of more overt signs of anticholinergic toxicity(354). In the elderly, anticholinergic agents which may have been used without harm at a younger age, may subsequently cause adverse effects. Additionally, adverse effects can occur not only at toxic doses, but also at therapeutic doses when taken by the elderly, or those with mild cognitive impairment (345, 354).

Carbamazepine was the most frequently reported anticholinergic agent in the population, but in our multivariate analysis there was no significant association between neurological disease and higher ACB scores. This may be in part, due to the fact that 30% of those who were taking carbamazepine did not have reported epilepsy, and the drug may have been used as a mood stabiliser. In addition to its potential for anticholinergic adverse effects, carbamazepine is also a potent inducer of hepatic P450 isoenzymes, and is metabolised by CYP3A4, meaning it has the potential to interact with many antidepressants, antipsychotics, benzodiazepines, and other agents, therefore, extensive care is needed in monitoring use of this agent(28).

While we identified no association between level of ID, and anticholinergic burden in our multivariate regression, after adjusting for relevant confounders, it is worth noting that 85% of those with severe or profound ID were exposed to anticholinergic medications, and over one-third had an ACB score of 5+. Anticholinergic medications may carry considerable risk in these individuals, due to the potential for idiosyncratic

responses, evidence of cognitive impairment, and given their inability to communicate adverse reactions associated with anticholinergic medicines, and require ongoing monitoring(29, 207, 287).

Unsurprisingly, those exposed to polypharmacy were likely to be have higher anticholinergic burden scores; in our study nine in ten of those exposed to polypharmacy were exposed to anticholinergic agents, and over four in ten of those exposed to polypharmacy had an ACB score of 5+. The risk of high anticholinergic exposure in those exposed to polypharmacy is consistent with previous studies in the general population (344, 364, 391). Since the majority of participants in our study (53.7%), take 5 or more medicines, many of which have known anticholinergic properties, it is possible that anticholinergic toxic syndrome could result from a complicated medication regimen in which several medicines with modest anticholinergic effects are prescribed concurrently. The net risk of anticholinergic toxicity may be high, even if the patient is not reporting receiving a readily identifiable anticholinergic medication(360). However, since so many medicines were spread across different therapeutic classes and were contributing to exposure, it might be difficult to find suitable alternatives.

While anticholinergic burden scores were significantly higher for those living in residential settings at bivariate level; four in ten had an ACB score of 5+, compared to one-fifth of those in community group homes and less than 10% of those living independently, after adjusting for relevant confounders, we identified no association between anticholinergic burden and place of residence. There was a higher prevalence of mental health conditions in those living in institutional settings, which may in part, account for the greater burden. These findings are important in the context of deinstitutionalisation. The attitudes and understanding of primary care health professionals and care staff of the complex pharmaceutical care needs of people with intellectual disabilities will be important upon movement from institutional care back into community settings (29).

We could not examine the relationship between multiple conditions, and anticholinergic burden at multivariate level due to correlation with type of condition, however, at bivariate level our findings revealed a significant association between number of conditions, and higher ACB score; two thirds of those with two or more conditions were exposed to an ACB score of 5+, in contrast to one-fifth of those who reported none or one chronic condition. A relationship between multiple morbidities

and higher anticholinergic load has been established in another study in the elderly (345, 353).

It was not possible for us to examine those with dementia at a multivariate level, due to the small numbers with a diagnosis of dementia, however, we noted that in those with dementia, 40% had an ACB score of 5+, and 43.2% had a score of 1-4., There is substantial evidence in the literature relating to the harm of use of anticholinergic agents in those with dementia , or at risk of cognitive decline(190, 353). The use of definite anticholinergics represents a modifiable risk factor for the development of dementia and deterioration in cognitive function. Efforts should be made to reduce and limit use of medications with anticholinergic effects, particularly in those most vulnerable to cognitive decline; Down's syndrome and Alzheimer's disease.

The National Task Force on Intellectual Disability and Dementia Practice Consensus Recommendations for Evaluation and Management of Dementia in Adults with Intellectual Disability recommends reviewing the medication list "thoroughly" paying special attentions to medications that are "psychoactive, antiepileptic or anticholinergic or those with sedating properties" (90) . The Consensus guidelines also list medication classes with "potential deleterious effects on cognition".

5.4.5. ACB 3 Medicines and Multiple Anticholinergics

Antipsychotics and anticholinergic agents accounted for almost three-quarters of ACB 3 medicines consumed in our population, and two of the four most frequently consumed anticholinergic agents in the cohort had an ACB score of 3; olanzapine and biperiden. Moreover, we established a high prevalence of use of concurrent multiple severe anticholinergics agents; our findings revealed that over one-third of those with medicines with severe properties, or 15% of the total sample were exposed to two or more agents with severe anticholinergic properties.

Our findings identified that anticholinergic medicines (N04A) accounted for 16% of the total AC burden. While our findings are limited by the fact that we did not have information in relation to side effects of medications, prevalence of Parkinson's was negligible in the study, it is probable that these anticholinergic agents are being to some extent used to treat or in prophylaxis of extra-pyramidal symptoms associated with psychotropic agents, in particular the older antipsychotics. Anticholinergics can be used for dystonia in those with cerebral palsy, but in our study only 3% of those

with cerebral palsy used anticholinergics. This is supported by the finding that that nine in ten participants who were exposed to anticholinergics (N04A) were concomitantly taking an antipsychotic with anticholinergic properties, and over one-third of those taking antipsychotics had anticholinergic medications. It is also possible that anticholinergics were used prophylactically in a non-verbal person who is unable to communicate the side effects of dystonia. Our findings of concurrent antipsychotic and anticholinergic use are higher than reported in other ID populations, in the UK, Paton reported that 14% of people with ID who consumed antipsychotics had concurrent anticholinergics(11). This practice may reflect the phenomena of "the prescribing cascade", and has been reported in other populations, where adverse effects associated with medications with anticholinergic properties are treated with additional medicines (anticholinergics such as biperidin), as opposed to withdrawal, dose reduction (125, 363). The STOPP START criteria deem that "Anticholinergic or antimuscarinic agents to treat extrapyramidal effects of neuroleptic medicines" (risk of toxicity) to be potentially inappropriate in the older population. Prevalence of use of anticholinergics for this indication is much higher than reported in the general Irish community dwelling population over 50 years, where a prevalence of 0.09% of anticholinergics to treat extrapyramidal effects of psychotropic agents was reported (336).

Although first generation H1 antihistamines were only reported by by 3.2% of participants, these agents readily cross the blood-brain barrier and cause significant central anticholinergic adverse effects and may be a risk factor for falls. They were previously used to treat insomnia, however much safer alternatives are now available and they are not recommended (387).

Our findings in relation to the appropriateness of these regimens is limited by the fact that we did not have information in relation to length of exposure to concurrent agents, however evidence suggests that use of these combinations of potent anticholinergic agents identified places people at increased risk of anticholinergic toxicity and adverse effects, and is no longer recommended(355).

5.4.6. Anticholinergic Adverse effects

Findings from our study revealed a positive association between increasing anticholinergic score and presentation of constipation, laxative use, risk of daytime dozing, but no significant association with falls, dentate status or self-rated health.

While interpretation of these findings must be restrained, as there are at univariate level only, and do not account for other confounding factors contributing to outcomes, the 171harmacody correction did control for the potential problems of multiplicity. In terms of central adverse effects, higher burden was associated with the risk of daytime dozing, which could have significant effect on quality of life and on the ability to carry out activities of daily living.

In relation to peripheral adverse effects, we identified a significant association between AC exposure and constipation, with over one-quarter of those with an ACB score of 5+ with a doctor's diagnosis of chronic constipation, in contrast to 7.6% of those with no AC exposure. This relationship between higher AC exposure and constipation is consistent with another study in older American veterans(364) . Furthermore, our findings revealed that over half of those with an ACB score of 5+ were taking laxatives, and over one-quarter were taking two or more laxatives , while one-fifth of those with no exposure were consuming laxatives and only 1.4% had laxative polytherapy, which may to some extent may also reflect the prescribing cascade.

Peristalsis consists of two processes; contraction and relaxation, with acetylcholine mediating contraction in this process. Anticholinergic medications constipate by inhibiting the first phase of peristalsis: contraction.(392). Given that people with ID may be already at risk of constipation due to poor fluid intake, inactivity, neural origin(94), assessment of the contribution of medicines to symptoms is of great importance, and reducing the use of anticholinergic medicines where possible represents a predictable way of modifying the risk of morbidity, and improving the quality of life in older people (370).

We had to use indirect indicators of anticholinergic adverse effects, as we did not have specific information in relation to dry mouth, dry eyes, blurred vision or confusion. A higher proportion of those with an ACB of 5+ were edentate (30.6%), compared to 19.8%, but this was not significant after adjusting with the Bonferroni correction. While we cannot establish cause and effect in our study, and were limited by a lack of detailed information about xerostomia or other aspects of dental health, coupled with the acknowledgement that people who had higher ACB score may be older, have poorer diets, and mental health difficulties that may negatively affect dental health, the relationship between anticholinergic medications and xerostomia, decay and subsequent tooth loss has been established(393, 394); medications with

anticholinergic activity are potent inhibitors of saliva production leading to salivary hypofunction, as dysregulation of the oral cavity where saliva plays a key role in homeostasis(347). Given that people with ID may already be at risk of poor dental outcomes and tooth loss, the oral impact of anticholinergic medications must be considered, and it may require further consideration by clinicians and dentists as a modifiable contributory risk factor for tooth decay in this population.

It is also important to note that another possible hypothesis for higher reported rate of anticholinergic symptoms in those with higher ACB scores is that these patients are frailer, have more illness and mental illness overall, and thus are more likely to present with more symptoms. Nevertheless to prevent the prescribing cascade, these findings highlight the need for review of medications in older multimorbid individuals, and to consider the impact of anticholinergic load on the quality of life and health of an individual.

5.4.7. Study Strengths

Our study had a number of strengths. To our knowledge, this is the first study to calculate the prevalence of anticholinergic use, to determine the cumulative anticholinergic exposure and factors associated with high anticholinergic exposure in ageing people with intellectual disability. The use of a large, randomly sampled population-representative sample enabled us to have sufficient power for our multivariate analysis, and means our findings may be 172harmacodynam to the Irish ID population, and ID populations in other countries. We had sufficient power to test for differences in the three different levels of AC exposure used in the study, and the use of a higher threshold (ACB 5+) enabled us to identify those at greatest risk of adverse outcomes. Furthermore, for our study, participants and/or proxy respondents underwent a detailed assessment of health characteristics, allowing us to examine potential confounders on our regression model that are usually unavailable to many pharmacoepidemiological studies. One of the other considerable strengths of the study was that, we refined the use of a robust scale, which was up to date and had been previously used and was developed by expert consensus. We also added to the content validity of the scale by reviewing the literature in relation to other anticholinergic medicines that were available in Ireland, and had an independent expert for consensus on additional medicines to include. The ACB provides a holistic method of capturing cumulative load, many drugs that contribute to AC exposure, and all of these drugs

may not identified as problematic in appropriateness criteria such as Beer's criteria. Serum anticholinergic assays (SAA) measure "in vitro" muscarinic activity, and have been in the past considered as the "gold standard" in quantifying anticholinergic load(386). However, assays are difficult to interpret, expensive and not readily available in routine practice. It is accepted currently, allied to a careful review of the patients' symptoms and medicines, scales and lists such as the ACB scale remain the best aid to guide clinical decision making (354). We were also able to link the medications used to the indications in many cases as we had information about the principal medical conditions.

5.4.8. Study Limitations

There are a number of methodological limitations to be considered when interpreting the results of this study; first, both chronic conditions and medication use was based on participant or proxy self-report. However, several steps were taken to improve the accuracy of the clinical and medical information: cross-checking of the medicines information in the pre-interview questionnaire at time of interview and participants receiving the pre-interview questionnaire at least one week in advance of the interview, thus giving them time to gather information about their medicines use. Information was not recorded about the severity of diseases reported, which may be a critical factor as to why anticholinergic drugs were prescribed.

In addition, while almost all participants were able to provide information about medicines used, full information was not always provided in some cases with respect to dose and frequency of medicines. Information about the length of time during which participants had been taking medicines and thus were exposed to anticholinergic medications was also not available.

Similar to the validity limitations of all prescription appropriateness tools in the elderly, the ACB scale does not take into account the influence of implicit patient variability in drug response associated with older age, frailty, multimorbidity, cognitive reserve, individual 173harmacodynamics factors (hepatic and renal function) and polypharmacy. Furthermore, anticholinergic prescribing risk scales inherently have limitations, due to the difficulty in predicting extent of manifestation of anticholinergic central effects in particular, for example, while amitriptyline and paroxetine both have an ACB score of 3, they have different potencies at muscarinic receptors. It is likely

that administration of amitriptyline in an older adult will result in greater memory deficits compared to paroxetine(395).

We did not have full information in relation to dose of anticholinergic medicines, and adverse effects may be dose dependent(354), and the ACB scale does not take dose of medicine into account. While a higher dose of an anticholinergic agent would be expected to give rise to greater central effects compared to a lower dose, this may not necessarily occur in a linear fashion(395).

We did not gather information as to whether physicians were aware of risk associated with anticholinergic prescribing, and as to how often medication was reviewed, or if effects of AC medicines on cognition was reviewed.

As this medication data is drawn from Wave 1 of IDS-TILDA, it is observational and cross-sectional in design, thus it is not possible to draw conclusions on definite cause and effect relationships between anticholinergic burden and clinical and demographic factors. For our multivariate analysis, we attempted to reduce bias by adjusting for known confounding, however we cannot rule out the possibility of residual confounding. However, future waves of the study will provide additional data in relation to causation and the implications longitudinally of anticholinergic exposure in this population.

While we examined potential adverse effects associated with AC exposure at bivariate level, we cannot rule out that other factors contributed to presentation of these effects, other than anticholinergic burden. A limitation in relation to the evaluation of association between medicine use and health outcomes is the difficulty in determining the possible effects of confounding, or reverse causality.

We were unable to specifically examine the influence of functional status, or baseline cognitive status, which are likely to influence the prescription of anticholinergics.

5.5. Conclusion

Drugs with anticholinergic properties have a number of clinical uses, but are also associated with substantial .adverse effects. While anticholinergic medicines are not in themselves inappropriate, they may carry increased risk in older people. An older person with ID is likely to be multimorbid, may have mental health or neurological concerns and exposed to polypharmacy, and may be placed at increased risk of poor outcomes. Older people with ID may tolerate anticholinergic drugs less favourably

than healthy older adults, especially given increased sensitivity and decreased ability to recognise and communicate adverse effects. We identified that antipsychotic agents accounted for over one third of the total anticholinergic burden in the population, findings that are in contrast to the general elderly population, and that the high prevalence of first generation highly anticholinergic antipsychotics that are no longer favoured in the elderly elevated the burden. Evaluation of the anticholinergic burden for older people with ID should be considered as an additional important method to optimize rational and appropriate polypharmacy. We identified a wide range (71) of different medicines with anticholinergic properties in our sample that influence the cholinergic system. Therefore, clinicians should be mindful of the impact of medicines with anticholinergic properties on cognitive function, and the cumulative effects of concurrent use of multiple medicines with modest anticholinergic effects. The Anticholinergic Burden Scale may offer a simple and effective tool to identify drugs and combinations contributing to ACB. This may draw attention to the total anticholinergic load in a patient in a more holistic and focused manner, and identify those at risk. Where possible, avoiding anticholinergic drugs may maximize and preserve physical and cognitive function in vulnerable older people with ID, and prevent adverse outcomes such as falls (356). Given the growing evidence of the association of anticholinergic medications with adverse cognitive outcomes, as people with ID grow older, clinicians, other health care professionals and carers need to be vigilant to adverse effects that may not manifest in the younger patient. Clinicians and pharmacists should regularly review the indications, risks and benefits of anticholinergics in older people, especially those at risk of cognitive decline and multimorbid, mental health conditions.

What is already known about this topic:

- Drugs with anticholinergic properties have a number of clinical uses, but there is accumulating evidence of increased risk of adverse cognitive and functional outcomes in older people who use medicines with anticholinergic properties.
- Medication scales have been developed to capture the cumulative anticholinergic load of a patient from multiple drugs.
- It is likely that older people with ID may be exposed to anticholinergic drugs due to high prevalence of mental health conditions present and other age-related conditions in this population.
- Older people with ID may tolerate anticholinergic drugs less favourably than healthy older adults, especially given increased sensitivity and decreased ability to recognise and communicate adverse effects.
- No studies to date have assessed cumulative anticholinergic burden in a population with ID.

What this study adds:

- Anticholinergic Exposure was high in older people with ID; seven in ten were exposed to anticholinergics (ACB ≥1), and almost 30% had an ACB score of 5+.
- Our multivariate model revealed that older age, and having a mental health condition were associated with higher anticholinergic burden, but gender, level of ID or place of residence had no significant effect.
- Antipsychotics accounted for over one-third of the cumulative anticholinergic burden in the sample.
- Use of anticholinergic drugs is a potentially modifiable risk factor in relation to cognitive function in the elderly with ID A decreased load may result in a decreased likelihood of experience of adverse effects.
- Given the growing evidence of the association of anticholinergic medications with adverse cognitive outcomes, as people with ID grow older, clinicians, other health care professionals and carers need to be vigilant of adverse effects that may not manifest in the younger patient.
- Evaluation of anticholinergic burden for older people with ID should be considered as an additional important method to optimize rational and appropriate polypharmacy.
- The ACB Scale may reflect a simple and effective tool to identify drugs and combinations contributing to ACB. The ACB Tool may draw attention to total anticholinergic load in a patient in a more holistic and focused manner, and identify those at risk of adverse outcomes.
- Our study indicates that those with higher ACB exposure may be experiencing anticholinergic adverse effects such as constipation. Longitudinal analysis from future waves will enable us to assess the relationship between ACB scores and longer term health outcomes for people with ID.

Chapter 6. Patterns of Antiepileptic Drug Use in an Ageing Population with Epilepsy and Intellectual Disability

6.1. Introduction

The prevalence rates of epilepsy in persons with intellectual disability (ID) are high with estimates of 14-44% (76, 77), exceeding those observed in the general population, where estimates of 1.1% have been reported (78, 266, 396). A recent Irish study examining prevalence rates of epilepsy estimated that up to 37,000 Irish people have epilepsy; a point prevalence of 0.08% (397). Epilepsy has been recognised as a chronic disabling condition with a substantial burden on individuals, carers, families and the healthcare system(398). People with ID exhibit different seizure types and frequency compared to the general population (178), with higher frequencies of some types of epilepsy, e.g., Lennox-Gastaut syndrome. Many people with ID suffer from "refractory" or "pharmacoresistant" epilepsy due to the underlying presence of abnormalities of the nervous system and idiosyncratic response to therapies (85, 86). Indeed, adults with intellectual disabilities compromise a substantial proportion of the prevalent epilepsy population (399). In particular, the severe form (s) of ID has been associated with a range of "treatment – resistant" neuropsychiatric conditions, including epilepsy(400). It may also be difficult to accurately differentiate epileptic seizures in this population from other comorbid conditions, or side effects from psychotropic medications due to communication difficulties and the high prevalence of multimorbidity (85, 86).

Although the life expectancy of people with ID is increasing , in line with the general population , those with intellectual disability co-existing with epilepsy have a significantly higher mortality rate (87, 88), due to sudden unexplained deaths, aspiration episodes, pneumonia (87, 88, 401), which may also in part be explained by the fact that epilepsy is positively associated with ID severity(87). While prevalence rates of 30 % for adults with ID in one European study aged 19-34 years have been described (47), a lower prevalence rate for those over 65 with ID of 15% has been reported (266), which may reflect higher mortality among those with epilepsy and ID (83). An association of seizures with cognitive decline in individuals with Down syndrome and dementia has been reported(402). Epilepsy in this population may also be a risk factor for falls, fractures and impaired quality of life (403). Unrecognised seizures, or those which are inadequately treated may impair cognitive function (404, 405). Epilepsy may have a "pervasive" effect, and significant psychosocial impact on life of people with intellectual disabilities and their families or carers (81, 84, 178).

Epilepsy is among the disorders that is strongly associated with significant psychological and social impacts on daily living(80, 406).In the general population people with epilepsy are among the most vulnerable in society, in part attributed to the disorder itself, and also discrimination associated with the condition; people with epilepsy often experience prejudicial behaviour in many facets of life and cultures (80, 407). For people with ID and epilepsy, there is increased vulnerability and potential for discrimination.

The primary goal of care for patients with epilepsy is the prevention of further seizures, maintenance of a normal lifestyle, which is preferably free of seizures, and with minimal side effects from medications (80). Diagnosis and management of epilepsy may require contributions and collaboration from a number of health care disciplines, in a variety of settings including primary, secondary and tertiary care (408). In addition, studies in the general population have shown that a majority of patients with epilepsy will be urgently admitted to secondary or tertiary care (mostly through Accident and Emergency Departments), at some point in their illness, and for a significant number, they will require multiple visits(409, 410). In the general population, it is estimated that up to 70% of people can become seizure free with appropriate treatment(80).

There are few observational and intervention studies, and high quality studies of the treatment of epilepsy in ID cohorts(250). A Cochrane review by Beavis (2007) assessing pharmacological interventions for epilepsy in people with ID concluded that data is lacking in relation to many AED interventions(250). In particular efficacy, safety and seizure reduction of newer AEDs have not been investigated.

- Guidelines developed have noted a "dearth of high-quality evidence from well-constructed studies" (400). For people with intellectual disabilities, "no recommendation can be given for a specific drug of choice for patients with epilepsy and learning disability"(178).
- In a Cochrane review of the effectiveness of pharmacological treatment of epilepsy in intellectual disability, Beavis concluded that "drugs should be chosen on the basis of patient's seizure type, seizure syndrome and aetiology and being cognisant of a side effect profile of a drug"(250). Sodium valproate and lamotrigine are recognised as appropriate 1st line agents for generalised seizures in ID, while carbamazepine second line(411) ,and all three deemed suitable for partial seizures.

- It is recommended, where possible that AEDs that have a lower rate of cognitive adverse effects be selected such as lamotrigine, levetiracetam and valproic acid(412, 413) .
- A Cochrane Review assessing the evidence for pharmacological effectiveness for evidence of antiepileptics in epilepsy trialled in people with ID concluded "a moderate reduction in seizure frequency and occasional seizure freedom was obtained" with use of therapeutic interventions(250).
- Despite use of AED interventions, it has been reported that only 25%-35% of patients with ID may achieve seizure freedom (85, 414).

The few epidemiological studies assessing patterns of AED use in an ageing population with ID , and studies to date have often relied only on institutional setting populations (179, 415), and noted a high prevalence of seizures that may be refractory to seizures despite the use of polytherapy (85, 414). An additional challenge for managing treatment for healthcare providers is the high proportion of ageing people with ID are taking multiple medicines, which may interact with AEDs or lower the seizure threshold(28, 177, 416). Pharmacokinetic interactions between antiepileptics and antidepressants or antipsychotics are common (28, 417), and primarily mediated through CYP enzymes. Polytherapy, rapid upward titration schedule of doses or high doses of AEDs may significantly increase the risk of cognitive and behavioural side effects(400).

There are similar challenges in treating epilepsy in older adults. Incidence of epilepsy in elderly patients is higher than any other period of life (418), and there is little research on assessing the efficacy and safety of antiepileptic drugs older patients, although it has been recognised that elderly patients handle drugs differently (due to decreasing renal and hepatic function associated with aging which decreased the ability of the body to eliminate medicines)(419). AEDs represent a heterogeneous class of medications, with respect to structure, their postulated mechanism of action and their clinical indications. Clinical guidelines are usually based on data from younger patients despite evidence that a standard dose of a highly protein bound antiepileptic drug (e.g. phenytoin, carbamazepine) appropriate in a younger patient may result in toxicity in an elderly person(420). Increased incidence of adverse drug reactions, polypharmacy, and sedative burden associated with AED therapy and drug-drug and drug-disease interactions have been noted in the older population(419).

In the general elderly population practice guidelines are discouraging the use of many older (first-generation) AEDs such as phenytoin, phenobarbital and carbamazepine due to the prevalence of significant adverse effects, drug interactions, suboptimal response rates and adverse drug reactions(419, 421) . Guidelines are also encouraging the use of newer generation AEDs such as lamotrigine, topimirate and zonisamide that have demonstrated lower potential for drug-drug interactions and exhibit improved tolerability and safety profiles compared to older AEDs (419) Single drug therapy is recommended for epilepsy (monotherapy) (422) (423), and polytherapy (use of two or more AEDs) is then recommended, to gain seizure control if monotherapy fails. Consensus guidelines relating to the management of epilepsy in adults with ID have also been developed (178), which in addition, arguing that appropriate acute seizure treatment is a central tenet of quality of care (178).

People with ID and epilepsy often have both psychiatric and somatic comorbidities (177, 178, 400). Even in the general population, epilepsy is associated with increased prevalence of mental health and other somatic disorders(424-426) Comorbidities may be as a direct consequence of epilepsy such as stroke, or be in a complex relationship with epilepsy e.g. psychiatric morbidity or have no apparent relationship e.g. heart disease (424, 427). While seizure freedom is the optimum goal, optimal care should also take into account management of other morbidities and concurrent medicines. In addition, choice and type of AED should take in to consideration the potential for interactions with other medicines or morbidities (424)In particular , people with epilepsy have a higher prevalence of psychiatric co-morbidity compared to the general population or those who report other chronic medical conditions (400). However, there are differing views. Turky carried out a prospective study examining the impact of seizure activity on psychiatric disorders, and noted that people with both epilepsy and ID had a 7 fold increased risk of development of psychiatric disorders, compared to those with ID alone(428). A recent study by Arshad noted lower rates of psychopathology in people with epilepsy and intellectual disability compared to people with intellectual disability alone, and suggested that this effect of AEDs may account for this(429). Furthermore, both seizures and antiepileptic agents may play a role in behavioural disturbances in people with ID and epilepsy(177) .In addition, AED related adverse effects such as hyperactivity and aggressive behaviours are particularly evident with GABA-ergic drugs such as barbiturates and vigabitrin (430).

Moreover , many enzyme inducing AEDs may lower plasma levels of other psychotropics e.g. SSRIs, antidepressants and impair control of psychiatric symptoms(424). In addition, Tricyclic Antidepressants may inhibit AED metabolism, causing toxicity. Cognitive function as a consequence of decreased brain function reserve or degenerative disease may be aggravated by AED use. People with ID may be more susceptible to these AED side effects(250). Enzyme-inducing AEDs and phenytoin may accelerate catabolism of vitamin D, and increase bone turnover, while valproic acid may interfere with the function of osteoblasts(424, 431).

No previously published paper to our knowledge has described the pattern of antiepileptic use among a representative older population with ID.

Our aim was to investigate the patterns and prevalence of AED used in the management of epilepsy in an ageing population with epilepsy and ID in Ireland.

Our objectives were; i) to determine the pattern of AED use among the cohort reporting epilepsy, including AED monotherapy and polytherapy ii) to determine the clinical and demographic characteristics of those with antiepileptic therapy, including co-morbid conditions and medications iii) to determine the level of control provided by AEDs in terms of seizure frequency, seizure records and to describe associated healthcare utilization. Our secondary aim was to also describe the prevalence of use of psychotropic agents for which care or avoidance is recommended in epilepsy.

6.2. Methods

6.2.1. Study Design

The details of the study, and of medication data collection have been presented in *Chapter 3*. Included participants in this study are outlined in *Figure 6-1*.

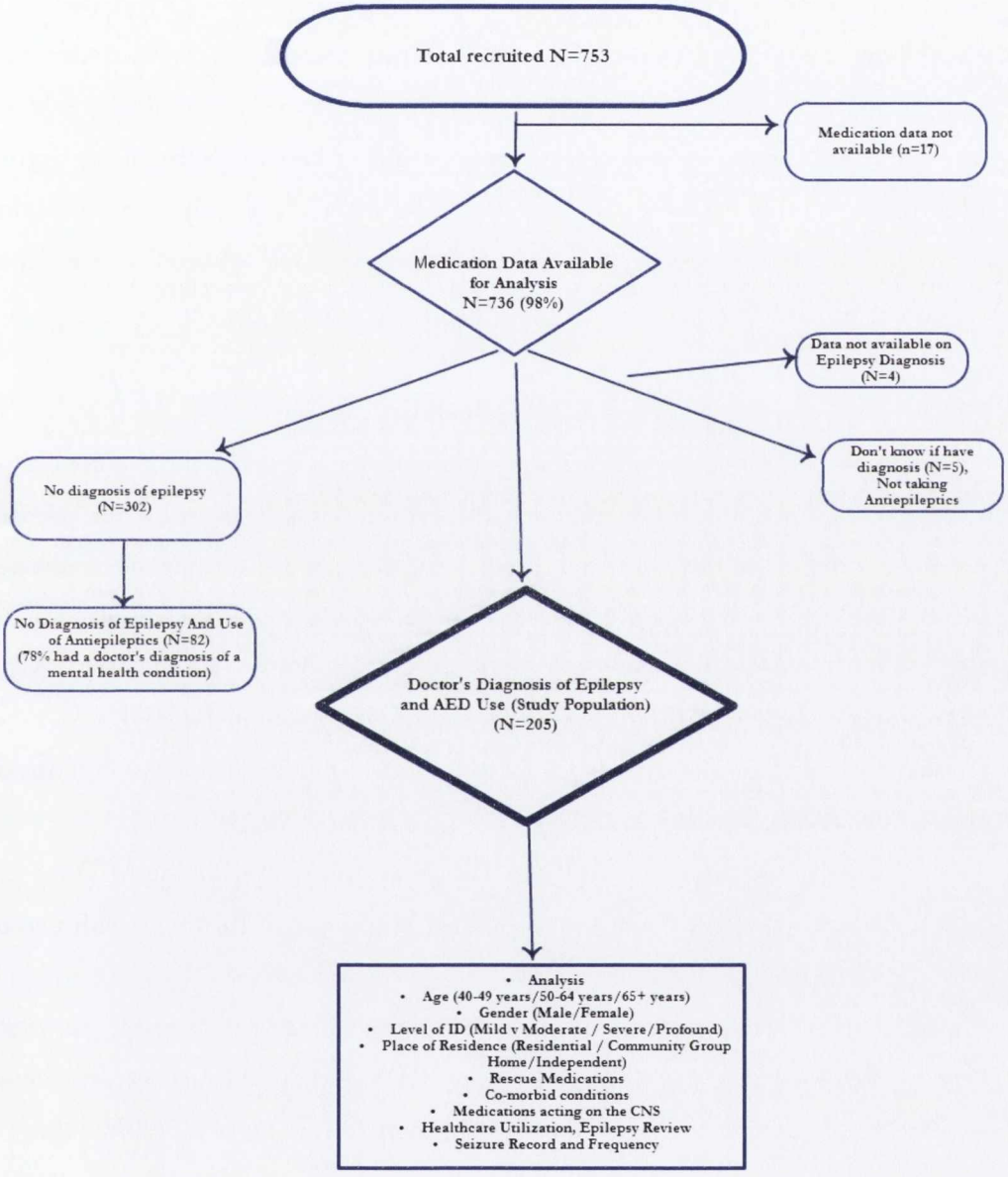

Figure 6-1: Flow chart for the Study

6.2.2. Epilepsy Variables

Specifically, in relation to epilepsy each participant/caregiver respondent in the Pre-Interview Questionnaire reported (1) if the individual with ID was ever diagnosed by a doctor/relevant health professional with epilepsy; (2) seizure types, for example; Tonic-Clonic, Atonic, Myoclonic, Absence, Simple partial or Complex partial seizure activity; (3) attendance at an epilepsy clinic or a specialist; (4) who reviewed their epilepsy for example, general practitioner, psychiatrist, neurologist; (5) when they had their epilepsy reviewed –within the last 12 months, last 2 years , more than 2 years or never; (6) if they kept a record of seizure events and (7) how often they had a seizure in the past two years reported as more than 2 years ago; daily, weekly more than once a month. Data were also collected on related medication use. Diagnosis of epilepsy and medications identified in the PIQ, was then confirmed in person.

6.2.2.1. Antiepileptic Medications, Diagnosis of Epilepsy

Reported use of antiepileptic medicines to primarily treat epilepsy (i.e. regular use of medicines in those reporting a physician diagnosis of epilepsy) was our primary exposure of interest. For this study, first, we considered Antiepileptic medicines (AEDs) with approved indications for epilepsy and seizures available in Ireland up to 2009 / 2010 (when data collection took place for Wave 1). Seventeen AED medications were identified. The list of these drugs is included in *Table 6-1*.

We also structured participants' exposure to these antiepileptic medicines in terms of number of antiepileptics taken.

- Antiepileptic "monotherapy" was defined as treatment with one AED.
- Antiepileptic "polytherapy" was defined as concurrent treatment with two or more AEDs (243, 244, 432).

Antiepileptic medicines were also divided into those which were available pre-1990, these were defined as "old" or first-generation AEDs , and those which were marketed after 1995 were classified as "new" or second-generation AEDs (433) (*Table 6-1*).

Table 6-1: List of AEDs authorised in Ireland considered for the study

Drug Substance	ATC Code	Type	Reported in study
Valproic Acid / Valproate / Sodium Valproate	N03AG01	Old	√
Carbamazepine	N03AF01	Old	√
Phenytoin	N03AB02	Old	√
Phenobarbital	N03AA02	Old	√
Clonazepam	N03AE01	Old	√
Clobazam	N05BA09	Old	√
Primidone	N03AA03	Old	√
Ethosuximide	N03AD01	Old	-
Oxcarbamazepine	N03AF01	Old	-
Lamotrigine	N03AX09	New	√
Levetericam	N03AX14	New	√
Topimirate	N03AX11	New	√
Pregablin	N03AX16	New	√
Zonisamide	N03AX15	New	√
Gabapentin	N03AX12	New	√
Rufinamide	N03AF03	New	-
Lacosamide	N03AX18	New	-
Tiagibine	N03AG06	New	-
Vigabitrin	N03AG04	New	-
Acute Seizures , Medications			
Buccal Midazolam	N05CD08*	-	√
Rectal Diazepam	N05BA12*	-	√

AEDs available before the mid-1990s are often considered "old" AEDs. (1)
**Identfication and coding described in methods*

6.2.2.2. Antiepileptics, indications

In order to distinguish between AEDs used for other indications and those used to treat epilepsy, we divided our population who reported use of AEDs into two groups:
1.) Those who reported regular use of AEDs combined with a reported diagnosis of epilepsy (N=205); here we identified that AED use was primarily used to control epilepsy (this was our exposure population of interest), and
2.) Those reporting AEDs but having no diagnosis of epilepsy *(Figure 6-2).*
Overall, 287 participants reported use of AEDs, of whom 205 reported a doctor's diagnosis of epilepsy. It is acknowledged that in addition to use in the control of epilepsy, the mood-stabilizing antiepileptics are frequently employed in the population with ID to treat mental health and behavioural issues (239, 434). In our cohort, 82 people reported use of AEDs in the absence of a diagnosis of epilepsy (these were

primarily mood-stabilising antiepileptics); of these 78% reported a mental health condition.

6.2.2.3. Fast acting Agents for the Control of Acute Seizures

These were defined separately to the AEDs (not used on a regular basis) as: rectal diazepam, buccal midazolam, intravenous lorazepam and intravenous clonazepam. There were no reports of intravenous lorazepam or intravenous clonazepam in the study. There is no separate ATC code for rectal diazepam, buccal midazolam, so one pharmacist (MO'D) manually examined original report records, separated them from oral formulations, and created new variables for these rescue agents.

6.2.2.4. Covariates

In addition to the variables related to epilepsy, other covariates investigated from the study were sex, age, level of intellectual disability (mild/moderate/severe /profound), residential setting (independent, community group home or residential setting), other co-medications acting on the CNS, and concurrent medications that may lower the seizure threshold (*Figure 6-2*). Each participant / caregiver respondent reported if the individual with ID had ever been diagnosed by a doctor or other relevant health professional with one or more of 12 chronic health conditions, including a mental health condition (*Appendix 6*)(53). We also examined frequency of use of primary, secondary and tertiary care in the previous year; number of visits to general practitioner, number of outpatient visits, if participants had spent any nights in hospital, or had one or more Accident and Emergency admissions. As there was not a specific question as to whether admission was due to seizure activity, some participants had recorded reason for admission in an open ended answer, and these answers were analysed.

6.2.3. Concurrent Use of Medications that lower the Seizure Threshold

We examined the number of cases of the main co-medications that may lower the seizure threshold (relevant antipsychotics and antidepressants). We adopted the list of medications where there was sufficient evidence of the agents' ability to lower the seizure threshold, and/or to provoke epileptic seizures to warrant caution/ avoidance of use from the Maudsely prescribing guidelines in psychiatry (28). Specifically, we examined prevalence of the following agents in those taking AEDs for epilepsy:

1). Antipsychotics; chlorpromazine, depot antipsychotics, aripiprazole, quetiapine, olanzapine, risperidone, amisulpride,

2.) Antidepressants: amitriptyline, dosulepin, clomipramine, bupropion, mirtazapine, venlafaxine and duloxetine, and

3.) Lithium.

6.2.4. Statistical Analyses

Descriptive statistics were generated to describe the characteristics of the study population (the participants with a diagnosis of epilepsy who reported use of antiepileptics; n=205). The characteristics of the sample were expressed as percentages, means with standard deviations (±SD) and 95% confidence intervals (C.I.s) as appropriate to the variable. A p-value of <0.05 was considered significant. For continuous variables a one-way ANOVA was used to test for a significant difference between means.

All statistical analysis was carried out using the Statistical Package for Social Sciences, Version 20.0 (SPSS Inc.).

6.3. Results

6.3.1. Demographics and Medication Use

Of the 736 participants who provided data on medication use, 287 reported use of AEDs. In the sample, 225 had a doctor's diagnosis of epilepsy. In the sample, 20 people had a diagnosis of epilepsy and no reported AED medicines. Of these participants who reported AED use, 71.4% (205) reported a doctor's diagnosis of epilepsy; this was assumed to be the primary indication *(Figure 6-2)*. The characteristics of these 205 participants are presented in *Table 6-2*. The majority (61%) lived in residential settings, and the greatest proportion (45.9%) were aged 50-64 years. Four in ten of those with specified ID (N=197) had severe/profound ID.

Table 6-2 : Characteristics of the Study Population (N=205)

Characteristic	N(%) 205	Male 83	Female 122
Age			
40-49 years	80(39.0)	34(41.0)	46(37.7)
50-64 years	94(45.9)	37(44.6)	57(46.7)
65+ years	31(15.1)	12(14.5)	19(15.6)
Level of ID (N=197)			
Mild	32(16.2)	14(17.3)	18(15.5)
Moderate	84(42.6)	32(39.5)	52(44.8)
Severe/Profound	81(41.1)	35(43.2)	46(39.6)
Residential Setting			
Independent	25(12.2)	7(8.4)	18(14.8)
Community Group Home	55(26.8)	24(28.9)	31(25.4)
Residential	125(61.0)	52(62.7)	73(59.8)
Self-rated health (n=204)			
Excellent/very good/ good	170(83.3)	77(81.9)	105(86.1)
Fair/poor	34(16.7)	17 (18.1)	17(13.9)
AED Monotherapy	102(49.8)	37(44.6)	65(53.3)
AED Polytherapy	103(50.2)	46(55.4)	57(46.7)

6.3.1.1. Clinical and Demographic Characteristics of those who Used AEDs

Overall, 225 participants (30.8%) reported a diagnosis of epilepsy. Of these, 91.1% (205) reported use of one or more antiepileptics.

Seizure Activity. Tonic-clonic seizures were the seizure type reported most frequently (57%) , followed by absence seizures (23%), tonic seizures (13.2%), simple partial seizures (8.8%), myoclonic seizures (8.8%) and complex partial (5.4%), clonic and atonic. A further 19% of participants reported that they did not know their seizure type (unclassified).

Clinical and demographic characteristics of the sample by age are presented in *Table 6-3.*

Table 6-3: Clinical and Demographic Characteristics of the Study (n=205), by Age

	Age			Total
	40-49 years	**50-64 years**	**65+ years**	
	80	**94**	**31**	**205**
Gender				
Male	34 (42.5)	37 (39.4)	12 (38.7)	83 (40.5)
Female	46 (57.5)	57 (60.6)	19 (61.3)	122 (59.5)
Level of ID (n= 197)				
Mild/ moderate	45(57.7)	56(60.9)	15(55.6)	116 (58.9)
Severe/profound	33(42.3)	36(39.1)	12(44.4)	81 (41.1)
Cause of ID (n=201)				
Down Syndrome	9 (11.7)	16 (17.2)	1 (3.2)	26 (12.9)
Other	68 (88.3)	77 (82.8)	30 (96.8)	175 (87.1)
Residential Setting				
Independent	9 (11.2)	14 (14.9)	2 (6.5)	25 (12.2)
Community Group Home	20 (25.0)	27 (28.7)	8 (25.8)	55 (26.8)
Residential	51 (63.8)	53 (56.4)	21 (67.7)	125 (61.0)
Co-morbid mental health condition	38 (47.5)	44 (46.8)	17 (54.8)	99 (48.3)
Any Sleep Problem	56(70.0)	68(72.3)	23(74.2)	147(71.7)
AED Monotherapy	35 (43.8)	45 (47.9)	22 (71.0)	102 (49.8)
AED Polytherapy	45 (47.2)	49 (52.1)	9 (29.0)	103 (50.2)
Medicines used to treat acute seizures	43 (53.8)	33 (35.1)	10 (32.3)	86 (42.0)
Buccal Midazolam	31 (38.8)	26 (27.7)	6 (19.4)	63 (30.7)
Rectal Diazepam	12 (15.0)	7 (7.5)	4 (12.9)	23 (11.2)
Mean (±S.D) other drugs	5.8 (±3.8)	5.8 (±4.0)	6.3 (±3.9)	5.9(± 3.9) (max 16)
Concomitant Drugs acting on the CNS				
Antipsychotics	33 (41.3)	35 (37.4)	11 (35.5)	79 (38.5)
Antidepressants	17 (21.3)	26 (27.7)	7 (22.6)	50 (24.4)
Hypnotics/ sedatives	16 (20)	20 (21.3)	4 (12.9)	40 (19.5)
Anxiolytics	30 (37.5)	27 (28.7)	3 (9.7)	60 (29.3)
Opioids				
Anticholinergic Agents	16 (20.0)	13 (13.8)	6 (19.4)	35 (17.1)
Cholinesterase Inhibitors	2(2.5)	5(6.8)	4(12.9)	11 (5.4)
Other Classes				
Calcium/Vitamin D Supplements	15(18.8)	33(35.1)	14(45.2)	62(30.2)
No. other Clinical Conditions				
0	11 (13.8)	11 (11.7)	1 (3.2)	23 (11.2)
1	24 (30.0)	13 (13.8)	11 (35.5)	48 (23.4)
2+	55 (56.4)	70 (74.6)	19 (61.3)	134 (65.4)

**Less than 1% reported dopaminergic agents*

6.3.2. Antiepileptic Medications

Of the participants who reported a diagnosis of epilepsy and use of AEDs (n=205), 49.8% reported use of one AED (monotherapy) and 50.2% reported concurrent use of two or more AEDs (maximum 5) (*Table 6-4*). A total of 399 AEDs were reported by these participants, corresponding to a mean (±S.D) of 1.9 (±1.1) AEDs. In terms of those with polytherapy (103), almost half (47.6%) took two AEDs, 30% took three AEDs, and one-fifth took four or more.

Participants who reported a doctor's diagnosis of epilepsy and use of one or more AEDs reported use of 14 different AEDs in total *(Table 6-4).* The most frequently reported AEDs in decreasing prevalence were: valproic acid 48.7% (n=100), carbamazepine 46.3% (n=89) and lamotrigine 27.8% (n=57). In total 83.6% (188) of the sample used one or more of these three agents and together these agents accounted for over 61.9% of AEDs in the sample.

6.3.2.1. AED Monotherapy, Polytherapy

When an AED was used as monotherapy (n=102), eight different monotherapy regimens were reported. Six of these monotherapy regimens were first-generation AEDs and two were second-generation. The two most frequently reported monotherapy regimens, valproic acid and carbamazepine accounted for almost three-quarters (73.5%) of reported monotherapy regimens (*Table 6-4).*

When AED use was reported as polytherapy, 63 different polytherapy regimens were reported by 103 participants. The most frequently reported polytherapy regimen was valproic acid in combination with lamotrigine (11) followed by carbamazepine and valproic acid (10). Carbamazepine, phenobarbitone, phenytoin, clobazam, clonazepam, levetiracetam and topimirate were more frequently as part of polytherapy regimens. First generation AEDs accounted for almost two-thirds (64.6%) of polytherapy regimens reported, while second-generation AEDs accounted for over one-third (35.4%).

Table 6-4 Antiepileptics and corresponding monotherapy and polytherapy regimens

Drug Substance	ATC	Type	Enzyme-Inducing	N (%) Total (205)	Monotherapy 102	Polytherapy 103
Valproic Acid / Valpraote / Sodium Valproate	N03AG01	Old	×	100 (48.8)	40	60
Carbamazepine	N03AF01	Old	√	89 (43.4)	35	54
Phenytoin	N03AB02	Old	√	21 (10.2)	7	14
Phenobarbital	N03AA02	Old	√	19 (9.3)	3	16
Clonazepam	N03AE01	Old	×	17 (8.3)	4	13
Clobazam	N05BA09	Old	×	25 (12.0)	-	25
Primidone	N03AA03	Old	√	8 (3.9)	1	7
Lamotrigine	N03AX09	New	×	57 (27.8)	12	45
Levetiracetam	N03AX14	New	×	33 (16.1)	1	32
Topimirate	N03AX11	New	√	9 (4.4)	-	9
Pregablin	N03AX16	New	×	2 (1.0)	-	2
Zonisamide	N03AX15	New	×	7 (3.4)	-	7
Gabapentin	N03AX12	New	×	4 (2.0)	0	4
Rufinamide	N03AF03	New	×	4 (2.0)	0	4
Acute Seizure Medications						
Buccal Midazolam	N05CD08		×	63	24	39
Rectal Diazepam	N05BA01		×	23	14	9

AEDs available before the mid-1990s are often considered "old" AEDs. (1)

6.3.2.2. Agents to treat acute seizures/status epilepticus

Of the 205 participants who reported an epilepsy diagnosis and use of AEDs, 38.9% (n=89) reported of a medication to treat acute seizures or status epilepticus *(Table 6-4).* 37.3% of those who reported AED monotherapy (n=102) reported a rescue medicine, and 45.0% of those who reported AED polytherapy recorded use of a rescue medicine.

Two types of medicines to treat acute seizures were reported; buccal midazolam by 63 participants, while 22 participants (25.9%) reported use of rectal diazepam. A greater proportion of those living in residential settings reported a medication to treat acute seizures; 51%, compared to 33% of those living in community group homes and 12.9% of those living in the community. Of the 24 participants who reported a diagnosis of epilepsy but no AED medicines, two reported a rescue medicine.

6.3.3. Clinical Conditions, Concurrent Medications

Overall, almost nine in ten participants (88%) reported one or more concurrent conditions in addition to epilepsy, with 65.4% (134) reporting two or more additional chronic conditions (*Table 6-3).* Psychiatric co-morbidities were common, with over four in ten (48.3%) reporting a concurrent mental health condition.

Other than AEDs and medicines to treat acute seizures, participants reported a mean (±S.D.) of 5.9 (±3.9) other medicines (maximum 16 additional medicines). Overall, the most common co-medication was the laxatives, by over half (53.7%) of the sample. In terms of co-medications acting on the central nervous system, antipsychotics were the most frequently reported therapeutic class by 38.5%, followed by the anxiolytics (29.3%), and the antidepressants (24.4%).

6.3.4. Medications that may lower the seizure threshold

Psychotropic medications that may lower seizure threshold are presented in *Table 6-5).* Of the sample, 13.7 %(28) recorded one or more concurrent psychotropics that are recommended to be avoided in epilepsy, almost one-third (31.7%) had a psychotropic where care is required when used in epilepsy, and 4.9 %(10) reported taking a medication in each category. In total, there were 101 incidences of antipsychotics,

antidepressants or lithium identified that may lower the seizure threshold; the antipsychotics accounted for the greatest proportion of this (82%).

Table 6-5: Frequency of use of Antipsychotics and Antidepressants that may lower the seizure threshold in those with AEDs and Epilepsy (n=205)

Class, Number of Incidences	Safety in Epilepsy	Special considerations
Antipsychotics (N=87)		
Chlorpromazine(N=19)	*Avoid*	Most epileptogenic of older antipsychotics. Ideally avoided completely
Depot Antipsychotics (N=7)	*Avoid*	None of depot preparations are thought to be epileptogenic; however: The kinetics of depots are complex (seizures may be delayed) If a seizure does occur , the offending drug may not be easily withdrawn, Depots should be used with extreme care
Aripiprazole(N=2)	*Care required*	Very limited data and clinical experience.
Quetiapine(N=4) Olanzapine(N=31) Risperidone(N=24)	*Care Required*	Seizures have been reported rarely Probably reasonably safe Olanzapine may affect EEG, and myoclonic seizures have been reported. Olanzapine and quetiapine may be more epileptogenic than risperidone(435) Seizures reported rarely with quetiapine but also shown to have anticonvulsant activity in ECT Both olanzapine and quetiapine may decrease the seizure threshold up to two-fold
Antidepressants and Lithium (N=15)		
Amitriptyline(N=1) Dosulepin(N=1) Clomipramine(N=1)	*Avoid*	Most TCAs are epileptogenic, particularly at higher doses, as is bupropion. Ideally, should be avoided completely
Mirtazapine(N=2) Venlafaxine(N=4)	*Care Required*	Fewer data and clinical experience than with SSRIs. Venlafaxine proconvulsive in overdose. Use with care
Duloxetine(N=1)	*Care required*	Very limited data and clinical experience. Seizures have been reported rarely
Lithium(N=4)	*Care required*	Low proconvulsive effect at therapeutic doses. Marked proconvulsive activity in overdose

Guidance adapted from Maudsley Guidelines(28)

6.3.5. Seizure reviews, recording and seizure frequency.

Information on seizure frequency, record and review is presented in *Table 6-6*. Of the 185 participants that answered questions in relation to the last time their epilepsy was reviewed, eight in ten (80.5%) were reviewed in the previous twelve months, 10 (5.4%) in the previous two years, 22 (11.9%) more than two years ago and 4(2.2%) reported

that their epilepsy had never been reviewed. Of the 90 participants who answered the question and reported antiepileptic monotherapy, 74.4% had their epilepsy reviewed in the previous twelve months, 4.4% were reviewed in the previous two years and 17.8% were reviewed more than two years ago, 3.3% of those reporting AED monotherapy had never been reviewed. Of the 95 participants who answered the question and reported AED polytherapy, 86.3% had their epilepsy reviewed in the previous 12 months, 6.3% in the previous two years, and 6.3% more than two years ago. 1 participant who reported AED polytherapy reported never having their epilepsy reviewed. 88.9% of those taking three AEDs, 94.1% of those taking four AEDs and 100% of those taking five AEDs had their epilepsy reviewed in the previous 12 months.

Of the 188 participants who answered the question in relation to the type of practitioner who reviewed their epilepsy, five in ten reported that their epilepsy was reviewed by a general practitioner and 139 participants (72.9%) reported that their epilepsy had been reviewed by a neurologist or psychiatrist. Of those who answered the question and reported antiepileptic monotherapy (91 participants), 43 (47.3%) reported being reviewed by a general practitioner and 63 participants (69.2%) reported being reviewed by a neurologist or psychiatrist. Of those who reported taking antiepileptic polytherapy (91 participants), 51 (52.5%) reported being reviewed by a general practitioner and 74 participants (76.3%) reported being reviewed by a neurologist or psychiatrist. In terms of polytherapy and review, 68% of those taking two AEDs , 85.7% of those taking three AEDs, 77.8% of those taking four AEDs and all of those taking five AEDs reported being reviewed by a neurologist or psychiatrist. One third reported being reviewed by more than one practitioner.

Of 188 participants who answered the question in relation to seizure record, 155 participants (82%) stated that they kept a record of seizures. Of 182 participants who reported seizure frequency, 57.8% of those taking 1AED reported being seizure-free for the previous two years, compared to 35.4% of those taking 2 AEDs, 28.6% of those taking 3 AEDs and 16.7% of those taking 4 AEDs. Of the 4 participants that reported use of 5 AEDs all reported seizure frequency greater than once monthly, none were seizure free for the previous two years.

Table 6-6: Seizure Review and Frequency in Study

	Total	Age		
		40-49 years	50-64 years	65+ years
	205	80	94	31
Seizure Frequency (n=182)	182	70	85	27
More than once per month	46(25.3)	22(31.5)	21(24.7)	3(11.1)
Less than monthly	56(30.8)	15(21.4)	35(41.2)	6(22.2)
Seizure-free for previous two years	80(44.0)	33(47.1)	29(34.1)	18(66.7)
Keep seizure record(n=186)	186	72	85	29
Yes	155(83.3)	60(83.3)	76(89.4)	19(65.5)
No	31(16.7)	12(16.7)	9(10.6)	10(34.4)
Review of Epilepsy(n=185)	185	71	86	28
Previous 12 months	149(80.5)	59(83.1)	69(80.2)	21(75.0)
Previous two years	10(5.4)	3(4.2)	5(5.8)	2(7.1)
More than two years ago	22(11.9)	8(11.3)	10(11.6)	4(14.3)
Never	4(2.1)	1(1.4)	2(2.3)	1(3.5)
Attend an epilepsy clinic (n=201)	130(64.7)	42(53.2)	67(72.8)	21(70.0)
Epilepsy review practitioner(n=188)*	188	73	86	29
GP	94(50.0)	35(47.9)	43(50.0)	16(55.2)
Neurologist	78(41.5)	26(35.6)	44(51.2)	8(27.6)
Psychiatrist	76(40.4)	30(41.1)	37(43.0)	9(31.0)
More than one practitioner	64(34.0)	19(26.0)	37(43.0)	8(27.1)

**Categories not mutually exclusive, participant may have reported review by more than one practitioner*

6.3.6. Other HealthCare Utilization

Patterns of healthcare utilization by the sample of those reporting AED monotherapy and polytherapy are presented in *Table 6-7*. Over half of the sample visited the GP six or more times in the previous year, and there was no significant difference between those with monotherapy or polytherapy. There was a significant association between AED monotherapy and polytherapy and outpatient visits (p=0.03), with 44% of those exposed to polytherapy having two or more outpatient consultations in the previous year, compared to over one-quarter (26.6%) of those with monotherapy. There were no significant differences in A and E admissions; almost one-quarter (24.5%) of the sample had one or more A and E admission in the previous year. Of these, 11

participants noted that this admission was as a result of a seizure or status epilepticus. Overall, 16.8% had spent one or more nights in hospital in the previous year, with no significant (p=0.07) difference between those with monotherapy or polytherapy.

Table 6-7 Healthcare Utilization in the Previous 12 months

HealthCare Utilization	AED Monotherapy 102	AED Polytherapy 103	Total 205	p-value
General Practitioner Visits (n=176)				
0-1 visits	9(10.2)	9(10.2)	18(10.2)	0.98
2-5 visits	34(38.6)	33(37.5)	67(38.1)	
6+ visits	45(51.1)	46(52.3)	91(51.7)	
Outpatient Visits (n=187)				
0	48(51.1)	33(35.5)	81(43.3)	**0.03**
1	21(22.3)	19(20.4)	40(21.4)	
2+ visits	25(26.6)	41(44.1)	66(35.3)	
Accident and Emergency visits in previous year (n=192)	22(23.4)	25(25.5)	47(24.5)	0.7
Hospital admissions(n=190)	11(11.8)	21(21.6)	32(16.8)	0.07

6.4. Discussion

6.4.1. Principal Findings

In our study, a high prevalence of epilepsy was noted; 30.7% (79), and thus a high frequency of AED use was reported. Nine in ten of those with a diagnosis of epilepsy reported use of one or more AEDs on a regular basis. This is in line with high rates of AED utilization in the general population with epilepsy, given that relatively few patients can remain seizure-free through use of non-pharmacological measures, so AEDs are the mainstay of treatment (423). Notably, we identified that five in ten of those reporting antiepileptic use for epilepsy consumed two or more AEDs. We identified a 67 different polytherapy regimens, reflecting the complexity of prescribing in the population. Despite the use of multiple medicines, over half had seizures in the previous two years, and there was high utilization of all levels of health services,

although there was no difference between those using AED monotherapy, and AED polytherapy.

6.4.2. Patterns of AED Use, and Drug Selection

We identified that monotherapy and polytherapy were almost equally reported in the sample; half of our sample were taking two or more agents to treat epilepsy. Comparisons to patterns and prevalence in the general population are to Some extent limited, as there is a higher proportion of complex epilepsy that may be refractory treatment, and may require treatment intensification in the ID population(178, 399). Our findings are in contrast to recommendations in the general population, where "one drug is adequate for the majority of patients, but a small number may require benefits of rational polytherapy"(422).

We identified 14 different antiepileptics, and 63 different combinations utilised in our sample, reflecting the range of therapeutic options for clinicians, but which also increases the complexity of prescriber decision making. Our findings showed that among the three most frequently reported agents; carbamazepine, valproic acid or lamotrigine, eight in ten participants were exposed to one or more of these three agents. These findings are similar to studies of older, or institutionalised population where carbamazepine and valproic acid still frequently used, and similar findings have been reported in the ID populations(179, 415), where carbamazepine and valproic acid, appear to be used as first line agents, while lamotrigine more often employed as an adjunctive agent. In Canada, among 52,404 people aged 18-64 years receiving primary care, 8.1% received valproic acid derivatives, and a further 6.8% had carboxamide (which includes carbamazepine) derivatives (141).

For people with intellectual disabilities one review concluded that, "no recommendation can be given for a specific drug of choice for patients with epilepsy and learning disability"(178). Sodium valproate and lamotrigine are recognised as appropriate 1st line agents for generalised seizures in ID , while carbamazepine is second line(411) ,and all three deemed suitable for partial seizures. Both valproic acid and carbamazepine have been extensively used over the last 30 years, and lamotrigine for around 20 years, with side effects and efficacy well established. However despite the effectiveness of the two older agents, they have a high associated risk of adverse drug reactions, and potential for interaction with other drugs (28, 436). A limitation was that we did not have information as to length of exposure, it is possible that these

AED therapies were initiated at a younger age and may be continued in older patients, although not recommended, and given that they have less favourable side effect profile in the elderly(418, 419). Older antiepileptics accounted for almost 70% of prescribed AEDs, and high use of older agents particularly as monotherapy was identified; almost nine in ten of monotherapy regimens consisted of older antiepileptic drugs, while newer agents were more frequently employed in polytherapy regimens. Carbamazepine was the second most frequently reported agent; Carbamazepine is a potent inducer of hepatic cytochrome P450 enzymes, and is metabolised by CYP3A4. Thus, plasma levels of most antipsychotics, antidepressants and benzodiazepines may be decreased by carbamazepine(28). It is worth noting that lamotrigine, a newer AED was the third most frequently employed, and it is well tolerated in the elderly(436). Lamotrigine appears to be a particularly suitable choice in intellectual disability, as it may improve seizures and mental state (437)and enhance quality of life and increase alertness (422), however lamotrigine is less useful in myoclonic seizure types.

While the principles of anti-epileptic drug therapy for an elderly person with ID are essentially the same as the generic elderly population, there are unique issues associated with this group that also need to be addressed: the nature of the underlying disease and higher frequencies of epilepsies that may be refractory to conventional treatments, atypical presentation of symptoms, consideration of the appropriateness of monotherapy as opposed to rational polytherapy and the presence of co-morbidities and understanding the consequences of a limited evidence base associated with safety and effectiveness of AED use in the ID population(77, 178).Our findings revealed a relatively high frequency of use of phenytoin and phenobarbital; one in ten used phenytoin, and one in ten phenobarbital. Both were more commonly employed as part of polytherapy, but are drugs that are recognised as no longer appropriate for use in the elderly(421). In the ID population, new prescriptions of phenytoin are discouraged, due to behavioural side effects in paediatric studies (178, 438). Potentially, participants may have been stabilised on these drugs over many years and there is risk:benefit balance and challenge associated with changing therapy. Irreversible neurological damage has been attributed to phenobarbital and phenytoin (77), and phenytoin has been associated with a deterioration in cognitive function (439). Patients with phenytoin need "regular, at least yearly serum drug concentration measurements"(178). Further waves of data collection will add longitudinal value to this observation to assess if these potentially difficult AEDs are being phased out.

We found that the use of the benzodiazepines clonazepam and clobazam was part of polytherapy regimens, as adjunctive treatment in refractory epilepsy (440), but are associated with adverse effects such as sedation, tolerance and disinhibition (290).

6.4.3. Antiepileptic Polytherapy

Our findings revealed that over half of the sample had two or more agents, and almost one quarter had three or more AEDs. Monotherapy would be regarded as preferable due to decreased potential for interactions, adverse drug reactions, and improvements in compliance and more simplified drug administration regimen(422, 432). These findings of a high frequency of use of multiple agents are similar to ID samples (179, 415, 441), but in contrast to general population, among a study examining prevalence of antiepileptic use among seven European Union countries health care databases, 12% of those with AED therapy used two or more AEDs, and 2.1% had three antiepileptic agents (433), reflecting increasing complexity and severity of epilepsy of people with ID.

The most common polytherapy regimens identified were lamotrigine and carbamazepine by 5.4%, and carbamazepine with valproic acid by 4.9%. Newer novel drugs such as zonisamide, rufinamide and topimirate appeared to be only employed in this population as add on therapy (polytherapy), presumably to attempt seizure control and when reviewed by specialists (psychiatrists and neurologists). Studies have revealed a 20-30% decrease in seizure frequency by the addition of a second AED to refractory cases (442, 443). This needs to be balanced with the increased number of adverse effects with increasing number of AEDs prescribed (443, 444). Moreover, predicting pharmacokinetic and pharmacodynamic interactions between two or more antiepileptics is difficult. Despite polytherapy, many in our sample were not seizure-free, so a balance of risk benefit in relation to multiple antiepileptic therapy is required.

Notably, over 25% of participants with epilepsy who reported use of AEDs reported taking over three AEDs concurrently, with four participants reporting concurrent use of five AEDs. While rational polytherapy may be justified in many instances, despite medication use 72 % of participants with polytherapy still reported seizures in the previous two years. It is not possible for us to comment on the rationality of polytherapy, as we did not have information on previous reponses to monotherapy. A rational approach recommends "the fewest AEDs at the lowest effective dose"(422). We also did not have full information on doses, and as to whether

maximum monotherapy doses were employed before switching to polytherapy. However, given that the use of multiple AEDs may have detrimental effects on psychosocial function and independence, independent of seizure frequency(445, 446), causing sedation, cognition and psychomotor impairment (416, 422), review of risk-benefits of polytherapy would be appropriate.

6.4.4. Demographics

Our findings revealed a lower prevalence of epilepsy, and in particular of AED polytherapy among those oldest, 29% of those over 65 had polytherapy, compared to half of those aged 40-49 years, and half of those aged 50-64 years. While there are many possible confounding reasons, these findings could reflect a survival bias, and the increased mortality associated with epilepsy. Also, given the association with increasing severity of ID and older age (447), with Holland noting that older people have less severe ID than the ID population in general (448).

6.4.5. Seizure Freedom

Our findings revealed that despite the use of AEDs, "active epilepsy" was prevalent; only 44% had been seizure-free in the previous two years, with almost one quarter experiencing a seizure at least once a month. Despite the drug burden incurred with AED polytherapy, and increased risk of adverse effects associated with taking concurrent multiple AEDs, 55.6% of those taking 4 AEDs and all 4 participants (100%) who reported taking 5 AEDs reported experiencing seizures more than once monthly which could have detrimental impact on quality of life. Seizure frequency was greater with those with AED polytherapy, with over 70% experiencing seizures in the previous two years. Clinically, we were not able to establish if these patients were refractory to treatment, as we were not able to determine previous response to monotherapy, and participants may have experienced a reduction in seizure frequency with use of AEDs. Our findings reflect evidence from a Cochrane review that in the majority of cases where AEDs have been trialled in people with ID noted "a moderate reduction in seizure frequency and occasional seizure freedom was obtained" (250).

Our findings are similar to other studies in the ID population: Forsgren identified that 32% of patients were seizure free, Branford reported 25% were seizure free, Tiffin indicated that 75% were refractory to treatment, and McGrother indicated that 68% had seizures despite the use of AEDs(85, 88, 414, 415). As the main goals

of AED treatment is ideally seizure freedom, or reduction in seizure frequency, and maintenance of quality of life to allow participation in daily activities, balancing these goals is more challenging for people with ID (139, 414). In a case-controlled study, Nilsson and colleagues reported that people who had not been seizure-free in the previous year had a 23-fold increased risk of SUDEP (sudden unexpected death in epilepsy) compared to people with fully-controlled seizures(449). Furthermore, the risks increased with increasing seizure frequency. Regular review is therefore required.

6.4.6. Rescue Medicines

Our results showed that four in ten of those in the sample had use of a rescue medicine. Two agents were reported; 70% used buccal midazolam and 30% rectal diazepam. We noted that a greater proportion of those living in residential settings had a rescue medicine; 51% compared to one-third of those in community group homes, and 12.9% of those in independent settings. A study from 2001 of 75 inpatients with ID identified that rectal diazepam was more frequently employed in status epilepticus (415). Evidence based guidelines developed by the National Institute of Clinical Excellence (2012) in relation to epilepsy care recognise that those with ID are at increased risk of SUDEP, and mortality associated with epilepsy, therefore prompt access to rescue medicines is essential in this population(450). The treatment of acute seizures has evolved, recognising the need for rapid seizure control to improve morbidity, mortality and outcome, with prompt at home administration of benzodiazepines recommended as a safe intervention (451). Trans-mucosal administration of midazolam is now considered the most acceptable in terms of efficacy, safety, portability and ease of administration (452).We identified that 3 in 10 of those using rescue medicines had rectal diazepam, while accepted as an acute option, is limited in the need to remove clothing to administer, and route of administration may be considered socially embarrassing. It is possible that there may have been under-reporting of rescue medicines as they may not have been regarded as a regular medication, and in homes and residential settings a stock supply may be maintained rather than a supply for an individual. Further investigation of the accessibility of these medicines to people with ID living at home, as well as in community group homes would be valuable.

6.4.7. Review of Epilepsy and HealthCare Utilisation

We found a high frequency of review of epilepsy, with eight in ten being reviewed by a psychiatrist or neurologist, half by a general practitioner, and one third were reviewed by more than one practitioner. Almost two thirds attended an epilepsy clinic in the previous 12 months, and epilepsy appeared to be managed by a combination of primary care and consultants. Overall, eight in ten reported being reviewed in the previous 12 months. Our findings were limited as we did not have information on quality or nature of review, monitoring or co-ordination of care between professionals. It is recognised that review, quality of review and co-ordination of care are vital in epilepsy.

In terms of other health care utilization, we identified that one-quarter of the sample had an Accident and Emergency admission in the previous year (11 reported that this admission was as a direct consequence of epilepsy or status epilepticus), and 16% had been admitted to hospital in the previous year. While we did not have information as to whether hospital admissions were as a direct consequence of epilepsy, studies have shown that the majority of people with epilepsy in the general population will be admitted to secondary or tertiary care at some point in the history of the disease. Morgan and colleagues found those with epilepsy and ID, compared to those with intellectual disability alone had a higher rate of hospital admissions, outpatient visits and Accident and Emergency admissions (266) They also identified that patients with ID and epilepsy in institutions were less likely to be admitted to hospital compared to those in community settings and had lower use of outpatient services. There is the potential for health utilisation of those with severe ID and epilepsy in institutions to be concealed from the study, because of the high availability of medical care and the acute services provided in the institution. In our study, every six in ten lived in institutional settings. It may be speculated that with the deinstitutionalisation, there may be an increase in healthcare utilisation in acute providers of epilepsy care(266). However, we did not find any difference between those receiving AED monotherapy or AED polytherapy with respect to healthcare utilisation, and this could be taken as a proxy for epilepsy severity.

Adherence to antiepileptic therapy is crucial to seizure control. The influence of place of residence on medication has not been well studied in the ID population. One recent study examined AED adherence among 793 individuals with ID by examining pharmacy records and found that, after controlling for age and gender, non-

adherence was associated with living arrangement, with those living in semi-independent settings or family homes being significantly less adherent to therapy(453).

6.4.8. Co-morbid Medications and Conditions, and Medications that may lower the seizure threshold

Our study revealed that almost nine in ten had at least one other comorbid condition, with almost two-thirds having two or more chronic conditions. Mental health was the most common co-morbid condition, with almost five in ten reporting a doctor's diagnosis of a psychiatric condition. Antiepileptics may be used for their secondary mood stabilising effects. These findings in relation to psychiatric comorbidity are similar to another study in the ID population (414). In addition to antiepileptic medicine, participants took an average of almost six other medicines, reflecting the high burden of medicines.

The most common co-medication acting on the CNS was the antipsychotic agents, by 38.5%, this prevalence is in line with, but slightly higher than that reported by Leunissen among 246 institutionalised patients with epilepsy and ID in the Netherlands. (179). It is acknowledged that people with intellectual disability are commonly prescribed both antipsychotics and antiepileptics(416). Anxiolytics and antidepressants were also frequently taken; 29.3% and 24.4%, respectively, these prevalence being higher than those reported by Leunissen where 11.8% were exposed to anxiolytics, and 11.8% antidepressants(179). While seizure freedom is the optimum goal, optimal care should also take into account management of other morbidities and concurrent medicines. In addition , the choice and type of AED should take into consideration the potential for interactions with other medicines or morbidities(424). Even in the general elderly population, concurrent use of psychotropics is common in epilepsy patients (425, 454, 455). Furthermore, side effect monitoring for adverse effects from these therapies may be complicated given that people with ID may be "managed by proxy" ; many individuals cannot communicate adverse drug reactions or changes in perception, so carers are relied upon to give an accurate description, with concern about validity and reliability of such reports(76).

We examined the prevalence of use of psychotropics that may lower the seizure threshold. Our findings were that 13.7% of the sample had medicines that were recommended to be avoided in epilepsy, while almost one-third were exposed to a psychotropic requiring care when used in epilepsy. Antipsychotics with potential

epileptogenic potential accounted for 80% of these medications. However, it is important to note that the potential for drug interactions is not regarded as a contraindication for use. Emphasis should be placed on recognition of the possibility of an interaction, and taking steps to prevent and minimise it (178). Furthermore doses of antipsychotics employed may not have been high enough to cause problems in these patients, as the most frequently used antipsychotics were mostly used at recommended doses *(Chapter 4)*.

6.4.9. Study Strengths

This study had a number of key strengths. While we did not have a doctor's diagnosis of epilepsy, participants and/or the proxy reported if they had a doctor's diagnosis of epilepsy, and also answered a wide variety of questions in relation to seizure control and epilepsy review, further confirming the reported diagnosis. In addition, 90% of those who reported epilepsy reported antiepileptic use, adding reliability to the data. This information provided us with a broad range of data in relation to antiepileptic use, seizure frequency, and review practitioners, which may often not be available to epidemiological studies. A key strength was our ability to differentiate for the most part between antiepileptics used for epilepsy and those used for mood stabilising indications. We had information about co-morbid conditions, concurrent medications and healthcare utilization, which enabled us to create a more holistic profile of those with epilepsy and ID for people with ID.

6.4.10. Study Limitations

There are a number of methodological limitations to be considered when interpreting the results of this study.

First, both diagnosis of epilepsy and medication use were based on participant or proxy self-report, which may result in some misclassification bias. However, several steps improved the accuracy of the clinical and medical information: cross-checking of the medicines information in the pre-interview questionnaire at time of interview and participants receiving the pre-interview questionnaire at least one week in advance of the interview, thus giving them time to gather information about their medicines use and , if applicable seizure history, frequency and healthcare access.

In addition, while almost all participants were able to provide information about medicines used, full information was not always provided in some cases with

respect to dose and frequency of medicines. Information about the length of time during which participants had been taking medicines and thus were exposed to antiepileptic medications was also not available. It is possible that someone may have been taking two or more concurrent medications, while weaning off one and starting another.

These issues will be further addressed in Wave two of the IDS-TILDA study, where there are additional questions in relation to management of epilepsy, length of exposure to medicines and availability of rescue medicines. We did not gather information in relation to compliance or adherence with antiepileptic medications.

6.5. Conclusions

The treatment of epilepsy is complex, and places a considerable burden on patients, care staff and specialist services. The care process seems to be working well as there are frequent reviews of therapy for people with ID and epilepsy. Whether further optimisation of therapy is possible is open to question. However, balancing of the benefits of certain AEDs and other drugs must be weighed against the potential for adverse effects, and the lowering of the seizure threshold. As in *Chapter 5*, it is important to conduct a holistic review of AEDs and other treatments. AED use is common in ageing people with ID and may represent a high risk group for drug-drug, drug-disease and adverse drug reactions(301). In addition to a high burden to AEDs, people were also exposed to a high burden of other medications, that need to be monitored and regularly reviewed.

What is already known about this topic:

- Epilepsy is over-represented in the population with ID.
- Furthermore, people with ID exhibit different seizure types and frequencies compared to the general population, and are more likely to experience "pharmacoresistant" or "refractory epilepsy".
- Those with ID and epilepsy have a significantly higher mortality rate and reduced quality of life.
- There are few high quality intervention studies on the benefits of AEDs in people with ID.

What this study adds:

- There was a high prevalence of epilepsy in our study: 30.7%, with 9 in 10 of those with a diagnosis of epilepsy recording use of one or more AEDs on a regular basis.
- Our study identified that 5 in 10 of those reporting antiepileptic use for epilepsy consumed two or more AEDs. There were 63 different polytherapy regimens recorded, reflecting the complexity of prescribing in the population.
- Despite the use of multiple AEDs, over half had seizures in the previous two years, and there was high utilisation of all types of health services.
- Our findings revealed that 4 in 10 recorded use of a rescue medicine. Of the rescue medicines recorded, two agents were reported; 70% used buccal midazolam and 30% rectal diazepam, with a greater proportion of those living in residential settings had a rescue medicine.
- Our study revealed that almost 9 in 10 had at least one other comorbid condition, with almost two-thirds having two or more chronic conditions. Mental health was the most common co-morbid condition, with almost five in ten reporting a doctor's diagnosis of a psychiatric condition.
- Our findings revealed that 13.7% of the sample had medicines that were recommended to be avoided in epilepsy, while almost one-third were exposed to a psychotropic where care is required when used in epilepsy. Antipsychotics with potential epileptogenic potential accounted for 80% of these medications.
- As the primary goals of optimal AED treatment are to achieve complete freedom from seizures, ideally without adverse events, to reduce morbidity and mortality and improve the person's quality of life, this is often not achievable for many older patients with ID and epilepsy.

Chapter 7. Discussion

7.1. Principal Findings

The objectives of the thesis were:

- To investigate the prevalence of, the patterns and predictors of multiple medicine use in an ageing population with Intellectual Disability,
- To examine the prevalence of, and factors associated with, use of psychotropics, and psychotropic polypharmacy,
- To determine anticholinergic burden, and factors associated with higher anticholinergic burden and,
- To examine treatment patterns of antiepileptics for epilepsy, and associated healthcare utilization.

The principal findings from this thesis revealed that:

- The use of multiple medications was commonplace, with 5 in 10 using five or more medicines, and 2 in 10 recording ten or more medicines.
- Antipsychotics, antiepileptics and laxatives represented the most commonly reported agents overall, and use of multiple agents within these classes further contributed to multiple medicine use.
- For older people with ID, multimorbidity was common, greater than 7 in 10 had two or more chronic conditions. In particular, the presence of mental health, neurological and gastrointestinal disease made strong contributions to increased medication burdens. This appeared to be a different pattern of morbidity and medicine use when compared with the general elderly population.
- Place of residence was strongly associated with multiple medicines, and exposure to psychotropics, after adjusting for confounders, with those living in institutional settings having a greater burden of use.
- There was a high burden of multiple medicines observed across women and men, and across all age groups.
- Despite the high levels of interventions with antiepileptic medications, most people still had "active epilepsy" and still experienced seizures.

What this research project adds to the existing literature:

- This is the first study to our knowledge to examine prevalence and factors associated with polypharmacy and excessive polypharmacy in an older population of people with ID.
- While previous studies in samples with ID have highlighted high use of psychotropic medicines, particularly first-generation antipsychotics

7.1.1. Gender and age

Our study findings identified no significant association between gender and multiple medicine use; exposure to multiple medicines was equally high among men and women. These findings are similar to other ID studies, where gender had no effect on patterns of medicine utilisation (140, 144, 233), but in contrast to the general elderly population, where women are consistently identified as being more likely to be exposed to both multiple medicines and use psychotropic agents (122, 135, 246).

In contrast to evidence in the general elderly population, where older people are more likely to use multiple medicines to treat a variety of age-related chronic conditions(185, 235, 251), our findings identified no significant association between older age and polypharmacy, or excessive polypharmacy , or psychotropic exposure in our multivariate analysis (*Table 3.3-6, Table 4.3-9*), after adjusting for relevant confounders. Findings in the ID population with regard to the effect of age on medicine use have remained inconsistent; in a recent study in Australia, Haider and colleagues identified a significant association between polypharmacy exposure and older age, while Tsiouris identified no significant association between advancing age and psychotropic drug use among adults with ID in New York(140, 144). There are two potential reasons for these findings; people with ID have a higher burden of chronic disease from a younger age, such as epilepsy or mental health conditions, and are therefore already exposed to a higher pharmacologic burden, compared to the general population. It could also be possible that those over 65 years in our study could reflect a survival bias, with those with severe disease having a shorter life expectancy, but we don't have longitudinal data to draw conclusions about cause-and effect. A lower proportion of those aged over 65 in our study had epilepsy, which may be related to the fact that mortality for people with epilepsy and ID is higher(178, 401).

With regard to the influence of age on anticholinergic burden, our findings did confirm our initial hypothesis that those who were older were more likely to have a higher anticholinergic burden to treat age-related morbidities, and these findings were consistent with those in the general elderly population(344, 356). This implies that although the number of medicines does not increase by much with age, the medicines used in those aged over 65 must differ, otherwise there would be no difference in the Anticholinergic Burden. This is an area that requires further study. As cumulative anticholinergic burden has not been studied before in the ID population, we could not draw any comparisons with other ID cohorts. While medicines with anticholinergic properties may be required in those who are older, these agents carry greatest risk in those who are oldest (186).

7.1.2. Level of ID

When considering the influence that level of ID has on patterns and prevalence of medicine use in our study, after adjusting for confounders, our multivariate analysis identified no association between severity of ID and psychotropic use, and levels of anticholinergic exposure. Having severe or profound ID was associated with polypharmacy, but not excessive polypharmacy exposure. Findings relating to the influence of severity of ID on patterns of medicine use have remained inconsistent in the ID literature; Haider noted a significant association between ID severity and polypharmacy, while previous studies investigating polypharmacy and cognitive function in people with ID found no association between psychotropic polypharmacy and ID severity, and Tsiourus identified no effect of level of ID on psychotropic use in regression analyses among a large number of adults with ID in New York(140, 144, 181). Some conditions that may necessitate multiple therapy have a greater prevalence in those with severe/profound ID, such as epilepsy(87). Although it was not significant in our multivariate models, in our study we found that the use of medicines was high for those with severe or profound ID; almost half were exposed to psychotropic polypharmacy, almost 3 in 10 were exposed to ten or more medicines, and almost 9 in 10 had anticholinergic exposure, with over one-third recording an ACB score of 5+. The use of medicines carries greatest risk in those with severe or profound ID; most people with severe or profound ID will have atypical disease presentation, some evidence of CNS damage, already have significant cognitive and/or functional impairment, and so may be more likely to have adverse drug reactions or idiosyncratic

response to pharmacotherapy, and may be unable to communicate side effects (9, 29, 287). Therefore, medicines carry extra risk in those with severe or profound ID. It could also be that the cause of ID has more effect on the pattern and number of medicines used, as opposed to simply the severity of ID or that severe intellectual disability may not present symptoms in greater prevalence or of more severe impact,. Further work is required to look at the impact of cause of ID on patterns of medication use.

7.1.3. Place of Residence

In our study, almost half of the population lived in residential settings. Place of residence was consistently identified as one of the strongest factors associated with multiple medicine use in the study, after adjustment for relevant confounders. Our multivariate analysis identified that those living in residential settings were more likely to be exposed to polypharmacy and excessive polypharmacy, to record psychotropic use and psychotropic polypharmacy, but there was no significant association with anticholinergic burden, when compared to those living in community group homes or independent settings.

In particular, psychotropic medication utilization was greater among those living in residences; 7 in 10 of those living in residential settings were exposed to psychotropics, compared to over half of those living in community group homes, and over one-quarter of those in independent settings. These findings of greater burden of medication use are consistent with other findings in the ID populations of institutionalised patients. These trends had previously been described by Spreat and colleagues and Robertson and colleagues who found higher rates of psychotropic use among institutional residents(145, 180), while Tsiouris and colleagues found no difference in the prevalence of psychotropic use between those living in developmental centres or community group homes, but lower rates for adults living with family(144). Most studies to date in the ID population have focused on psychotropic use and place of residence, as opposed to broader use patterns. The higher use of multiple medicines, psychotropics and anticholinergic exposure has also been identified among institutionalised general elderly residents compared to those who are living in community settings (253, 254), due to higher prevalence of physical and mental health morbidity (230). The lower rates of medicine use in community group homes or independent settings may reflect the tendency for those who may be more frail, have

more severe mental health conditions or other co-morbidities to be placed in or remain in institutional settings. In Ireland, these findings of greater morbidity and complex needs are confirmed in the "Time to move on from congregated settings" report in 2011, which identified those living in institutional settings to be older, and have more complex needs and challenging behaviours, compared to the overall population with ID registered on the National Intellectual Disability Database (69).

In addition to the higher prevalence of physical and mental health conditions there could remain other factors associated with institutional settings that could be associated with medicine use; those in institutional settings may be exposed to poorer health behaviours such as inactivity or poor diets, and thus lead to greater medicine use, such as laxatives. Conversely, increased access to medical professionals and medical monitoring may result in a higher rate of medical interventions which could lead to a higher burden of medicine use compared to those who live in less supervised settings. However, as this study is cross-sectional we could not determine if institutionalisation was causing increased medicine use. Nevertheless, the substantial gradient in use from "independent" to residential care for the three most commonly reported therapeutic classes; antipsychotics, antiepileptics and laxatives (*Chapter 3, Figure 3-3)* should be examined in more detail. A further limitation of our study was that in the multivariate analyses, we could not examine differences in those living independently and community group homes due to small numbers of those living independently, but there did appear to be a gradient, with those living in independent settings receiving substantially less medicines compared to community group homes.

These findings are of importance as people with ID continue to transition from residential settings in Ireland into community placements and access primary care more frequently, and the longitudinal nature of the study will enable us to address questions in relation to the influence of place of residence, effect of transition of environment on mental health, and consequently on psychotropic patterns.. As many people with severe ID and multiple needs transition into community settings, these complex medical and pharmaceutical care needs will be managed within community group homes or more independent settings by primary care professionals. Findings in the ID literature in relation to the effect of deinstitutionalisation on patterns of medicine use to date have varied, with early research suggesting that medication use may increase for people with ID after community placement (324, 325). In contrast, Thinn found no significant difference in rates of use of antipsychotics for people with

ID moved from long stay hospitals into community placements (326), and Nottestad and colleagues found no significant difference in psychotropic or antipsychotic use before or after deinstitutionalisation(327). These studies probably vary because the health services (the institutions and the primary care services) differ. The longitudinal element of our study will enable us to examine the effect of change of setting on the pattern of medication use. It may be speculated that with deinstitutionalisation there may be an increase in healthcare utilisation in acute providers of care for people with ID. , It is also likely that the same extent of medication supervision may not be available in the community. One recent study examining AED adherence among 793 individuals with ID by examining pharmacy records found that after controlling for age and gender, non-adherence was associated with living arrangement, with those living in semi-independent settings or family homes being significantly less adherent to therapy(453). Issues around monitoring of medications will be important as people transition from settings.

7.1.4. Conditions

Our findings revealed that the presence of a mental health condition was the strongest clinical condition associated with polypharmacy, excessive polypharmacy, higher anticholinergic burden, and use of multiple psychotropics. Almost half of the sample reported a mental health condition, but we did not have access to records of clinical diagnoses. Neurological disease and gastrointestinal disease were associated with multiple medicine use, but not psychotropic exposure or higher anticholinergic burden. Similar to the findings of Straetmans and colleagues, our findings identified different patterns of morbidity that contributed to multiple medicine use compared to the general population(37). The association of mental health, neurological and gastrointestinal disease identified in our study may also reflect the fact that treatment in this population, may be reactive in nature, and these are symptomatic conditions that are more easily recognised and therefore prompt a response. The presence of multiple physical and mental health concerns often offers a therapeutic rationale for the use of multiple drugs, in particular, psychotropic drugs and drugs for neurological conditions, of which many have anticholinergic properties (304, 456).

Our findings indicated that what appears to be contributing to multiple medicine use in the population is not just the use of medicines to treat multiple conditions but use of multiple agents to treat particular conditions, such as complex

mental health conditions, or epilepsy that appears to be refractory to treatment. Our findings revealed that a key determinant of multiple medicine use was treatment intensification of these three conditions: Those with a mental health condition received an average of 2.5 medicines to treat the condition, those with neurological disease took 2.8 associated medicines, and those with gastrointestinal conditions had an average of 4.1 medicines from the relevant ATC class. These patterns remain different to treatment intensification patterns identified in the general population, where multiple medicines are often employed to treat cardiac and endocrine disease(122, 457).

Few studies to date in the ID literature have examined the medical conditions that influence polypharmacy at a holistic level, there has been a tendency to focus on psychotropic use or neurological medications in isolation(197). As multimorbidity appears to be the norm for many older people with ID (53, 54), we felt it was important to examine total drug burden, and associated factors in our population. We could not examine the effect of multimorbidity in predicting medication use in our multivariate model, as we examined individual conditions and multimorbidity was commonplace, however multimorbidity was commonplace in our study population; seven in ten had two or more chronic conditions. Individuals with multimorbidity may present significant challenges for healthcare professionals; they may be prescribed several drugs, each of which is recommended by a disease-specific guideline, but the result is that the overall drug burden is high and has the potential to be harmful (219, 260). Furthermore, polypharmacy is an important risk factor for additional inappropriate medication prescribing (273, 458, 459), and most individuals who report use of five or more medications are taking a unique combination of drugs with effects that cannot be predicted from literature and studies (135, 261).

In the general population it has been established that particular disease clusters, for example, cardio-metabolic disease clusters, are associated with polypharmacy (130, 259). While use of multiple medicines to manage some chronic conditions is increasingly recognised as being appropriate(124), there is a lack of research regarding medicines use in elderly patients with multiple morbidities in general, and for individual ageing with an ID in particular. Most internal medicine clinical research projects focus on individual diseases, without taking into account the complexity and overlapping conditions commonly experienced by older adults (260, 460), and particularly by people with ID. The presence of an intellectual disability is often an exclusion rather than inclusion criterion for participation in clinical research, therefore evidence for the

rationality of multiple therapies in multimorbid ageing individuals with ID is even more lacking. Further work is called for to assess side effects from multiple medications and to examine if particular and different disease clusters in ageing participants with ID (53), are associated with polypharmacy as evidence already exists that demonstrates that diseases cluster in a different pattern in this population (53) . Patients on multiple medicines are more likely to experience drug side effects, related to the number of co-morbidities , rather than the effect of patient age (461). The evidence base is still poor for multiple interventions across several condition(116, 129, 457), so extra care is required in prescribing and monitoring in these individuals. Guidance has been published in the ID literature on recommendations for treatment of psychiatric conditions that co-occur in patients with ID and epilepsy (400). Given the increased life span, and growing cohort of older people with ID in Ireland and elsewhere, the effect of multiple medicine use in multimorbidity, which is compounded by disability and frailty must be considered. Our findings were limited in that we did not have specific information on which physician initiated and managed complex regimen or the implicit prescriber decisions that took place.

In particular, in this population, the high prevalence of mental- physical multimorbidity found (53) adds further complexity to managing pharmaceutical care. In the general population, when long term physical and mental-health problems co-occur, they may act synergistically and have a negative impact on level of disability, health outcomes, hospital admissions, quality of life, cost and mortality. (219, 462-464) Evidence on best practice in delivering co-ordinated best care to people with several disorders, particularly at the physical – mental health interface is limited (219, 463, 465). In the general population, evidence exists that quality of life of those with co-morbid physical and mental health problems is considerably worse compared to quality of life of those with two or more physical health problems (466). In addition, those with co-morbid physical and mental health problems have greater difficulties in self-care such as diabetes management , and poor adherence to medication (467). Our findings were limited in that we did not have specific information on which physician initiated and managed complex regimens or the implicit prescriber decisions that took place.

7.1.5. Other Determinants of Medicine Use

Our findings identified no significant association between self-rated health and polypharmacy exposure, psychotropic utilization, anticholinergic burden or use of multiple antiepileptic drugs. These findings could reflect effective treatment with medicines, and the importance of medicine use in maintaining quality of life in older people with ID. However, as this is a more subjective question and was answered by proxy in the case of participants who were unable to respond themselves, the validity of proxy responses in more subjective topics has been called into question(270). In keeping with the goals of inclusion of the IDS-TILDA study, those with severe or profound ID were more likely to have a proxy only interview or a mixed answer style. The validity of proxy responses on more subjective items has been called into question (270). Access to clinical records would help clarify several issues, but would only be feasible for a sample of the cohort. Further research is warranted in the ID population to determine the effect of the differing response styles and inclusive research.

In the general elderly population, other key determinants of use of medicines include lower socioeconomic status, having health insurance, not being married and having lower educational attainment (122, 134, 228, 262, 263). For this study, it was not possible to examine the effect of these characteristics in any detail; our sample was uniform with respect to many of these characteristics; almost all had a full medical card, few were employed, nearly all were unmarried and levels of educational attainment and literacy were low. Haider and colleagues noted an association between polypharmacy and fair or poor self-reported health status, and inability to get help from family and friends(140).

Further research is needed to examine influence effect of discrimination, deprivation, social connections on patterns of medicine use in this population. Furthermore, given the low level of education and literacy established in our population, tailored and appropriate education for patients and carers regarding medicines is needed, and appropriate advocates with regard to healthcare related decision making. To further examine these issues, Wave Two of the IDS-TILDA study contains questions in relation to knowledge of carers and participants in relation to medication administration, medication side effects, education received with regard to medications, and whether participants have been offered easy to read education leaflets.

7.1.6. Epilepsy

Epilepsy was common among the study population; 3 in 10 reported a diagnosis, with almost all reporting regularly taking antiepileptics for treatment. Findings revealed that 5 in 10 were exposed to AED polytherapy, with newer agents appearing to be more often added in as part of polytherapy regimens. Despite the high level of medical intervention and specialist care for those with epilepsy, a substantial proportion still experienced seizures on a regular basis; over half had experienced seizures in the previous two years, and almost one-quarter experienced seizures more than once per month. These findings are similar to other studies in the ID population, where a majority of patients with ID continue to have seizures despite AED interventions (290, 414, 415). This reflects evidence from a Cochrane review on efficacy of AED use in people with ID that concluded that "a moderate reduction in seizure frequency, and occasional seizure freedom was obtained" for those with ID and epilepsy(250). These findings reflect the difficulties faced by practitioners, people with ID, carers, family and staff that arise from trying to have a treatment plan for epilepsy with regard to balancing conflicting and competing priorities for treatment. AED polytherapy is often necessary, due to the adverse risks associated with seizures, and the high importance of seizure control. However, these medicines are also adding to a large drug burden, and carbamazepine to the anticholinergic burden, so this also needs to be considered. There has been renewed interest in the psychosocial impact of epilepsy and its treatment among people with ID (81).

Our study findings revealed that only 4 in 10 reported access to a rescue medicine for the treatment of status epilepticus, with more of those in residential settings having access; over 5 in 10 compared to one-third of those in community group homes, and 13% of those in independent settings. However, it is possible that access to rescue medicines was under-reported, for example, in institutional settings there may have been a stock supply. A development since the study was carried out is that buccal midazolam is now authorised and may be prescribed on the medical card scheme, it was an unlicensed product in 2009/2010. Further investigation of the accessibility of these medicines to people with ID living at home as well as in community group homes is warranted, particularly as those with complex active epilepsy move into less supervised community settings. As a result of these findings, further questions have been added into Wave two of the study with regard to access

of these agents, and whether staff and carers had education in relation to their administration.

Our findings indicated that almost 9 in 10 of those with epilepsy had at least one other comorbid condition, with almost 2 in 3 having two or more chronic conditions. Mental health was the most common co-morbid condition, with almost 5 in 10 reporting a doctor's diagnosis of a psychiatric condition. The most frequently reported AED medicines in the cohort were the mood stabilising older AEDs carbamazepine and valproic acid. It is likely that in some cases, these medicines may have been used secondarily for mood stabilising indications. In addition to antiepileptic medicine, participants took an average of almost six other medicines, resulting in high burden of medicines, and 13.7% reported medicines that were recommended to be avoided in epilepsy, while almost one-third were exposed to a psychotropic where care is required when used in epilepsy. While these agents are not contraindicated, and we do not have information as to whether the dose reductions of medications with epileptogenic potential had been made in the sample, our findings highlight the need to recognise the possibility of side effects and particularly with the introduction of new agents, and engage in regular monitoring.

It has been acknowledged that diagnosis and management of epilepsy may require collaborations and contributions from a number of health care professionals and disciplines, in a variety of settings including primary, secondary and tertiary care(398). Findings from our study confirmed this, and indicated that those with epilepsy and on therapy had their condition reviewed frequently, with 8 in 10 reporting being reviewed by a neurologist or psychiatrist, and one third were reviewed by more than one type of practitioner. We did not identify any difference between those taking one or two or more AEDs in relation to healthcare utilization.

7.1.7. Health Care Utilisation

Our findings identified high levels of engagement and utilization of healthcare professionals, particularly at primary and secondary care levels, with tertiary care being less frequently accessed by people with ID, and unsurprisingly, those with greater burden of medicine reported accessing medical services at a greater frequency compared to those who did not use multiple medicines. Almost all of our sample had a full medical card, which entitles the holder to free access to health care services and medicines, so there is no economic barrier to healthcare utilization. The area of the

relationship between healthcare utilization and polypharmacy exposure has not been studied in detail in the ID literature; in a recent study Haider and colleagues reported an association between five or more GP visits and other healthcare checks and exposure to polypharmacy (140). Straetmans and colleagues in the Netherlands identified that people with ID accessed general practitioners at a greater frequency, and received more prescriptions compared to a matched population with no ID(37). These findings are also reflected in the general population, where increased health care utilization has been correlated with polypharmacy, with Jorgensen reporting that visiting a primary care physician five or more times per year increased the risk of using five or more medicines by 15 times(267). However in this study, we cannot correlate directly increased health care utilization with more polypharmacy; it may be that those with more chronic and complex conditions may access healthcare practitioners at a greater frequency.

Findings from the study revealed that while use of specialists such as psychiatrists and neurologists was high for those with chronic conditions, such as mental health conditions, and epilepsy, but there was lower use of tertiary care, with less than one in ten of the sample having spent nights in general hospital in the previous year. Despite the high prevalence of psychotropic use, psychotropic polypharmacy, and mental health conditions, for those with psychotropic use, less than 1% had spent nights in a psychiatric hospital in the previous year. While this may relate to conditions being well managed in people's own place of residence, we did not have information as to whether attempts had been made to gain hospital admission. These findings may reflect concerns that have been highlighted by the Royal College of Psychiatrists in 2011 with regard to out of state placement of people with ID who had acute or severe mental disturbances, and the lack of dedicated inpatient beds for people with ID (113). Over half of our sample lived in institutional settings, it is likely, because of the high availability of ID-specific medical and other acute services that may be provided in the institution, that the threshold for admission to secondary care may be higher for those who live in institutions. It may be speculated that with deinstitutionalisation there may be greater use of tertiary services. In the UK, a recent report indicated that some people with ID and their families want learning –disability mental health services to be closed, and to use universal mental health services, with these services making the necessary adjustments to be inclusive of people with ID, alongside others(158). The longitudinal element of the study will enable us to track

patterns of healthcare utilization as people continue to transition into community settings.

Studies in the UK have shown that people with ID have greater difficulty accessing primary care services and health promotion(468). Deinstitutionalisation may be associated with higher levels of non-specialised care, and professionals without specialist knowledge of the health care needs provide care (5). Movement out of institutional settings may not necessarily increase the health of people with ID, unless quality healthcare is available in community settings. People with ID need tailored primary care programs, health promotion and screening. As a result there may need to be more education of professionals in primary and secondary care of the needs of people with ID.

There is increasing evidence and interest in the effectiveness of psychosocial treatments and applied behaviour analysis methods for assessment and treatment in this population(469). Encouringly, our findings revealed that over half of those who answered the question in relation to psychological treatment reported currently receiving psychological treatment, with nearly all receiving this treatment alongside psychiatric treatment and psychotropic medications.

7.1.8. Appropriateness

There has been increased research and interest in the general older population with regard to appropriateness of medicines use, and evaluating potentially inappropriate medicines (PIMs), and their relationship with functional and cognitive decline (116, 470). Evidence to guide prescribing among the elderly is limited by the exclusion of older adults with multiple medical conditions from participation in controlled drug trials (186). Therefore, the determination of appropriateness of medicine use in older people is predominantly guided by expert consensus, such as Beer's criteria, or the STOPP/START prescribing criteria (302, 355).

In the elderly, it has been recognised that a medication is considered to be appropriate when the evidence base for its indication is clear, it is well tolerated and cost effective (355). By contrast, medicines that have no clear evidence base, that have a high risk of adverse effects, that are not cost effective, and that have an unfavourable risk benefit are considered to be potentially inappropriate. Certain drugs are considered to be inappropriate or problematic in older patients not only because of the higher risk of intolerance related to adverse pharmacokinetic or pharmacodynamics or drug-drug

or drug disease interactions, but also because they are prescribed in high doses or for too long(129). However, currently there is no specific tool available to assess appropriateness of medicine use among people with ID. The Criteria to Assess Appropriate Medicine Use among Complex Elderly Patients (CRIME) guidelines were recently developed in the general population to guide prescribing in complex, multimorbid patients with evidence of functional and cognitive impairment, however their focus remains on cardiac conditions(457). The Assessing Care of Vulnerable Elders (ACOVE) quality indicators for medicine use may have some applicability to the population with ID(366), however, ID specific appropriateness guidelines could be developed to take account of the different morbidity patterns present in this population.

Furthermore, most interventions in the geriatric population focus on educating prescribers on the appropriate use of these medicines or the identification of potentially inappropriate medicines (PIMs) Very little guidance currently exists about how to deal with a PIM once it has been identified.(471) However some evidence is emerging to support a structured approach to "deprescribing"; the process of withdrawing, tapering or discontinuing medicines in older patients in a systematic manner, particularly in general practice (472). A structured evidence based approach to drug discontinuation in the older population with ID would be particularly important as many frequently reported therapeutic classes, for example the antipsychotics, anticholinergics, and antidepressants may be associated with discontinuation syndromes(472). These require slow weaning and monitoring and necessitate the support and collaboration of a multidisciplinary team. There have been studies in the ID population that have focused and shown success in patient outcomes upon discontinuation or dose reduction of long-term antipsychotics and other psychotropics (237, 473-475). While medication reduction and discontinuation may be a complex process, "prescribers have a responsibility to minimise the potential for harm and waste of resources arising from inappropriate polypharmacy in vulnerable older persons" (472).

7.1.9. Anticholinergic Burden

Findings in this study identified that exposure to medications with anticholinergic properties was widespread; 71 different medicines with anticholinergic potential were used, from 15 different therapeutic classes. Therefore, reducing the anticholinergic

burden will pose a challenge in this population, given the variety of agents contributing to the burden. Given the growing evidence of the effects of anticholinergic burden on cognitive and functional impairment in the elderly(356, 383), and given the evidence that people with ID are already cognitively impaired, reducing anticholinergic exposure if possible may represent an intervention to aid preservation of cognitive function, and maintaining quality of life. Longitudinal analysis will enable us to examine the effect of anticholinergic exposure in more detail on functional and cognitive outcomes. In addition, central nervous system compromise is associated with specific intellectual disabilities (epilepsy and cerebral palsy , for example) (53), so the effects of medicines with anticholinergic properties on cognitive function in these patients must be examined. Published lists such as the ACB tool may prove to be a useful aid for making clinical decisions in practice, and optimising polypharmacy in this population.

7.1.10. Side effects

A key limitation of our study was that we did not gather specific information about whether participants experienced side effects associated with prescribed medicines, or if side effects were monitored or reported. However, we identified a correlation between higher anticholinergic burden scores at bivariate level and problems of constipation, and doctor's diagnosis of chronic constipation, and higher anticholinergic burden and likelihood of daytime drowsiness. Evidence suggests that people with ID are at greater risk of drug-related side effects (29, 114), for example tardive dystonia (138). The high prevalence of anticholinergic use among those with antipsychotics in the absence of a diagnosis of Parkinson's disease may also signal that these patients were experiencing extra-pyramidal side effects, particularly associated with the older typical agents. We also did not gather information as to whether regular side effect monitoring took place.

In the UK, national audits carried out by the Prescribing Observatory for Mental Health suggest that people with ID are being regularly assessed for antipsychotic side effects in secondary care, but data is unavailable as to whether these checks happen in primary care, and are targeted as high risk groups (476).Furthermore side effect monitoring for adverse effects from these therapies may be complicated given that people with ID may be "managed by proxy" ; many individual cannot communicate adverse drug reactions or changes in perception, so carers are relied upon to give an accurate description, with concern about validity and reliability of such

reports(76). The limited research available has also documented a long standing concern that many adults with even mild ID may be lacking information on the purpose and potential side effects of medicine (477-479). As a result of this limitation, questions were added to the Wave Two study as to whether participants had drug related side effects, and if they were monitored for side effects.

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7.1.11. Psychotropics

Rates of use of psychotropic agents were high across our study population; almost six in ten used at least one psychotropic agent. According to our findings, there was a high prevalence of concurrent use of psychotropic agents from different classes and complex pharmacologic regimens; two thirds of those with psychotropic exposure had inter-class polypharmacy with antipsychotics with anxiolytics/hypnotics reported by one third of those with psychotropic consumption, and antipsychotics with antidepressants (29%) being the most commonly reported combinations. While combinations of psychotropic agents may place patients at increased risk of drug-related adverse effects, it is important to also bear in mind that clinical research does provide some support for psychotropic combinations, when remission from psychiatric disorders is not achieved with monotherapy(114, 172, 173, 278) For example, the addition of an antipsychotic to an antidepressant for major depression with psychotic features, or the addition of an antipsychotic to a mood stabiliser for acute mania represent examples of empirically supported polypharmacy(480, 481). A limitation in the study was that we did not have information as to severity of conditions, or if monotherapy had failed. From examination of antipsychotics among the four most frequently reported agents, doses employed were conservative. Changes made to the Wave Two medication data questionnaire will improve collection of dosing data. The need to accurately identify and treat mental illness in older people with ID must be balanced against the established evidence of psychotropic-related adverse effects (175, 275, 284). With increasing concerns about inappropriate use, there is a strong need to monitor the use of these agents. More work is needed to better understand the relationships between psychotropic agent use, diagnosed mental health concerns, challenging behaviours and therapeutic outcomes in people with ID to better understand the counterbalancing of therapeutic needs with polypharmacy and adverse effects concerns such as sedation and risk of falls

Appropriate use of psychotropic agents in particular with regard to their use in challenging behaviours has received increased attention in recent times(148, 154). In the UK, the 2012 Department of Health Review "Transforming Care: A National Response to Winterbourne View Hospital" highlighted "deep concerns" about overuse of psychotropic medicines for people with ID (159) A limitation of our study was that we did not gather information on prevalence of challenging behaviours. In Wave Two of the study questions have been added about challenging behaviours. While use of psychotropics improve quality and function of life for those with psychiatric disorders, there is less evidence for long term use in challenging behaviours, and increased risk of harm for this indication(148).

7.1.12. Antipsychotics

The antipsychotics represented the most frequently used medication class in the cohort, with over 4 in 10 exposed to an agent. Our findings also revealed that use of older typical agents that are no longer favoured in the elderly; chlorpromazine and haloperidol were still used frequently among this population with ID. We were limited in our ability to ascertain the appropriateness of use of these agents, as we did not have length of exposure to these agents, but it is possible that use of these typical agents may relate to historic prescribing , where these antipsychotics were initiated years ago.

We identified that one quarter of those with antipsychotics had two or more agents concurrently. Combinations of risperidone low dose and zuclopenixol as the depot causes reduces the medication burden and may also improve adherence. It may be appropriate to administer two antipsychotics, as a temporary measure in the treatment of acute schizophrenia (114). However, a limitation of this study is that we do not have detailed information in relation to clinical notes and prescriber decision making.

7.1.13. Antidepressants

Our findings identified that 1 in 4 in our sample used antidepressants, and depression was the second most commonly reported mental health diagnosis; almost 4 in 10 of those with a mental health condition had depression, with the SSRIs accounting for over 70% of antidepressants recorded. These findings may reflect that depression is being increasingly recognised and treated in this population.

7.1.14. Anxiolytic and Benzodiazepine Use

Findings in our study identified that 3 in 10 used anxiolytics or hypnotics, with one quarter using two or more concurrently. Guidelines state that the elderly should use benzodiazepine anxiolytics only at low doses(302), for short-term use (249), avoid use of long-acting agents (249, 302, 482, 483) and hypnotic benzodiazepines should not be prescribed in the elderly (484). Interpretation of appropriateness of anxiolytic use is limited by the fact that we did not have full information in relation to dose or length of prescription. However, there was a high prevalence of use of long-acting agents: diazepam and lorazepam, with these agents often used in combination with other psychotropics. It has been acknowledged that there are a small number of people in whom maintenance medication to treat mental illness may include low dose of benzodiazepines (330). A key limitation in assessing appropriateness of benzodiazepine use in our study, was that we did not have information on duration of use, as use for longer than four weeks is often cited in appropriateness criteria. Given the evidence relating to adverse effects, particularly as this population ages; aggravation of constipation, sedation, anticholinergic burden, cognitive impairment and mortality (281), and given the additional evidence for increased risk associated with these agents for people with intellectual disabilities(168), our findings highlight the need to frequently review use of benzodiazepines and hypnotics in this population.

7.1.15. Prescribing Cascade

It is likely that , due to communication difficulties, and atypical disease presentation, that people with ID may be more at risk of experiencing the "prescribing cascade", or incremental prescribing(125). In our study, the higher use of laxatives among those with higher anticholinergic burden may represent an example of this phenomenon; over half of those with an ACB score of 5+ recorded laxative use, and over one-quarter had two or more laxatives, compared to a prevalence of 19% for laxative use among those with no anticholinergic burden, and 1% for laxative polytherpy. However, we were limited in this assertion as we did not know which medications were initiated first.

7.1.16. Potential Underuse of some Therapeutic Classes

While multiple medication use was commonplace for the majority of the study population, our findings identified two potential areas of under treatment; eye

conditions, and treatment of pain. Eye disease was the most common chronic condition reported in the cohort, but each person with eye disease only recorded an average of 0.13 eye medications. It is possible that people did not report eye preparations, or some conditions were not amenable to therapy. In relation to utilization of analgesics, use of paracetamol was commonplace, but there was negligible use of any opioids or other stronger agents, Under-prescribing is also gaining recognition in the general population(116, 355). Paradoxically, in some cases drugs recommended for some conditions, may not be prescribed(116). A patient already exposed to polypharmacy may not receive other medicines, due to fears of interactions with drugs already prescribed, and this needs to be examined in more detail in the ID population.

7.2. Recommendations/ Implications for Practice

A number of recommendations follow from this appraisal of research findings, and are relevant for health professionals, carers, policy makers involved in the delivery of care for ageing people with ID, and for people with ID.

1. *Comprehensive Medication Review to optimise medicines use*

This research identified that over half of the older population with ID were exposed to five or more medicines, and psychotropics, antiepileptics and laxatives were most commonly used. The high burden of medications noted in the research underlines the importance of conducting regular, structured medicines reviews in this population. These reviews should take place at frequent intervals, and assess the risks and benefit of use of multiple therapies. Care should also be taken that medicines that are needed are prescribed, as our findings revealed low availability of rescue medicines for acute seizures.

Additionally, findings in the study identified the frequent use of medicines in this population that require extra care and regular monitoring, for example carbamazepine and lithium. Prescribers should look at the impact of medicines on physical and cognitive function, which are both important determinants of quality of life among older people with ID that are needed to maintain independence. The Canadian Consensus guidelines for adults with ID in primary care settings recommends a comprehensive review of medicines at regular intervals (e.g. every three months(5).

Evidence suggests that many people may stay on medicines beyond the point that are gaining therapeutic benefit from them (116). As part of the structured medication review. prescribers should consider if it is appropriate to stop at a treatment, particularly if there are significant risks or impact on dependency or quality of life, such as psychotropics, make a plan for controlled discontinuation .Unless drugs are reviewed on a continuous basis, there is a risk therapies that may now be ineffective may be continued, and cause harm. Regular structured medication reviews can bring order to the complexity of prescribing in this population and make a meaningful difference to patient outcomes. There must be clear and documented reasons and regular review of the use of psychotropic medications for challenging behaviours.

2. *Multidisciplinary teams caring for people with ID should include pharmacists*

Clinical medication reviews led by, or including pharmacists in the elderly in primary care and in care homes have demonstrated significant reductions in number of inappropriate medicines, and to a lesser extent improvement in some patient outcomes, including falls (192, 193). However, pharmacists have not been included in planned multidisciplinary teams providing mental health services for people with ID (55). The limited evidence available and reviewed in the literature demonstrates that when pharmacists initiate pharmaceutical care interventions in people with ID, they can make positive contributions in relation to the quality and safety of the medication use process for people with ID , in collaboration with other healthcare professionals, carers and patients with ID(194-196). However, further research will be required to increase the evidence base with regard to the benefits of providing pharmaceutical care to patients with intellectual disability. For example, a review of the limited evidence base to date suggests that pharmacists as part of a multidisciplinary team were successful in identifying drug therapy problems in people with ID (194). Further interventions that measure the benefits of medication reviews by pharmacists as part of a MDT are warranted. This would also create awareness among people with ID, carers and other health professionals that they have the necessary skills to be active members of the primary healthcare team when caring for people with ID. There is a need for pharmacists to create an active research agenda to promote appropriate and quality use of medicines in older people with ID.

3. *Holistic Evaluation of Medicine Burden*

Findings from the study highlighted the high burden of medications for many people with ID, with multiple therapeutic classes contributing to the burden for individuals. Prescribing and monitoring should happen in a manner that explicitly considers the overall effect of total drug burden on people with ID, including the possibility of drug-drug interactions, drug-disease interactions and the impact of total "pill burden" on the patient and carer.

4. *Guidelines should be developed for identifying medication management of long term conditions that commonly co-exist in older people with ID*

Findings in the thesis identified that multiple medicines use was much greater for people with ID compared to the Irish population over 50 in Ireland, over one-fifth of those with IDhad ten or more medicines compared to 2% in the community dwelling Irish population. Furthermore, findings in the thesis have identified a different pattern of multiple medicines use for older people with ID compared to the general population, with greater use of agents to treat mental health and neurological conditions compared to the general population. Therefore, use of appropriateness tools that are used in the elderly such as STOPP START prescribing criteria have limited applicability to this population. Work had begun identifying the disease clusters that commonly co-occur in people with ID (53). There is a need for specific prescribing guidelines for ageing with ID, including medication recommendations for particular disease clusters that commonly co-occur in this population. Some work has been in this regard by Kerr and colleagues with regard to treatment of neuropsychiatric conditions in patients with ID and epilepsy (400), and this work needs to be expanded upon to include other clusters of conditions commonly experienced by people with ID. These guidelines would be particularly important to be directed at non-specialist clinicians and pharmacists to aid screening so that appropriate referrals for more specialist treatments can then be made if appropriate. With deinstitutionalisation, people with ID and complex comorbidities are now living in community settings and accessing non-specialist primary care services at greater frequency. Pharmacists should play a role in the multidisciplinary team writing guidelines.

5. *Use of the ACB tool to evaluate Anticholinergic Burden for Older People with ID*

The high anticholinergic burden highlighted in our study highlights the importance of evaluation of the cumulative anticholinergic burden in older people with ID. Findings

identified 71 different medicines from 15 therapeutic classes that were contributing to this burden, so reduction of anticholinergic burden may be a complex task. However, given the evidence that exists in the general elderly population of the risks associated with exposure to anticholinergic medications (353, 356, 373), and the unique risks of frailty, cognitive decline and adverse drug reactions in people with ID (122, 203, 374, 375), evaluation of the ACB of an individual should be considered as an additional strategy for optimizing appropriate polypharmacy, and improving outcomes in this population. The ACB Scale may reflect a simple and effective tool that could be used by doctors and pharmacists to identify patients with high burden who need medication review, and who may benefit from a reduction in anticholinergic load. The ACB Tool may draw attention to total anticholinergic load in a patient in a more holistic and focused manner, and identify those at risk of adverse outcomes, and could be a useful tool in routine clinical practice. Lists with Alternatives to definite anticholinergic medicines are also available to aid clinician decision making in this process (485). .

6. *Awareness of the potential of the prescribing cascade among all healthcare professionals*

Our findings identified that the high use of laxatives in those with ACB score of 5+ may represent an example of the prescribing cascade in this population. Prescribers may not recognise that symptoms for people with ID may not be iatrogenic, and may unwittingly prescribe new medicines to counter adverse effects experienced with other medicines, which is the prescribing cascade(125). Those with severe/profound ID or those who are non-verbal may be at increased risk. of experiencing the prescribing cascade. More education is needed about the unique pharmaceutical care issues for people with ID, including atypical disease presentation and communication difficulties for doctors and pharmacists in primary care, particularly as people with ID continue to transition into community settings and access health services in the community at a greater frequency.

7. *More studies are needed in the ID population to increase the evidence base*

Difficulties were encountered making direct comparisons with regard to medicines use in our population compared to other ID populations, as definitions of polypharmacy often did not capture total load of medicines, More studies of patterns and prevalence of multiple medicines use in the ID population are needed, encompassing the broader

definitions of polypharmacy and excessive polypharmacy employed in the general population, particularly as life span continues to improve for people with ID and they acquire age-related morbidities anticholinergic burden,.

8. *Identification of the patient and carer perspective of experience of use of multiple medicines in people with ID*

Due to the high proportion of people with intellectual disabilities that have limited educational attainment, caregiver involvement in decision making and medicine management will promote rational drug therapy ., . Some work assessing perspectives and views of patients with ID and use of medicines has been carried out to date(486). The capacity for people with ID to make decisions, or to be supported to make decisions may be improved through the use of appropriate communication tools, like easy to read information, and good communication by healthcare professionals. Involvement of staff, keyworkers, family or carers in this process is vital. Patients and carers need education in use of medicines, in particular those with complex regimens.

7.3. Future Research

Since completion of this analysis, Wave Two of IDS-TILDA was carried out in 2013, the Wave Two report was published in 2014 (487), and the medication data is in the process of being analysed. As a result of limitations identified in this study, additional questions were added to the Wave Two questionnaire. Questions were added regarding patient and carer experience of side effects, availability and use of rescue medications, if patients or carers had received education on how to take medicines and if patients and carers knew what medications were for. Questions were also added with regard to access to pharmacy services, and whether participants had ever been offered or had used to easy-to read medicines information. The addition of these questions will provide a more holistic picture of the medication use process for people with ID and capture experience of people with ID and their carers around use of medicines, and access to medication information and pharmacy services.

With regard to recording of medicines information, this study identified that doses and frequency of medication was not always recorded, that it was possible that topical or eye preparations may not have been always recorded and information was

not gathered on duration of prescriptions. As a result, modifications were made to the medication data collection form for Wave Two of the study, to ensure other preparations like creams and ophthalmological preparations were recorded, and that dose was recorded where possible. An additional question about length of exposure to medicines was added to the questionnaire, which will enable determination of length of exposure of therapies, and so enable examination of appropriateness of use.

The longitudinal data from Wave Two will transform the study from a cross-sectional analysis into a cohort study and will provide a comprehensive insight into resultant changes in medication patterns as people age, and move into community settings and will enable us to examine the effect of medication use on clinical outcomes. The longitudinal design will enable us to further examine the effect of long term use of medicines on functional and cognitive outcomes, and detect these changes in people with ID as they get older. The longitudinal design is more likely to suggest cause and effect relationships, compared to a cross-sectional decline. For example, with longitudinal data we will be able to detect for this first time if higher anticholinergic burden causes cognitive decline or increase in mortality. Objective measures were carried out in Wave Two, including measures of blood pressure, bone density and grip strength, this information will give us more detailed clinical information when assessing appropriateness of medicine use in the context of objective measures of health.

In the interim period between Wave One (2009/2010), and Wave Two (2013), there have been changes in the Irish healthcare system. Prescription levies on GMS prescriptions were introduced, as was generic substitution on many medicines, and there have been issues surrounding eligibilities for medical cards and other services. Wave Two of the study will provide information on change in patterns of health care utilisation, and generic medications.

For this thesis, it was not possible to study all patterns of medication use and clinical conditions in detail. However, the findings indicated that there substantial use of laxatives, and other gastrointestinal agents, including the proton pump inhibitors, in tandem with a high prevalence of constipation and other GIT conditions reported. Future work will examine patterns of use of these agents in more detail.

Initial work carried out by Peklar and colleagues identified that almost 4 in 10 of the study population took at least one supplement, which further contributes to the drug burden for people(22). Future work will examine the use of supplements among

people with ID in more detail, and their benefits and potential for interactions with prescribed medicines.

Work is ongoing to examine the differences in medication use and prevalence of clinical conditions between those with Down syndrome in the study, and those with ID of other aetiologies.

There are plans in progress to create a matched dataset with the TILDA cohort, whereby people with ID would be matched with a person of the same age, gender and geographic location to compare patterns of medicines use between the population with ID and the general ageing population.

7.4. Conclusions

The present position of individuals with intellectual disabilities in Irish society has evolved from the historical marginalisation of these citizens. While the quality of care provided to people with ID has improved immeasurably, there remain several barriers to the provision of optimal care for all people with ID. The pharmacotherapeutic management of people with ID, one dimension of clinical care enhances the quality of life and improves health for people with ID, when medicines are used appropriately, and when monitoring for efficacy and adverse effects takes place at regular intervals. Evaluating the benefits of multiple medicine use and their role in appropriate treatment of complex comorbidities in older people with ID must be balanced with risks of adverse outcomes associated with use of multiple drugs, particularly those which have anticholinergic or sedative properties. In particular, the use of multiple psychotropic agents should be re-evaluated frequently to assess benefits and risks. Prescribing and providing pharmaceutical care in this population should be carried out in a manner that explicitly considers the overall effect of the total drug burden. There is a need for development of ID specific medication appropriateness guidelines which would provide health professionals with a tool to evaluate medication regimens in a structured manner. Health professionals in primary care need education on the unique medical and pharmaceutical care needs of people with ID. While addressing the pharmacotherapeutic management of this group of people would undoubtedly address a number of clinical concerns highlighted in the thesis, the management of people with ID in the Irish healthcare system requires further improvements so as to optimise outcomes for people with ID as they grow older and continue to transition into community settings.

people with ID as they age, and their benefits and potential for interactions with potential medicines.

The effects of [illegible] to evaluate the differences in medication use and pharmacological [illegible] between those with Down syndrome in the study and those with [illegible].

There are plans to progress [illegible] with a further wave of IDS-TILDA [illegible], whereby people with ID would be reviewed and experiences the medication use and prescribing [illegible] patterns of use in [illegible] through the general ageing population.

7.4 *Conclusion*

The present practice of prescribing with intellectual disabilities to their poorly has evolved from the historical institutionalisation of these [illegible]. While the quality of care provided to people with ID has improved progressively, there remain several barriers to the provision of optimal care for all people with ID. The pharmacological management of people with ID, and dimensions of clinical care enhances the quality of life and improves health for people with ID, when medicines are used appropriately, and when monitoring for efficacy and adverse effects takes place at regular intervals. Evaluating the benefits of multiple medicines use and their role in appropriate treatment of complex comorbidities in older people with ID must be balanced with risks of adverse outcomes associated with use of multiple drugs, particularly those which have anticholinergic or sedative properties. In particular, the use of multiple psychotropic agents should be re-evaluated frequently to assess benefits and risks. Prescribing and providing pharmaceutical care to this population should be carried out in a manner that explicitly considers the overall effect of the total drug burden. There is a need for development of ID specific medication appropriateness guidelines which would provide health professionals with a tool to evaluate medication regimens in a structured manner. Health professionals' continued education on the unique medical and pharmaceutical care needs of people with ID. While addressing the pharmacotherapeutic management of this group of people would undoubtedly address a number of clinical concerns highlighted in this thesis, the management of people with ID in the Irish healthcare system requires further improvements so as to optimise outcomes for people with ID as they grow older and continue to transition into community settings.

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Appendices

Appendix 1 IDS-TILDA Study Participant Consent Form

CONSENT FORM

IDS-TILDA PARTICIPANT ID W 1

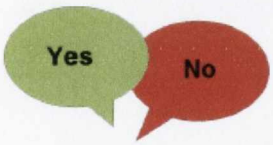
Please read the information below and sign this consent form if you wish to take part in this second wave of the study.

I agree with the following statement

I have gone through the information about this study ☐

I know who to contact if I have any other questions. ☐

Any questions that I might have had were answered. ☐



I know that it is my choice to take part in this study. ☐

10

Trinity College Dublin

I understand this study is for ten years and I will be visited again by a researcher from Trinity College Dublin. ☐

I understand that I will be asked questions about my:

- life
- health
- work
- friends

and things I like to do. ☐

I have gone through the information about this study ☐

I understand that I do not have to answer questions I don't feel happy with. ☐

As part of the study, I know that I will be asked to try and do some things such as write my name. ☐

I do understand that I can stop taking part in this study when I want to.

I do not have to give a reason. ☐

I understand that all information I give during this study will be kept safe and private. ☐

I will not be named in any reports.

I understand that there are no known risks with this study. ☐

YOUR CONSENT

Your name: _____

Your phone number: _____

Your address: _____

_____

_____

Please sign your name:

_____

Date: _____

12

THE PERSON SUPPORTING YOU

I have supported the person named above to fill out this form. I believe they understand the information and have freely agreed to take part in this study.

Print name: _____

Relationship to the person named above: _____

Phone number: _____

Signature: _____

Date: _____

Please return this consent form to the field researcher before the interview commences.

IDS-TILDA, The University of Dublin, Trinity College, School of Nursing & Midwifery, 24 D'Olier Street, Dublin 2

Tel: +353 1 8963186/8963187 Fax: +353 1 8693001 Email: idstilda@tcd.ie

Appendix 2: Study Family and Guardian Agreement Form

Intellectual Disability Supplement to TILDA
The University of Dublin, Trinity College
School of Nursing & Midwifery
24 O'Moy Street, Dublin 2.
Tel: + 353 1 896 3100/3187
Fax: + 353 1 896 3001 Email: idstilda@tcd.ie

Intellectual Disability Supplement to TILDA

Agreement Form for Family Members/Guardians

This study, the Intellectual Disability Supplement to The Irish Longitudinal Study on Ageing (IDS to TILDA), aims to collect information on the health, social and living circumstances of people with intellectual disability aged 40 years and over in Ireland. Your family member/person with intellectual disability has been selected to take part in the study.

By signing this form, you are agreeing to support your family member/person with intellectual disability to participate in this study. They will be asked questions about their health, lifestyle, living circumstances and quality of life. Your family member/person with intellectual disability will also be asked to try and carry out some tasks such as brushing their hair and writing their name.

The study also involves taking some measurements, such as height and weight.

All the information collected during the study will be kept strictly confidential. It will be used exclusively for research purposes. The identity of your family member/person with intellectual disability will not appear in any publication or be disclosed to anyone outside of the research team.

Family Member/Guardian Declaration:

Please tick the following statements if you agree with them:

	Please tick ✓
• I have read, or had read to me, the information leaflet for this study and I understand the contents.	☐
• I knew who to contact if I had any questions.	☐
• Any questions that I might have had were answered.	☐
• I freely agree to support my family member/person with intellectual disability to be part of this research study.	☐
• I understand that taking part or not taking part will in no way affect the current or future services or supports offered to my family member/person with intellectual disability.	☐
• I understand that my family member/person with intellectual disability can withdraw from the study at any time.	☐

I voluntarily give my agreement for my family member/person with intellectual disability to participate in this study and I understand that this will not affect their rights.

Name: _____

Address:

_____

_____

_____

_____

_____

Phone number: _____ Best time of day to contact you: _____

Name of family member/person with intellectual disability:

_____

Relationship to family member/person with intellectual disability:

_____

Signature: _____ Date: _____

Appendix 3: Invitation Pack for Participants

Is the study confidential?

Yes. We will treat all the information from the study as strictly confidential and we will not publish the name of the person with intellectual disability or pass it on to anyone outside of the research team. The Faculty of Health Sciences Research Ethics Committee, of Trinity College, Dublin, has approved this study after ensuring that proper safeguards are in place.

Who is involved in the study?

This study has been set up by people who have a lot of experience of working with people with intellectual disability.

The advisory team consists of:

- Family Members
- Researchers
- Nurses
- Physicians
- Psychologists
- Psychiatrists
- Service Providers

People with intellectual disability also play an important role in our advisory team through participation in consultative workshops. These workshops will be ongoing with groups throughout the country as the study progresses.

Where can I get more information?

If you have any questions, or if you want more information about the study, please do not hesitate to call or email one of the contacts listed below.

Professor Mary McCarron
Principal Investigator
Phone: 01- 896 3186/3187
Email: mccarrm@tcd.ie

Ms Janet Swinburne
Project Manager / PhD Student
Phone: 01- 896 3186/3187
Email: swinburj@tcd.ie

Or write to:

Intellectual Disability Supplement to TILDA,
The University of Dublin,
Trinity College,
School of Nursing & Midwifery,
24 D'Olier Street,
Dublin 2.

Fax: 01- 8963001
Email: idstotilda@tcd.ie

The Intellectual Disability Supplement to TILDA is funded by the Health Research Board.

An Intellectual Disability Supplement to The Irish Longitudinal Study on Ageing (IDS to TILDA)

Trinity College Dublin

What is the study about?

The Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS to TILDA) is the most important study on ageing ever undertaken in Ireland.

It will look at the health, lifestyles and quality of life of about 800 people with intellectual disability as they grow older. It will also observe how their circumstances change over a 10-year period.

The information will be used to develop suitable health and social services that will benefit all people with intellectual disability as they age in Ireland.

We are inviting people with intellectual disability to take part in this study which we are carrying out.

How are participants selected for the study?

People who are registered on the National Intellectual Disability Database (NIDD) and are aged over 40 years may be selected to take part in the study. The sample will be randomly selected from this database.

Does the person with intellectual disability that is selected have to take part?

No. Taking part is voluntary. However, this is a very important study and the information we collect will be better if we have a large number of people taking part. We are inviting men and women aged 40 years and older with an intellectual disability to take part. The person with intellectual disability selected can decide to withdraw from the study at any time.

What if the person with intellectual disability does not take part?

If the person with intellectual disability does not take part or later decides to withdraw, then their decision will in no way affect the current or future services or supports offered to them.

What does the study involve?

A researcher with experience of working with people with intellectual disability will visit the person with intellectual disability and ask questions about their health, lifestyle, living circumstances and quality of life.

We understand that some people may not be able to give this information on their own and may need support. If this is the case then the person with intellectual disability may ask someone (for example, a family member, guardian or key worker) to support them in giving this information.

We will also ask the person with intellectual disability to try and carry out some tasks such as:

- brushing their hair
- writing their name
- naming some colours

The interview will take about 90 minutes. However, this will be different for each person.

At the end of the interview we will arrange a suitable time to take some important physical measurements such as height and weight. We will use these results to find out much more about the health of people with intellectual disability than we could by just asking questions about diet and lifestyles alone. The measurements will take about 15 minutes.

Are there any risks involved?

There are no known risks involved in this study. We will explain each stage of the study to the person with intellectual disability using suitable information booklets and show cards.

At all times, the well-being of the person with intellectual disability will take priority over the research activities. If the person with intellectual disability tells us or indicates that they do not want to take part, or if they decide to withdraw, we will fully respect their decision.

Appendix 4: Study Ethical Approval

THE UNIVERSITY OF DUBLIN
TRINITY COLLEGE

SCHOOL OF MEDICINE
FACULTY OF HEALTH SCIENCES

Trinity College, Dublin 2, Ireland
Tel: +353 1 896 1476
Fax: +353 1 671 2956
Email: medicine@tcd.ie

Professor Dermot Kelleher, MD, FRCPI, FRCP, F Med Sci
Head of School of Medicine
Vice Provost for Medical Affairs

Ms. Fedelma McNamara
School Administrator
Email: fmcnamar@tcd.ie

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,

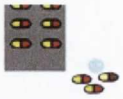
Further to the meeting of the Faculty of Health Sciences Research Ethics Committee on 27th May 2008, I am pleased to inform you that the above project has been approved without further audit.

Yours sincerely,

Dr. Orla Sheils
Chairperson
Faculty of Health Sciences Ethics Committee

Appendix 5: Medication Section of Pre-Interview Questionnaire

Section 8: Medication



We would like to record all medications that you take on a regular basis, like every day or every week. This will include prescription and non-prescription medications, over-the-counter medicines, vitamins, and herbal and alternative medicines.

Question 148: Please write down all medications you take and how often you take them.

Don't know what medication I am on	☐ 1
Don't take any medication	☐ 1

Please tick one box only on each line

Name of medication	Daily	Weekly	When required	Don't know
1.	☐ 1	☐ 2	☐ 3	☐ 98
2.	☐ 1	☐ 2	☐ 3	☐ 98
3.	☐ 1	☐ 2	☐ 3	☐ 98
4.	☐ 1	☐ 2	☐ 3	☐ 98
5.	☐ 1	☐ 2	☐ 3	☐ 98
6.	☐ 1	☐ 2	☐ 3	☐ 98
7.	☐ 1	☐ 2	☐ 3	☐ 98
8.	☐ 1	☐ 2	☐ 3	☐ 98
9.	☐ 1	☐ 2	☐ 3	☐ 98
10.	☐ 1	☐ 2	☐ 3	☐ 98
11.	☐ 1	☐ 2	☐ 3	☐ 98
12.	☐ 1	☐ 2	☐ 3	☐ 98
13.	☐ 1	☐ 2	☐ 3	☐ 98
14.	☐ 1	☐ 2	☐ 3	☐ 98
15.	☐ 1	☐ 2	☐ 3	☐ 98
16.	☐ 1	☐ 2	☐ 3	☐ 98
17.	☐ 1	☐ 2	☐ 3	☐ 98
18.	☐ 1	☐ 2	☐ 3	☐ 98

Appendix 6: Chronic Conditions Included In the Study (53).

Condition	Has a doctor ever told you that you have:
Eye disease	'Age related macular degeneration? '
	'Glaucoma?'
	'Cataracts?'
	'Have you ever had cataract surgery?'
	'Other eye diseases?'
Mental health disease	'Emotional, nervous or psychiatric condition?'
	'Depression?'
	'Schizophrenia?'
	'Hallucinations?'
	'Anxiety?'
	'Emotional problems?'
	'Mood swings?'
	'Manic depression?'
	'Psychosis?'
	'Any other emotional, nervous or psychiatric conditions?'
Neurological disease	'Cerebral palsy?'
	'Epilepsy?'
	'Multiple sclerosis?'
	'Parkinson's disease?'
	'Spina Bifida?'
	'Muscular dystrophy?'
	'Alzheimer's disease?'
	'Dementia, organic brain syndrome or senility?'
	'Serious memory impairment?'
Gastrointestinal disease	'Constipation?'
	'Encopresis?'
	'Coeliac disease?'
	'Gastro-oesophageal reflux disease (like heartburn)?'
	'Phenylketonuria?'
	'Stomach ulcers?'
Joint disease	'Arthritis including osteoarthritis or rheumatism?'
	'Rheumatoid arthritis?'
	'Osteoarthritis?'
	'Scoliosis?'
	'Some other kind of arthritis?'
Bone disease	'Osteoporosis, sometimes called thin or brittle bones?'
Endocrine disease	'Diabetes or high blood sugar?'
	'Thyroid disease (hypo/hyperthyroidism)?'

Heart disease	'Heart murmur?'
	'High cholesterol?'
	'Abnormal heart rhythm?'
	'Angina?'
	'Heart attack including myocardial infarction or coronary thrombosis?'
	'Angioplasty or stent?'
	'Congestive heart failure?'
	'Open heart surgery?'
	'Other heart trouble?'
Hypertension	'High blood pressure or hypertension?'
Stroke	'Stroke?'
	'Ministroke or TIA?'
Liver disease	'Cirrhosis or serious liver damage?'
Lung disease	'Asthma?'
	'Chronic lung disease such as chronic bronchitis or emphysema?'
Cancer	'Cancer or a malignant tumour (including leukaemia or lymphoma but excluding minor skin cancers)'

Appendix 7: Other Variable Used in the Study

Derived Variable	Study Question
Any Sleep Problem (Yes/No)	Sleep questions inquired into the four central parameters of insomnia; 1. initial insomnia (difficulty falling asleep), 2. 2. interrupted sleep (difficulty staying asleep), 3. early wakening and 4. the need to doze during the day as a result of un-refreshing sleep. The questions were phrased as; 'How often do you have trouble falling asleep at night?' Response options were 'never', 'rarely', 'sometimes' and 'most of the time'. (For each question 'sometimes' and 'most of the time' were considered as a yes to each individual sleep question. An individual was considered to report a sleep problem if they had a yes answer to one or more of the four sleep questions.
Any Dementia (Yes/No)	"Have you received a doctors diagnosis of ▪ Alzheimer's Disease ▪ Dementia ▪ Serious memory impairment ▪ Organic brain dysfunction or senility'
Dentate Status (Dentate/ Edentulous)	Three options referring to dentate participants; "1. I have all my own natural teeth-none missing 2. I have my own teeth, no dentures – but some missing 3. I have dentures as well as some of my own teeth" were coalesced into one category which included all individuals reporting some teeth (this is referred to as "dentate") Two variables that considered individuals reporting no teeth "1. I have full dentures 2. I have no teeth or dentures" Were coalesced into another category (referred to as "edentulous")This created a dichotomous binary variable for analysis.

Appendix 8: Psychotropic use by One Psychotropic and Psychotropic Polypharmacy

	Antipsychotic (n=319)	Antidepressant (n= 193)	Anxiolytic (n=173)	Hypnotic/ sedative (n=100)	Mood stabiliser (n=88)
	N (%)	*N (%)*	*N (%)*	*N (%)*	*N (%)*
1 Psychotropic (n=148)	69 (21.4)	34 (17.6)	26 (15.0)	13 (13.0)	6 (6.8)
Psychotropic Polypharmacy	250 (78.6)	159 (82.4)	147 (85.0)	87 (87.0)	82 (93.2)

Appendix 9: Psychotropic Use by Class and Number of Reported Prescriptions

Medications	Number (n)of prescriptions	Number (n) of persons	Percentage Based on participants using Psychotropic Class*	Percentage based on all people in the population (n=736)
Antipsychotics	412	319	100.0	43.2
Atypical	259	250	78.6	34.0
Typical	153	132	41.5	17.9
Antidepressants	201	193	100.0	26.2
SSRIs	133	133	68.9	18.1
TCAs	25	24	12.4	3.3
Other	45	44	22.8	6.0
Anxiolytics	183	173	100.0	23.5
Hypnotic / sedatives	102	100	100.0	13.6
Zopiclone/Zolpidem	59	59	59.0	8.0
Benzoderivatives	41	39	39.0	5.3
Melatonin	2	2	2.0	0.3
Mood stabilisers	115	88	100.0	12.0
Antiepileptics	96	76	86.4	10.3
Lithium	19	19	21.6	25.8

**Total Percentage may exceed 100% because patients may be using multiple psychotropic agents*

TCAs= Tricyclic Antidepressants, SSRIs = selective serotonin reuptake inhibitors

Appendix 10: Psychotropic Use and Mental Health Conditions

	No. of Psychotropics			Psychotropic Classes				
	1 psychotropic	**2 psychotropics**	**3+ psychotropics**	**Antipsychotics**	**Antidepressant**	**Anxiolytics**	**Hypnotics**	**Mood stabilisers**
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n(%)*	*n(%)*
Condition Type*								
Depression (n=139)	30 (21.6)	33 (23.7)	65 (46.7)	96 (69.1)	91 (65.5)	53 (38.1)	32 (23.0)	29 (20.9)
Manic depression (n=28)	2 (7.1)	7 (25.0)	16 (57.1)	21 (75.0)	7 (25.0)	12 (42.9)	9 (32.1)	15 (53.6)
Anxiety (n=193)	40 (20.7)	54 (28.0)	79 (40.9)	137 (71.0)	85 (44.0)	83 (43.1)	45 (23.3)	39 (20.2)
Schizophrenia and/or psychosis and / or hallucinations (n=86)	15 (17.4)	22 (25.6)	48 (55.8)	81 (94.2)	38 (44.2)	37 (43.0)	28 (32.6)	20 (23.3)
Mood swings(n=143)	27 (18.9)	43 (30.1)	66 (46.2)	109 (76.2)	67 (46.9)	57 (39.9)	35 (24.5)	35 (24.5)
Emotional Problems (n=99)	16 (16.2)	27(27.3)	49 (49.5)	77 (77.7)	48 (48.5)	40 (40.4)	24 (24.2)	25 (25.3)
None of these (n=21)	7 (33.3)	5 (23.8)	6 (28.6)	14 (66.7)	6 (28.6)	7 (33.3)	4 (19.0)	3 (15.0)
Don't know what type of mental health condition (n=16)	6 (37.5)	4 (25.0)	5 (31.3)	14 (87.5)	5 (31.3)	4 (25.0)	1 (6.3)	5 (31.3)