Patterns of Medication Use Associated with Epilepsy and Comorbid Behavioural and Mental Disorders in Older People with Intellectual Disability

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Declaration

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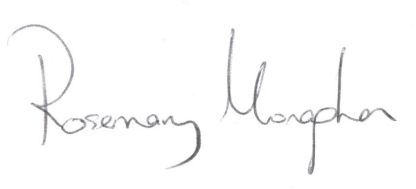

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Summary

Background

There is increasing concern worldwide regarding the levels of use and suboptimal prescribing of psychotropic medication in people with intellectual disability. Antipsychotics, in particular are often prescribed for challenging behaviours rather than a psychiatric diagnosis. A high prevalence of epilepsy can also be found in people with intellectual disability. The pro-convulsive and interactive potential of some psychotropics has led to concerns of possible worsening of seizure control. Antiepileptic drugs (AEDs) may also affect mood and behaviour in people with epilepsy and intellectual disability.

Objectives

The primary objectives of this thesis were i) to examine the demographic and clinical factors relating to the prevalence of epilepsy and use of AEDs, ii) to investigate AED therapy in people with epilepsy using three drug utilisation research methods – monotherapy/polytherapy, AED load <2/≥2 and numerical AED load iii) to examine the use of AEDs and co-prescribed psychotropic medications with the potential to lower the seizure threshold and assess the impact on seizure frequency iv) to determine the relationship between challenging behaviour, use of AEDs and AED load in people with epilepsy v) to investigate the demographic characteristics of older adults reporting a mental health disorder and examine the patterns and use of psychotropic medication.

Methods

Data were drawn from Wave 3 of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA). Medication data were available for 549 participants in Wave 3 (90.1%). For those with epilepsy, psychotropic drugs were categorised according to potential seizure threshold-lowering risk (low, moderate, high). The Behaviour Problems Inventory Short Form (BPI-S) was used to assess challenging behaviours. Antiepileptic drug (AED) load was calculated and median AED loads obtained for those with a reported doctor's diagnosis of epilepsy. Non-parametric tests and binary logistic regression were performed to determine the relationship between AED load and

challenging behaviours. Binary logistic regression was also performed to identify factors associated with seizure frequency and inter-class psychotropic polypharmacy.

Results

The prevalence of epilepsy was found to be 35.8% (n=196). Of participants with seizure data (n=190), 40.5% reported experiencing at least one seizure in the last year. Participants taking at least one medication classified as moderate/high risk for lowering the seizure threshold were significantly less likely to experience a seizure compared to participants taking no medication of this class after adjusting for confounders. Of participants with an epilepsy diagnosis, reporting a regular AED and having behavioural (BPI-S) data, 62.7% were found to exhibit challenging behaviours. Participants with a severe/profound intellectual disability exhibiting self-injurious behaviour (SIB) and aggressive/destructive behaviour were found to have significantly higher median AED loads compared to participants not exhibiting these behaviours. Of participants with medication data and confirmed mental health status (n=513), 61% reported taking psychotropic medication with 35.3% exposed to inter-class psychotropic polypharmacy. Inter-class psychotropic polypharmacy was found to be associated with reporting a mental health disorder and with exhibiting challenging behaviour. Reporting an epilepsy diagnosis was not found to be associated with inter-class psychotropic polypharmacy, adjusting for confounders.

Conclusions

This thesis highlights the significant psychiatric comorbidity associated with both epilepsy and intellectual disability**.** The findings suggest that psychotropic medication in therapeutic doses, recommended to be avoided or used with caution did not provoke increased seizure frequency in this cohort. Challenging behaviours were found to be a considerable problem for older people with intellectual disability and a diagnosis of epilepsy. The findings demonstrate the extensive use of psychotropic medication and the high levels of exposure to inter-class psychotropic polypharmacy in this population group. Understanding the pharmaceutical care complexities, both adverse effects and appropriateness of treatment, is a necessary step to ensuring a good quality of life for people with an intellectual disability.

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Table of Abbreviations

Abbreviation	Term
A&E	Accident & Emergency
AAIDD	American Association on Intellectual and Developmental Disabilities
AAMR	American Association on Mental Retardation
ACE Inhibitor	Angiotensin Converting Enzyme Inhibitor
ADAMS	Anxiety, Depression and Mood Scale
ADHD	Attention Deficit Hyperactivity Disorder
AED	Antiepileptic Drug
AMPA	α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid
ASD	Autism Spectrum Disorder
ATC	Anatomical Therapeutic Classification
BD	Twice daily
BMI	Body Mass Index
BPI-S	Behaviour Problems Inventory-Short Form
CAPI	Computer Assisted Personal Interview
CI	Confidence Interval
CNS	Central Nervous System
COREQ	Consolidated Criteria for Reporting Qualitative Studies
CSPD	Clinical Strategy and Programmes Directorate
CTR	Care and Treatment Reviews
CYP	Cytochrome P450 System
DC-LD	Diagnostic Criteria for adults with Learning Disability
DDD	Defined Daily Dose
DDI	Drug-Drug Interaction

Table of Abbreviations (*Continued*)

Abbreviation	Term
DF	Degrees of Freedom
DPS	Drugs Payment Scheme
DSM-5	Diagnostic and statistical Manual of Mental Disorders (Fifth Edition)
DSQID	Dementia Screening Questionnaire for Intellectual Disability
DURG	Drug Utilisation Research Group
EEG	Electroencephalogram
ELDQOL	Epilepsy and Learning Disability Quality of Life scale
ELSA	English Longitudinal Study of Ageing
ESRI	Economic and Social Research Institute
FDA	Food and Drug Administration
FMRP	Fragile X Mental Retardation Protein
GABA	Gamma (γ)-Aminobutyric Acid
GAS-LD	Glasgow Anxiety Scale-Learning Disability
GDPR	General Data Protection Regulation
GDS-LD	Glasgow Depression Scale-Learning Disability
GMS	General Medical Services
GP	General Practitioner
HA	Health Assessment
HIQA	Health Information and Quality Authority
HPRA	Health Products Regulatory Authority
HPRT	Hypoxanthine-Guanosine Phosphoribosyl Transferase
HRB	Health Research Board

Table of Abbreviations (*Continued*)

Abbreviation	Term
HRCDC	Health Research Consent Declaration Committee
HRR	Health Research Regulations
HRS	Health and Retirement Study
HSE	Health Service Executive
IASSIDD	International Association for the Scientific Study of Intellectual and Developmental Disabilities
ICD	International Statistical Classification of Diseases
ICD-10	International Statistical Classification of Diseases -10 (Edition 10)
ICF	International Classification of Functioning, Disability and Health
ID	Intellectual Disability
IDQOL	Intellectual Disability Quality of Life
IDS-TILDA	Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing
ILAE	International League Against Epilepsy
INN	International Non-Proprietary Name
IQ	Intelligence Quotient
IQR	Interquartile Range
LeDer	The Learning Disabilities Mortality Review
LTI	Long Term Illness
MAOI	Monoamine Oxidase Inhibitors
Mcg	Microgram
MESS	Multi-centre Trial for Early Epilepsy and Single Seizures

Table of Abbreviations (*Continued*)

Abbreviation	Term
Mg	Milligram
MUAC	Mid Upper Arm Circumference
NaSSA	Noradrenergic and Specific Serotonergic Antidepressant
NCPE	National Clinical Care Programme for Epilepsy
NCPPD	National Clinical Programme for People with Disability
NDRI	Norepinephrine and Dopamine Reuptake Inhibitor
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NIDD	National Intellectual Disability Database
NMDA	N-Methyl-D-Aspartate
NRI	Noradrenergic Reuptake Inhibitor
OECD	Organisation for Economic Co-operation and Development
OR	Odds Ratio
OTC	Over-The-Counter
PBSE	Psychiatric and Behavioural Side Effects
PCOS	Polycystic Ovarian Syndrome
PCRS	Primary Care Reimbursement Service
PDD	Prescribed Daily Dose
PEG	Percutaneous Endoscopic Gastrostomy
PI	Principle Investigator
PIN	Personal Identification Number
PIP	Potentially Inappropriate Prescribing
PIQ	Pre-Interview Questionnaire

Table of Abbreviations (*Continued*)

Abbreviation	Term
PMLD	Profound and Multiple Learning Disability
PRN	Pro Re Nata (As Required)
PTSD	Post-Traumatic Stress Disorder
QoL	Quality of Life
RANP	Registered Advanced Nurse Practitioner
RANSAM	Random Sample Design for Ireland
RAPA	Rapid Assessment of Physical Activity
RCT	Randomised Controlled Trial
RDDA	Regional Disability Database Administrator
RIMA	Reversible Inhibitor of Monoamine Oxidase A
SARI	Serotonin Antagonist Reuptake Inhibitor
SD	Standard Deviation
SENsE	Specialist Epilepsy Nurse Evaluation Study
SIB	Self-injurious Behaviour
SIGN	Scottish Intercollegiate Guidelines Network
SmPC	Summary of Product Characteristics
SMR	Standardised Mortality Ratio
SNRI	Selective Norepinephrine Reuptake Inhibitor

Table of Abbreviations (*Continued)*

Abbreviation	Term
SPSS	Statistical Package for Social Sciences
SR	Slow Release
SSRI	Selective Serotonin Reuptake Inhibitor
START	Screening Tool to Alert to Right Treatment
STOMP	Stopping Over Medication of People with a learning disability, autism or both
STOPP	Screening Tool of Older People's Prescriptions
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SUDEP	Sudden Unexpected Death from Epilepsy
SWLS	Satisfaction With Life Scale
TCA	Tri-Cyclic Antidepressant
TCD	Trinity College Dublin
TCAID	Trinity Centre for Ageing and Intellectual Disability
TGA	Transient Global Amnesia
TIA	Transient Ischaemic Attack
TILDA	The Irish Longitudinal Study on Ageing
UGT	Uridine Glucuronyl Transferases
UK	United Kingdom
US	United States
UNCRPD	United Nations Convention on the Rights of Persons with Disabilities
VIF	Variance Inflation Factor
WHO	World Health Organisation
WHOCC	World Health Organisation Collaborating Centre for Drug Statistics Methodology

Presentations & Publications

Presentations (National & International)

Monaghan, R., O'Dwyer, M., Henman, MC., McCallion, P., McCarron, M. Anti-epileptic drug load (AED load), occurrence of seizures and co-administration of pro-convulsive psychotropic drugs in adults with epilepsy and intellectual disability (ID) in Ireland. Sphere Network 6th Annual Conference, Data to Policy. 25th February 2020, RCSI (oral presentation).

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Papers from PhD:

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Monaghan, R., O'Dwyer, M., Luus, R., Mulryan, N., McCallion, P., McCarron, M., Henman, M.C. (2021). The relationship between antiepileptic drug load and challenging behaviours in older adults with intellectual disability and epilepsy. *Epilepsy & Behavior 122; 108191* https://doi.org/10.1016/j.yebeh.2021.108191

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Published Abstracts

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Chapter 1

Introduction

1.1 Intellectual disability

1.1.1 Definition of intellectual disability

'Mental retardation', 'developmental disability', 'learning disability' and 'intellectual handicap' are just some of the spectrum of terms that have been used to describe people recognised as having an intellectual disability. Indeed, 'mental retardation' and 'intellectual handicap' are now deemed to be derogatory terms and their absence in the current literature reflects this. Developmental disability and learning disability are terms widely used in the United States and United Kingdom respectively. Developmental disabilities has been described as an 'umbrella term', consisting of intellectual disability but also other disabilities that become evident in the childhood years [1]. The American Association on Intellectual and Developmental Disabilities (AAIDD) defines them as *"severe, chronic disabilities that can be cognitive or physical or both"*, appearing before the age of 22 and likely lifelong [1]. They can be divided into a physical disability e.g. epilepsy or cerebral palsy or a disability with both a physical and intellectual disability component e.g. Down Syndrome [1]. The AAIDD highlights that intellectual disability embodies the 'cognitive' portion of this definition [1].

With regards to learning disabilities, the National Health Service (NHS) of the United Kingdom defines it as a disability affecting *"the way a person learns new things throughout their lifetime"* [2]. They underline that a learning disability affects how a person understands information received and their communication abilities. In addition, they define a 'profound and multiple learning disability' (PMLD) as *"when a person has a severe learning disability and other disabilities that significantly affect their ability to communicate and be independent"* [2]. However, inability to understand what exactly

constitutes a 'case' has created an impetus to standardise this terminology internationally, resulting in wider use of the term 'intellectual disability' [3].

Different definitions of intellectual disability have also been presented. The World Health Organisation (WHO) defines intellectual disability as *"a significantly reduced ability to understand new or complex information and to learn and apply new skills (impaired intelligence). This results in a reduced ability to cope independently (impaired social functioning) and begins before adulthood, with a lasting effect on development"* [4]. Additionally, the WHO states that the disability is not contingent on a child's health conditions but also on the extent to which environmental factors aid the individuals 'full participation and inclusion in society' [4]. The WHO definition further encompasses children with autism who have intellectual impairments and children who were institutionalised due to perceived difficulties or family rejection who subsequently acquire developmental delays and psychological problems [4]. The AAIDD defines intellectual disability as a *"disability characterised by significant limitations in both intellectual functioning and in adaptive behaviour, which covers many everyday social and practical skills. The disability originates before the age of 18*" [5]. Further confusion arises with the debate as to whether intellectual disability can be considered a disability or a health condition.

1.1.2 Classification of intellectual disability

Three systems currently lead the current classification systems of intellectual disability [6]:

- American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) [7].

- World Health Organisation's International Classification of Diseases 10th Edition (ICD -10) [8].
- American Association on Intellectual and Developmental Disabilities (AAIDD) 12th Edition 2021 [9].

The WHO's International Classification of Functioning, Disability and Health [10], known as ICF, is employed less frequently for diagnostic purposes [6]. The WHO classification system classifies health conditions using ICD-10 with associated functioning and disability classified using ICF [6] .

The following diagnostic criteria are common to each classification system [6]:

a) Deficits in intellectual functioning
b) Deficits in adaptive behaviour
c) Onset during the developmental period

Deficits in intellectual functioning (IQ<70) and deficits in adaptive behaviour are calculated using standardised psychometric tests and scoring two standard deviations below the mean [6]. Both DSM and ICD categorise clinical severity using four classifications - mild, moderate, severe and profound. For ICD-10, IQ score determines the classification. An IQ score between 50 and 69 is classified as mild, between 35-49 is classified as moderate, 20-34 is classified as severe and below 20 is classified as profound [6, 8]. A new classification of mild, moderate, severe and profound intellectual disability was introduced by DSM-5 centred on deficits in adaptive behaviours with a focus in the areas of conceptual, social or practical skills [6, 7].

1.1.3 Prevalence of intellectual disability

In Europe alone, it is estimated that there are 4.2 million people with an intellectual disability [11]. This estimate is based on a 1% prevalence rate from a meta-analysis of 52 studies which found a prevalence of 10.37 per 1000 population [12]. The majority of individuals are believed to have a mild intellectual disability (85%) with 10% moderate, 4% severe and 2% having a profound intellectual disability [13]. The meta-analysis found a higher prevalence of intellectual disability in males in both adult and child/adolescent populations [12]. The male to female ratio fluctuated between 0.7 and 0.9 amongst adults and between 0.4 and 1.0 amongst children/adolescents [12]. Prevalence rates across different income countries were found to greatly differ with the highest prevalence of 16.41 per 1000 population (95% CI 11.14-21.68) found in low income countries, and a decreasing prevalence trend with increasing affluence in countries [12]. A prevalence of 15.94 per 1000 population (95% CI 13.56-18.32) was found in middle income countries and 9.21 per 1000 population (95% CI 8.46-9.96) in high income countries [12].

Regarding the study population, studies examining children/adolescents had a higher prevalence of 18.30 per 1000 population (95% CI 15.17-21.43) compared to adult only studies where the prevalence was found to be 4.94 per 1000 population (95% CI 3.66-6.22) [12]. This highlights a major problem in intellectual disability research. Most research uses 'convenience samples' drawn from easy to manage populations (individuals using services for people with intellectual disability, disability agencies etc.) [14]. However, in most countries, a significant number of adults with intellectual disability do not use services and thus are not known to these bodies/agencies. Emerson (2011) called these the 'hidden majority' [14]. He outlines a number of factors likely contributing to this phenomenon: a) general reduction in health/disability supervision following completion of

education in health and welfare agencies; b) specialised health and welfare support rationing to adults with disabilities; c) stigma of intellectual disability resulting in reluctance to self-identify as having intellectual disability or to use services; d) less impact of intellectual deficiencies in people with intellectual disability in non-educational settings [14].

1.1.4 National Intellectual Disability Database (NIDD) and prevalence of intellectual disability in Ireland

The National Intellectual Disability Database (NIDD) of Ireland is a database that collates information on people with intellectual disability that are entitled to use or avail of specialist disability services. The information collected in this database advises regional and national planning of services by providing information on demographics and current and future expected use [15]. At the end of December 2017, 28,388 people were registered on the NIDD in Ireland, representing a prevalence rate of 5.96 per 1,000 population based on the 2016 census of population figures [16]. The prevalence rate for mild intellectual disability (which is traditionally under-reported) was 1.92 per 1,000 population and the prevalence rate for moderate, severe or profound intellectual disability was 3.49 per 1,000 population [16].

Prevalence by county showed Sligo (10.3/1000) to have the highest prevalence rate and Leitrim (4.3/1000) to have the lowest [16]. Prevalence by gender showed 59.1% (16,768) to be male, while 40.9% (11,620) were female. Interestingly, more males than females were registered with an intellectual disability in all age groups with the exception of those aged 55 years and older, giving an overall ratio of 1.44 to 1 [16]. Of people with moderate, severe or profound intellectual disability, the prevalence of those aged 35 years

and over has increased from 28.5% in 1974 to 49.1% in 2017 reflecting the increasing lifespan of people with an intellectual disability [16]. In total, 27,985 people with intellectual disability were in receipt of services, representing 98.5% of the total population registered on the NIDD [16].

1.1.5 De-institutionalisation and its historical context in Ireland

A core value of the United Nations Convention on the Rights of Persons with Disabilities (UNCRPD) is the right to live independently in a place of one's own choosing [17]. Ireland is in the process of reducing its reliance on institutional residential living arrangements for people with intellectual disability. The focus now is in moving people from 'congregated settings' (institutions with 10 or more residents) to 'community living arrangements' (where each unit contains no more than four residents) [18]. This process follows the publication of two major housing policies for people with disabilities: the Health Service Executive's (HSE) report- 'Time to Move on from Congregated Settings: A strategy for Community Inclusion (2011)' [18] and the Department of the Environment, Community and Local Government's 'National Housing Strategy for People with a Disability 2011-2016' [19]. The 2017 NIDD register comprised of 42.3% of people with intellectual disability living in independent/family settings, 33.7% living in community group home settings and 24.0% living in residential/campus settings [20].

A systematic review on the effect of de-institutionalisation on the quality of life for adults with intellectual disabilities found that moving to community based settings was associated with improved quality of life compared with institutional living [21]. The review found moving to a community setting gave an improved sense of well-being, freedom and independent decision making [21]. Additionally, it was found that housemate compatibility

played an important role and when considered in advance of the move, resulted in individuals having higher quality daily living experiences [21]. Furthermore, the systematic review highlighted the importance of support from staff to facilitate integration into community settings and the essential need to maintain family and other social contacts for an individual's quality of life [21].

1.1.6 Aetiology of intellectual disability

A meta-analysis of population based intellectual disability studies found the causal factor for intellectual disability to be unknown in almost half of the cases that reported causal factors [12]. Antenatal, perinatal and postnatal causes were found to be equally accountable for the remainder with varying estimates for each across the studies. Down Syndrome was found to be a common antenatal factor [12]. Common perinatal factors included injury at birth, asphyxia and intra-uterine growth retardation. Developmental disorders were found to be the most common postnatal causes [12]. The AAIDD has presented a multifactorial approach to aetiology [6, 22]. Risk factors are grouped into four broad categories- biomedical, social, educational and behavioural. Under this classification, perinatal risk factors can comprise of injury at birth (biomedical), paucity of perinatal care (social), rejection by parents (behavioural) and absence of medical referral for intervention services (educational) [6, 22]. Similarly, postnatal risk factors can include malnutrition (biomedical), familial poverty (social), child negligence (behavioural) and delay in diagnosis (educational) [6, 22].

1.1.7 Mortality & life expectancy

For decades, higher rates of premature death have been found in people with intellectual disability compared to the general population [23-25]. Furthermore, people with more severe intellectual disabilities have reduced life expectancies compared to people with mild intellectual disabilities [24, 26]. A study in the UK examined mortality and death certificate reporting in adults with moderate to profound intellectual disability between 1993 and 2006 using standardised mortality ratios (SMRs) [23]. The study found that 17% (n=503) of adults died during the study period with high cause specific mortality found for deaths due to congenital abnormalities (SMR 8560), diseases of the nervous system and sense organs (SMR 1630), mental disorders other than dementia (SMR 1141) and bronchopneumonia (SMR 647) [23]. Over four in ten deaths (41%) recorded in adults with intellectual disability mentioned intellectual disability or an associated condition as a contributory factor [23].

The Confidential Inquiry into premature deaths of people with intellectual disability in the UK reviewed the deaths of 247 people with intellectual disability, aged four and older who were registered with a GP in one of five Primary Care Trust areas of Southwest England who died between the 1st June 2010 and 31st May 2012 [24]. Nearly a quarter (22%) were found to be younger than 50 years with a median age of death of 64 years (IQR 52-75). The median age of death for males with an intellectual disability was found to be 65 years (IQR 54-76), some 13 years younger than the median age (78 years) in the general population of England and Wales [24]. Similar findings for females were found. The median age of death for females with an intellectual disability was 63 years (IQR 54-75), 20 years younger than the median age for the general population (83 years) [24]. Of particular note, deaths which could have been avoided by good quality health care were more common in those

with intellectual disability (37%) compared to those in the general population of England and Wales (13%) [24]. Additionally, contributory factors to premature death in a subgroup of people with intellectual disabilities compared with a comparison group of people without intellectual disabilities included problems in advanced care planning (p=0.0003), adherence to the Mental Capacity Act (p=0.0008), living in inappropriate accommodation (<0.0001), adjusting care as needs changed (p=0.003) and carers not feeling listened to (p=0.006) [24].

In the Irish setting, a study examining the age of death of 1120 people with an intellectual disability who died between 1996 and 2001 found the average age of death to be 45.68 years with no difference in lifespan between men and women [26]. Participant data was drawn from the NIDD and the sample consisted of 52.7% men. The authors found the age of death varied according to factors such as level of intellectual disability, health board region, day services received and residential circumstances. A more severe intellectual disability was also predictive of a shorter life span with the average lifespan for profound intellectual disability found to be 29.38 years and 48.88 years for mild intellectual disability.

A comparative study by McCarron et al. (2015) examined mortality rates in the general Irish population and compared them to rates of those with an intellectual disability using the 2012 NIDD database and the Census of Ireland [27]. They found mortality in people with intellectual disability to be four times greater, with people dying 19 years earlier than those in the general population [27]. Overall mortality in those with an intellectual disability was found to be 8.35% with rates increasing with age of deaths - 27% of adults were aged 60-69 years, 45% aged 70-79 years and 72% aged 80+ years [27]. Males with intellectual disability were found to have a lower average age at death compared with

females with intellectual disability. McCarron et al. (2015) used standardised mortality ratios and found that in the youngest age group, mortality was almost seven times higher in the intellectual disability population [27].

1.1.8 IDS-TILDA study

IDS-TILDA is a nationally representative, longitudinal study of older adults with an intellectual disability in Ireland aimed at investigating the ageing profile, physical and behavioural health, medication use, health service needs, social networks, living situations, community participation and employment [28, 29]. The original sample (Wave 1, 2009/2010) was randomly selected from the NIDD. 1800 'pins' (participant identifiers) were randomly selected by the NIDD consistent with inclusion/ exclusion criteria [30]. Inclusion criteria comprised of age ≥40 years with an intellectual disability (to reflect the lower longevity of people with an intellectual disability), to be registered with the NIDD and to provide written consent to participate and/or family/guardian written agreement if required. Further detail on the IDS-TILDA study design can be found in *Chapter 2* of this thesis.

1.2 Epilepsy

1.2.1 Epilepsy background

Epilepsy is a multifaceted, spectrum disorder, estimated to encompass greater than 25 different syndromes and seizure types with variation in severity among individuals [31-33]. Epilepsy is more common in people with an intellectual disability than the general population [34]. Estimates of the prevalence of epilepsy vary greatly. In people with an intellectual disability, this may be the result of basic population biases and methods

employed [28, 35]. The prevalence of epilepsy in people without an intellectual disability ranges from 0.6% to 1% [36-38]. In studies of both children and adults with an intellectual disability, estimates of 14%-44% have been reported [28, 39]. Indeed, prevalence rates of epilepsy have shown a strong relationship with level of intellectual disability; those with a profound intellectual disability having a high prevalence of epilepsy (53%) and those with mild intellectual disability having a lower prevalence (18.9%) [38, 40].

Despite advances in antiepileptic drug (AED) development over recent decades, ≥30% of patients remain refractory to currently available treatments [41]. This is said to equate to 15 million of the 50 million people worldwide diagnosed with epilepsy and not achieving seizure control despite available AED treatment [41]. Costs attributable to active epilepsy have been estimated to exceed €20 billion in Europe alone [42]. Freedom from seizures is an important predictor of quality of life in people with epilepsy [41]. However, where this is not achieved, other factors such as mood and adverse effects of medication take precedence as quality of life predictors [41]. Little research has been conducted on the burden of epilepsy in people with an intellectual disability. Regardless, inadequately controlled epilepsy can have a considerable impact on quality of life, affecting social relationships, independence, education, work, daily activities, and mortality and can add substantially to the cost of care [43].

A Finnish population based cohort of 245 people with intellectual disability followed prospectively for 40 years, beginning in childhood showed overall mortality in people with epilepsy to be 24% or three times the rate expected in the general population [44]. Half of these deaths related to epilepsy, including a third of deaths due to sudden unexpected death from epilepsy (SUDEP) [44, 45]. Seizures are also the cause of preventable hospitalisations and premature death for people with intellectual disability

[46]. People with intellectual disability are also acknowledged to have a lower life expectancy than the general population, with the probability of survival declining as the severity of intellectual disability increases [27]. For those with co-existing epilepsy, the risk of mortality is increased. [39, 47, 48].

Defining seizure type in people with an intellectual disability can be problematic and is well recognised [49]. An English cross-sectional study of 643 children with intellectual disability found an increase in generalised tonic-clonic and myoclonic seizures and a decrease in partial seizures with increasing disability [50]. The study authors do concede, however, that there was a lack of satisfactory investigation in those with intellectual disability as only 10% of participants had electrophysiological tests conducted [39, 50]. Due to communication difficulties and comorbidities of those with an intellectual disability, it can also be challenging to differentiate epileptic seizures from other comorbid psychiatric conditions or adverse effects of psychotropic medication [29]. Common features of epilepsy in people with intellectual disability compared to those in the general population can be found in *Table 1.2-1.*

Table 1.2-1 Common features of epilepsy in people with intellectual disability compared with the general population (adapted from the Royal College of Psychiatrists UK [51])

Seizures appear early in life. Greater prevalence of genetic or structural brain damage.
Generalised seizures more common than complex partial seizures.
Seizure freedom on first treatment less likely with greater likelihood of life-long seizures.
Greater levels of SUDEP (Sudden Unexpected Death in Epilepsy) and status epilepticus.
Greater prevalence of AED prescriptions and polytherapy.
Greater risk of status epilepticus. Emergency rescue medication protocol more likely to be available.
Greater A&E attendance rates.
Multimorbidity. Difficulties with chewing, swallowing, constipation and PEG feeding.
Limited ability to communicate and contribute to treatment choices.
Greater challenges in measuring treatment success.

1.2.2 Differential diagnosis of epilepsy

A thorough investigation is required to ensure a correct diagnosis of epilepsy. It has been estimated that a quarter of individuals with a diagnosis of both intellectual disability and epilepsy referred to a specialist centre were misdiagnosed [3, 52]. Other potential diagnoses (*Table 1.2-2*) can mimic a seizure [3], such as syncope or paroxysmal disorders, leading to over-diagnosis and potentially inappropriate treatment [34]. Rare movement disorders like Sandifer Syndrome may be left untreated if misdiagnosed as epilepsy or episodic dystonia [53]. This is further compounded in the intellectual disability population with high levels of communication difficulties, comorbidity, polypharmacy and cognitive impairment. Difficulties in reaching a diagnosis are possible where a combination of epileptic and non-epileptic events occur [34]. Where a diagnosis is missed, people may not receive appropriate treatment [34]. An American study examining Rett syndrome in 82 females aged 2-30 years where video/polygraphic/EEG monitoring was undertaken, found that 30% of people with recorded EEG seizure discharges were not receiving AEDs [54].

Table 1.2-2 Differential diagnoses of epilepsy (adapted from Shankar et al. (2019) [3] and Johnson et al. (2008) [55])

	Differential diagnoses of epilepsy
Syncope	Vasovagal, cardiac (arrhythmia or structural), orthostatic hypotension (autonomic failure).
Vascular	Migraine (e.g. basilar artery migraines), transient ischemic attacks (TIA), transient global amnesia (TGA).
Psychiatric	Panic attacks, psychosis, affective disorder, dissociative disorder “pseudo-seizures”, non-epileptic seizures.
Behavioural	Stereotyped behaviour, sensory seeking behaviour, including self-injurious behaviour (SIB).
Metabolic	Hypoglycaemia, insulinoma, hypernatremia, hypocalcaemia.
Movement disorders	Paroxysmal dyskinesia.
Sleep disorders	Parasomnias, narcolepsy, enuresis, obstructive sleep apnoea, cataplexy, nightmares.
Toxic	Drugs - illicit and prescribed, alcohol.

1.2.3 New classification of the epilepsies

A new classification of the epilepsies (2017) was developed by the International League Against Epilepsy (ILAE) Commission for Classification and Terminology [56, 57]. A multilevel classification system was proposed. Motives for revision of the prior classification system included clarity of nomenclature, capacity to classify some seizure types as either focal or generalised, and classification when seizure onset is unknown [58]. The new system classifies seizures as focal, generalised, and unknown onset together with subcategories of motor, non-motor with retained or improved awareness of focal seizures. The following *Tables* (*1.2-3*, *1.2-4*) [58] show the adapted basic and expanded versions of the new classification system.

Seizure classification initially is determined by whether the onset is focal, generalised or unknown [58] . For focal seizures, the classification includes a level of awareness. A focal aware seizure relates to the previous term 'simple partial seizure' and the person is aware of self and environment during the seizure. A focal impaired seizure relates to the previous term 'complex partial seizure' [58].

Table 1.2-3 ILAE 2017 Classification of seizure types (basic version) (adapted from Fisher et al. (2017) [58])

Focal Onset	Generalised Onset	Unknown Onset
Aware/reduced awareness		
Motor Onset Non-motor Onset	Motor - Tonic-clonic - Other motor Non-motor (Absence)	Motor - Tonic-clonic - Other motor Non-motor
Focal to bilateral tonic-clonic		Unclassified [a]

[a] **Unclassified as information unable to place in other categories**

Generalised seizures are divided into motor and non-motor (absence) seizures. The subdivisions are comparable to the 1981 classification with a number of additions [58] - myoclonic-atonic seizures (Doose Syndrome), myotonic-tonic-clonic seizures common in juvenile myoclonic epilepsy, myoclonic absence, and absence seizures with eyelid myoclonia in Jeavons Syndrome [58].

Table 1.2-4 ILAE 2017 Classification of seizure types (expanded version) (adapted from Fisher et al. (2017) [58])

Focal Onset	Generalised Onset	Unknown Onset
Aware/reduced awareness		
Motor Onset - Automatisms - Atonic [b] - Clonic - Epileptic spasms [b] - Hyperkinetic - Myoclonic - Tonic	Motor - Tonic-clonic - Tonic - Clonic - Myoclonic - Myoclonic-tonic-clonic - Myoclonic-atonic - Atonic - Epileptic spasms	Motor - Tonic-clonic - Epileptic spasms
Non-motor Onset - Autonomic - Behaviour arrest - Cognitive - Emotional - Sensory	Non-motor (absence) - Typical - Atypical - Myoclonic - Eyelid myoclonia	Non-motor - Behaviour arrest
Focal to bilateral tonic clonic		Unclassified [a]

[a] Unclassified as information unable to place in other categories
[b] Focal or generalised – level of awareness may or may not be altered.

1.2.4 Alzheimer's dementia & epilepsy in people with Down Syndrome

Alzheimer's type dementia is the dementia type found in the majority of people with Down Syndrome, presenting with neuronal loss, neurofibrillary tangles and neuritic plaques [59]. Occurring over the age of 35 years in the majority of people with Down Syndrome, clinical symptomatology is comparable to symptomatology in the general population with loss of memory, cognitive decline, alterations in adaptive behaviour, neurological changes and

language difficulties [59]. An Irish cross-sectional study of 285 people between the ages of 35 and 74 years with Down Syndrome found a prevalence of dementia of 13.3% with mean age of onset of 54.7 years [59]. The presence of epilepsy was found to be strongly associated with dementia with the majority of cases (64%) of epilepsy occurring after the age of 35 in the dementia group [59]. Another Irish cross-sectional study by Mc Carron et al. (2005) of 124 people with Down Syndrome over 35 years of age, found that epilepsy was significantly more common in people with Alzheimer's dementia (55.5%) compared to people without Alzheimer's dementia (11.4%) [60]. Additionally, epilepsy was found to be more common in people with end stage Alzheimer's dementia (84%) compared to people with mid-stage Alzheimer's dementia (39.4%) (p=<0.001) [60]. A recent review of advances in the area of dementia and Down Syndrome by McGlinchey et al. (2020) highlighted the importance of inclusion of people with Down Syndrome in dementia research from both a scientific and equity viewpoint [61].

1.2.5 SUDEP - Sudden Unexpected Death from Epilepsy

Nashef (1997) proposed a definition for SUDEP *as "a sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicologic or anatomic cause for death* [62]*".* Specific criteria have been outlined to confirm SUDEP [63-65]*:*

1. The victim suffered from epilepsy, defined as recurrent, unprovoked seizures.
2. The death occurred suddenly (in minutes) when known.
3. The victim died unexpectedly, while being in reasonable health.

4. Death occurred during normal activities and benign circumstances.
5. An obvious medical cause of death was not found.
6. Death was not directly caused by a seizure or status epilepticus.

An electronic database study (n=697) in a North London intellectual disability service examined SUDEP using the '*SUDEP and Seizure Safety Checklist*' [66]. They found that one fifth (n=137) of people had a diagnosis of epilepsy, with three quarters having a moderate-profound intellectual disability. Despite the high prevalence of epilepsy and with one third of people suffering prior status epilepticus, surprisingly none of the people contacted (n=103) had awareness of SUDEP [66]. Whether due to difficulty in understanding this concept by people with intellectual disability or lack of education, health literacy in the area of SUDEP for people with epilepsy and intellectual disability would appear to be lacking [66].

1.2.6 Under-representation of people with epilepsy and intellectual disability in research

Despite a high prevalence of epilepsy in people with an intellectual disability, less research has been conducted in this population to date. A study by Shankar et al. (2018) considered all major US, UK, and European conferences for either intellectual disability or epilepsy that took place in the years 2015 and 2016 [67]. They found that less than 2% of presentations at epilepsy conferences were explicitly concerned with intellectual disability and epilepsy. In comparison, 15% were concerned with children with an epilepsy diagnosis [67]. With regards to major intellectual disability conferences, only 1.4% of research presentations were concerned with people with epilepsy and intellectual disability [67]. They also found

that 5% of published research in the field of epilepsy concerned those with intellectual disability while 12% of published research in intellectual disability explicitly identified epilepsy [67]. The study also examined significant international conferences in the fields of epilepsy and intellectual disability and found a similar trend of under-representation [67]. At the 12th European Congress on Epileptology (2016) in Prague, only 1.9% of research related to epilepsy and intellectual disability, compared to 13.6% relating to children with epilepsy. At the intellectual disability IASSID 6th World Congress (2016) in Melbourne, 0.8% (n=3) of research related to epilepsy and intellectual disability [67].

1.3 Healthcare

1.3.1 Morbidity and healthcare for people with intellectual disability

People with intellectual disability are more prone to encounter ill health and die at an earlier age than their counterparts without an intellectual disability [68, 69]. A secondary analysis of a British cross-sectional study examining a nationally representative sample of 12,916 children living in 7070 families (4.7% with intellectual disability), found that children with intellectual disability were significantly more likely (corrected odds ratio 2.49) to suffer ill health compared to those without an intellectual disability, after controlling for age and sex [68]. This study also found that 31% of the increased risk for poorer health can be linked to between group differences in socio-economic position and social capital [68].

The health status of people with an intellectual disability who do not avail of services is also of concern. A cross-sectional study by Emerson (2011) examined self-report data collected from 1,022 people with mild intellectual disability in England, a secondary analysis of data extracted from the survey 'Adults with Learning Disabilities 2003/4' [14]. He found adults with an intellectual disability not availing of intellectual disability services

were more likely to smoke tobacco and less likely to access some health services and promotion activities compared to adults with intellectual disability who avail of intellectual disability services [14]. They were also more likely to be exposed to some known social determinants of poorer health including greater material hardship, living in more deprived neighbourhoods, and reduced community and social participation [14].

1.3.2 Provision of healthcare in Ireland for people with intellectual disability

The Health Service Executive (HSE) in Ireland provides a variety of services for people with intellectual, physical and sensory disabilities [70]. Eligible individuals are able to access health services including assessment, rehabilitation, community, and residential care [70]. Medication can be obtained under a number of community drug schemes including the General Medical Services (GMS), Drugs Payment Scheme (DPS) and Long Term Illness (LTI) schemes. For GMS, the prescription charge is €1.50 for each item that is dispensed up to a maximum of €15 per calendar month in 2021. For people over 70 years, the GMS charge is €1 per item up to a maximum of €10 per calendar month in 2021. For people not entitled to a GMS (due to income threshold), a maximum DPS fee of €114 per family unit is payable per calendar month in 2021. The LTI scheme on the other hand, enables individuals with a limited number of illnesses/disabilities (n=16) to obtain medicines and approved appliances for free without the necessity to be means tested, in contrast to the GMS scheme. The LTI scheme is administered by the HSE under section 59 of the Irish Health Act 1970 which states *"A health board may make arrangements for the supply without charge of drugs, medicines, or medical and surgical appliances to persons suffering from a prescribed disease or disability of a permanent or long-term nature*" [71]. Intellectual disability and epilepsy are included as some of the illnesses/disabilities eligible under the

LTI scheme. Cerebral Palsy and Phenylketonuria may also be relevant for people with an intellectual disability. The following is a list of conditions covered by the LTI scheme:

a) Intellectual Disability

b) Mental Illness (under the age of 16)

c) Diabetes Insipidus

d) Diabetes Mellitus

e) Haemophilia

f) Cerebral Palsy

g) Phenylketonuria

h) Epilepsy

i) Cystic Fibrosis

j) Multiple Sclerosis

k) Spina Bifida

l) Muscular Dystrophies

m) Hydrocephalus

n) Parkinsonism

o) Acute Leukaemia

p) Conditions arising from use of Thalidomide

A full list of current eligible medications/devices for these conditions is available from URL (updated August 2020): https://www2.hse.ie/services/long-term-illness-scheme/approved-medications.html.

1.3.3 Provision of epilepsy care in Ireland

Historically in Ireland, the specialist care for epilepsy and mental health problems for people with intellectual disability was often managed by psychiatrists. In 2009, a major healthcare reform agenda launched in Ireland, with the HSE creating the Quality and Clinical Care Directorate which was then divided into the Quality and Patient Safety Directorate and the Clinical Strategy and Programmes Directorate (CSPD) [72]. The role of the CSPD was to *"develop a national, strategic and co-ordinated approach for the design of clinical service improvements, in order to deliver the triple aim of improved patient care, improved access and better use of resources"* [72].

Improvements in services were needed across many specialities, including epilepsy. A phenomenological study using one-to-one interviews with 19 participants regarding health care journeys experienced by people with epilepsy in Ireland by Varley et al. (2010) highlighted a number of deficiencies in the provision of care in Ireland at that time – delayed access to specialist epilepsy reviews, uncertainty as to the competency and function of primary care centres, significant unmet needs for women with epilepsy, poor organisation of existing epilepsy services, and inadequate patient information [73]. To address these historical deficits in epilepsy care in Ireland, the National Clinical Care Programme for Epilepsy (NCPE) was developed in 2010 and is now an example of emerging best practice [74, 75]. This programme aims to *"deliver a holistic model of integrated person-centred care that addresses the full spectrum of biomedical and psychosocial needs of people with epilepsy"* [76].

The objectives of the programme were [74]:

1. To improve access to expert care and information.
2. To improve the quality of care across the health care spectrum.

3. To improve value conscious care by shifting care where possible from expensive hospital care to the community.

Governance of the NCPE consists of two supervisory groups – a project group and a clinical advisory group [74]. A specialised doctor in intellectual disability is a member of the clinical advisory group [74]. The service is led by Registered Advanced Nurse Practitioners (RANP) in epilepsy seeking to improve existing services, reconfigure services to a more appropriate community setting, and develop outreach clinics in intellectual disability services and non-acute hospitals supported by a multidisciplinary specialist team [74].

The SENsE (Specialist Epilepsy Nurse(s) Evaluation) study was created to examine how Epilepsy Specialist Nurses in Ireland undertook their clinical role and the impact on care using a qualitative descriptive study design - 12 interviews with Epilepsy Specialist Nurses in five hospital based epilepsy services, 24 interviews with multidisciplinary team members and five focus groups of 35 people with epilepsy and their family members [77]. The study found that Epilepsy Specialist Nurses were 'key players' in helping people manage their illness through comprehensive assessments, person centred education, monitoring the impact of care and treatment, providing education to family and carers, and co-ordinating care to enhance a patients' journey [77].

1.3.4 Multimorbidity in Intellectual disability

Multimorbidity has been defined as the co-occurrence of two or more chronic health conditions in any one individual [78, 79]. It is linked to diminished health outcomes, poorer functioning and quality of life, explicit health care needs, with elevated health expenditure [80]. In the general population, Kirchberger et al. (2012) in the population based KORA-Age study of 4,127 people aged 65-94 years living in the German city of Augsburg and two

surrounding counties, found a greater propensity among older people to develop two or more chronic conditions [80]. They found a prevalence of multimorbidity of 58.6% with hypertension and diabetes, and hypertension and stroke as the diseases most commonly occurring in combination after adjusting for age, sex and presence of other conditions [80]. Factor analysis was undertaken and they identified four patterns of multimorbidity namely cardiovascular and metabolic diseases; joint, liver, lung and eye diseases; mental and neurological diseases; and gastrointestinal disease and cancer [80]. However, an Irish cross-sectional study of 551 people with intellectual disability from the IDS-TILDA Wave 2 cohort, found the prevalence of hypertension in older adults with intellectual disability to be lower than reports in the general population [81]. Interestingly, the total levels of treatment and control were higher in the intellectual disability population in this study (when diagnosed) compared to the general Irish population [81].

People with intellectual disability have considerable healthcare needs owing to significant comorbidity and increasing longevity [27, 79]. A large cross-sectional study by Carey et al. (2016) of an English Primary Care GP database involving 14,751 adults with intellectual disability aged 18 - 84 years, compared with 86,221 age, sex and practice-matched controls, found that patients with intellectual disability had increased prevalence of recorded epilepsy, severe mental illness and dementia, in addition to moderately increased prevalence of hypothyroidism and heart failure [82]. Surprisingly, they found the recorded prevalence of ischaemic heart disease and cancer to be approximately 30% lower than the general population [82]. Patients with intellectual disability had an average yearly number of primary care consultations of 6.29, higher than the 3.89 for the matched controls. However, patients with intellectual disability were found to be less likely to have longer doctor consultations and had lower continuity of care with the same doctor [82].

People with intellectual disability were also found to have a greater likelihood of multiple comorbidities with 22.9% having two or more recorded conditions, compared to 13.3% in the control group [82]. A 18.5% prevalence of epilepsy was found, lower than in other studies, but the authors note that this lower number may represent an improvement in diagnosis due to concern that epilepsy may be over-diagnosed in people with intellectual disability [82].

Furthermore, a population based cross-sectional study by Cooper et al. (2015) examining primary care data of 1,424,378 adults registered with 314 representative Scottish practices found a much greater burden of multimorbidity including earlier onset and different health condition presentation in adults with intellectual disabilities compared with the general population [83]. They found adults with intellectual disabilities had a significantly higher prevalence of five of the six mental health conditions examined (schizophrenia or bipolar disorder/anxiety and other neurotic, stress related, and somatoform disorders /dementia/depression/alcohol misuse) with no significant difference found for anorexia/bulimia [83]. Regarding mental health conditions, the biggest difference following adjustment for age, sex and deprivation was found for schizophrenia/bipolar disorder (OR 7.16, 95% 6.49-7.89) followed by anxiety (OR 2.62 95% 2.41-2.84). Depression was the most prevalent mental health condition in those with an intellectual disability (15.8%) compared to 10.1% of controls [83]. In this study, Cooper et al. (2015) highlight how adults with intellectual disability tend to lead sedentary lives with no exercise, suffer mobility issues, and have a poorer diet compared to the general population [83]. They also emphasise how polypharmacy is more likely to be prescribed, which can result in side effects and drug interactions [83].

An Irish study of 753 older adults with intellectual disability by McCarron et al. (2013) found that 71% of the IDS-TILDA sample in Wave 1 reported multimorbidity [79]. The highest prevalence was found in women, and multimorbidity was not solely established among the older age groups but also high (63%) among those in the 40-49 age group [79]. Mental health and eye problems were found to be most often associated with a second condition. Mental health/neurological disease was the most prevalent multimorbidity configuration [79].

1.4 Mental health

1.4.1 Prevalence of mental health problems in people with intellectual disability

Smiley (2005) highlights the methodological challenges of studying mental health in populations of people with intellectual disability [84]. The wide variation of prevalence rates need to be considered in the context of the individual study, including the population studied, the definition of mental health problems, diagnostic criteria employed, and method of assessment [84]. Unlike those suffering from a mild intellectual disability, case registers, social funding and intellectual disability services aid identification of adults with a moderate to profound intellectual disability. For those with mild intellectual disability, unless they avail of medical services (e.g. mental health services), a reduced use of services results in lack of identification, less inclusion in research activities, and ultimately sample bias [84].

The multiplicity of definitions for what constitutes a 'mental illness' also leads to difficulty in comparison of prevalence studies [84]. Many studies use terms like mental illness, psychiatric illness, mental disorder, psychotic disorder, and behavioural/emotional problems. Another issue lies in the diagnostic criteria - be it the WHO International

Classification of Diseases or the American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders (DSM), currently in its fifth edition. It is worth noting that these systems were designed for use in the general population and their sensitivity may be lacking in the intellectual disability population with dependence on subjective reporting of symptoms [84]. The Diagnostic Criteria for adults with Learning Disability (DC-LD) by the Royal College of Psychiatrists in the UK sought to improve the deficiencies in other diagnostic criteria in the intellectual disability population [84].

However, regardless of system used, identifying mental health problems in the intellectual disability population requires great skill as many people with an intellectual disability are incapable of identifying or indeed reporting psychiatric symptoms and rely on others to do so on their behalf [84]. Reid (1972) found that schizophrenia was difficult to identify in people with an intellectual disability due to communication deficits making diagnosing psychoses and hallucinations problematic [85]. A UK cross-sectional study by Bhaumik et al. (2008) found that among 2711 adults with intellectual disability, 45.9% accessed specialist psychiatric services at least once between 2001 and 2006 [86]. They found that people attending psychiatric services were more likely to be of older age and living in residential settings, whereas those less likely were of South Asian origin and have mild/moderate intellectual disability [86]. Of the total study population, the prevalence of psychiatric disorders was found to be 33.8%, with behavioural disorders (19.8%) and autistic spectrum disorders (8.8%) being the most prevalent. In addition, a high prevalence of epilepsy (60.8%) was found among those attending psychiatric services without a mental health diagnosis [86].

Epilepsy is associated with a variety of mental health problems [87, 88]. A systematic review of neuropsychiatric comorbidities in people with both epilepsy and

intellectual disability by van Ool et al. (2016) found that a greater epilepsy severity, having generalised seizures, increased frequency/severity of seizures, and a higher number of seizure types were risk factors for psychiatric and behavioural disorders [87]. A Scottish database study by Espie et al. (2003) examining a random sample of 186 adults with epilepsy and intellectual disability found that one third of patients with epilepsy and intellectual disability met criteria for having a psychiatric disorder, especially affective/neurotic disorders [88]. They found seizure related factors to be the strongest risk factors for a psychiatric diagnosis [88]. Furthermore, a Dutch cross-sectional study of 189 people with epilepsy and intellectual disability, part of the TRIANGLE study (The Relation between epilepsy, ID And Neuropsychiatric comorbidities in a Group of patients in Long-term care for Epilepsy), found that intellectual disability characteristics were significantly associated with depressive and anxiety symptoms [89].

1.4.2 Diagnostic overshadowing in mental health

Diagnostic overshadowing in mental health, meaning accrediting possible signs and symptoms of mental illness to the intellectual disability instead of consideration of a psychiatric diagnosis, poses significant difficulties for people with intellectual disabilities [84, 90]. In a study of 75 adolescents aged 12-19 years with intellectual disability in the UK, Hassiotis et al. (2012) found considerable mental health challenges faced by participants were often unidentified and untreated [91]. The prevalence of mental ill health rose from 51% reported by parents to 67% following clinical assessment. A UK study examining diagnostic overshadowing bias using case vignettes by Mason et al. (2004) of 133 psychologists and 90 psychiatrists found a reduced likelihood of considering a schizophrenic diagnosis and drug and alcohol problems, in addition to reduced

consideration of psychiatric admission or use of medication in people with intellectual disability [90]. The authors note that in some cases psychiatrists were affected by diagnostic overshadowing more often than psychologists [90].

1.5 Behavioural problems

1.5.1 Definition of challenging behaviour

Behaviour exhibited by people with intellectual disabilities was historically described as 'inappropriate', 'abnormal', 'disordered', 'dysfunctional', 'problematic,' or 'maladaptive' [92]. Newer terminology sought to avoid diagnosing the person and present the issues as a 'challenge to services' [92-94]. The term 'challenging behaviour' was thus defined as *"culturally abnormal behaviour(s) of such an intensity, frequency or duration that the physical safety of the person or others is likely to be placed in serious jeopardy, or behaviour which is likely to seriously limit use of, or result in the person being denied access to, ordinary community facilities"* [94]. However, despite attempts to focus the attention on the environment rather than the individual, the use of personal pronouns (e.g. his/her challenging behaviour) imply the problem lies with the individual [92]. Thus this interpretation neglects to recognise that environment plays a huge role and that behavioural issues have a social construct [92]. As Emerson and Einfeld highlighted, the setting where the behaviours occur influences whether or not the behaviour is considered challenging [94]. This has led to greater use of the term 'behaviours that challenge' in some settings. Categories of challenging behaviours or behaviours that challenge include self-injurious behaviour, aggressive/destructive and stereotyped behaviour [95].

1.5.2 Self-injurious behaviour (SIB)

In the simplest terms, SIB signifies a group of behaviours resulting in injury to the individual themselves [96]. The term has been said to encompass a string of 'self-injurious responses', often repetitive, occasionally rhythmical and devoid of noticeable 'reinforcers' [97]. It is a regularly observed phenomenon in people with epilepsy and intellectual disability [98]. An Italian, matched, controlled study of SIB, found a non-significant prevalence of SIB of 44% in the intellectual disability and epilepsy group (n=158), and 46.5% in the intellectual disability and no epilepsy group (n=195) [98]. The authors noted that the most common types of SIB exhibited were self-biting, and self-hitting with hands and objects [98]. Self-injurious behaviour has also been associated with more severe forms of intellectual disability [98-100]. A Finnish study in an institutional setting of 421 people with intellectual disability found an overall prevalence of SIB of 40.6%, intermittent in 27.1% of cases, becoming frequent in 13.5% [99]. Self-slapping, self-scratching, head banging, self-biting, and self-smearing were found to be the most common behaviours, appearing in greater than 10% of cases [99].

A higher prevalence rate in residential/institutional settings compared to community based settings may be accounted for by the increased necessity of residential care for people presenting with SIB [96]. An Irish epidemiological study of 429 people with a moderate, severe or profound intellectual disability who originated in a specific geographical area were traced to avoid studying a convenience sample which might contain a greater number of people exhibiting challenging behaviours [101]. A prevalence of 14.4% of SIB was found among the 429 children and adults with intellectual disability over a one-month interval [101]. The authors noted that exhibiting SIB is the reason many with SIB live in a residential setting [101].

1.5.3 Aggressive/destructive behaviour

Aggressive/destructive behaviours have been defined as *"abusive, deliberate attacks against other individuals or objects"* [102]. A review of aggressive behaviour in people with intellectual disability found that greater than 50% of people engage in some type of aggression with few engaging in aggression of high frequency or severity [103]. The review also highlights the multifactorial nature of aggression in adults, and notes that escape was the most likely factor where a single factor was identified [103]. A meta-analytic study examining risk markers associated with challenging behaviours in people with intellectual disabilities found that males were significantly more likely to exhibit aggression [104]. Aggression was also associated with a diagnosis of autism and lack of 'expressive communication' skills [104]. A Welsh vignette study by Tynan and Allen (2002) exploring carer attributions for aggressive behaviour in 42 residential care staff found that people with mild intellectual disability were believed to have significantly more control over factors causing the aggressive behaviour compared with people with severe intellectual disabilities [105]. Concerning epilepsy, a Dutch cross-sectional study of challenging behaviour in 189 people by van Ool et al. (2018) investigating challenging behaviour in adults with epilepsy and intellectual disability found that clinically deviant aggression was associated with intellectual disability characteristics rather than being related to epilepsy [106].

1.5.4 Stereotyped behaviour

Stereotyped behaviours have been defined as *"peculiar, or inappropriate voluntary acts which occur habitually and repetitively"* [102]. Intellectual disability is often associated with stereotyped behaviour [107], and stereotypy has been found to be more common in

people with a severe/profound intellectual disability [104]. In a Dutch cross-sectional study of 189 people with epilepsy and intellectual disability by van Ool et al. (2018), clinically deviant stereotyped behaviours were found with significantly greater frequency in people with a mixed seizure type epilepsy that is difficult to treat [106]. In addition, an Italian observational study of 121 children examining repetitive behaviours in autistic disorder found an association between stereotyped behaviours and developmental level [108]. Interestingly, it has also been shown that people with autism spectrum disorder (ASD) and intellectual disability exhibit more stereotypical behaviours than people with intellectual disability without ASD [109-111]. A Dutch study examining 59 participants with intellectual disability with and without ASD found that violent head banging and finger flicking was exhibited exclusively by people with ASD while pacing, bouncing and balancing of objects was only exhibited by people without ASD [110]. Typically, people with ASD were found to exhibit a greater variety of stereotypical behaviours, have a greater frequency of exhibiting stereotyped behaviours and exhibited the behaviours for longer durations [110].

The following *Table* (1.5-1) illustrates the behavioural phenotypes of some common genetic disorders associated with intellectual disability.

Table 1.5-1 Behavioural phenotypes of genetic disorders

Disorder	Behavioural Phenotype
Down Syndrome	Down Syndrome is the most frequent chromosomal cause of intellectual disability [112]. In the majority of cases (95%), it arises from trisomy 21 (extra chromosome 21) [113]. Other aetiologies include translocations between genetic material on chromosome 21 and another chromosome or mosaicism (a developing embryo/zygote with one cell line having the trisomy 21 error and one cell line not having the error) [113]. Most people with Down Syndrome have a mild or moderate intellectual disability [112]. With regards to epilepsy, a systematic review found a pooled prevalence of 12.4% for people with Down Syndrome with an increased prevalence in older age groups [114]. A UK longitudinal study of 201 people aged 16 years and older that examined epilepsy and associated effects on adaptive behaviour in adults with Down Syndrome, found that adults with Down Syndrome and epilepsy achieved significantly higher on the adaptive behaviour profile. However, they did not have significantly greater maladaptive behaviours [115].
Fragile X Syndrome	Fragile X Syndrome, formerly known as Martin-Bell Syndrome belongs to a group of FMR1 mutation related disorders, termed fragile X associated disorders [116]. It is caused by repetition of the trinucleotide sequence (CGG) in the X chromosome at position Xq27.3 leading to reduction in a protein called FMRP (Fragile X Mental Retardation Protein) resulting in irregular brain development and the characteristic phenotype [116]. Maximum mutation occurs when an individual has greater than 200 CGG repeats [117]. It is the most common inherited cause of intellectual disability, with a greater prevalence in males due to males possessing a single X chromosome [117]. This phenotype is most commonly identified by facial characteristics, notably a long face shape and pronounced ears. Individuals with Fragile X Syndrome often display distinctive behavioural and emotional instabilities [94]. The behavioural phenotype is characterised by distinctive behavioural features including hyperactivity, inattentiveness, restlessness, fidgeting, impulsive tendencies, distractibility, and stereotypical movements, for example hand flapping [116]. Word finding difficulties and verbal dyspraxia are common features of this syndrome [118]. Self-injurious behaviour (SIB) is common in individuals with Fragile X Syndrome [94]. A US survey study examining fragile X in young boys (n=55) found that 58% of participants exhibited SIB with a mean age of onset of 31 months [117]. They found biting to be the most frequently reported self-injury behaviour with a disproportionate focus on the fingers and back of the hand [117].
Angelman Syndrome	Angelman Syndrome results from the deletion of section 15q11.2-q13 on the maternally inherited chromosome [112]. Indeed, Angelman Syndrome and Prader Willi Syndrome represent the earliest depicted examples of 'genomic imprinting', whereby differential expression of a gene is governed corresponding to maternal or paternal origin [119]. In 1965, a seminal paper by Angelman [120] described this syndrome in what was termed '*puppet children'*. The behavioral phenotype portrayed included feeding issues, sleep disorders, restlessness, hyperactivity, excessive chewing, hand flipping, aggression, stubbornness, tantrums, euphoria, and anxiety [112]. Greater than 80% of people affected by this syndrome are believed to develop a seizure disorder with early onset (typically before age of 3 years), presenting with febrile convulsions [121]. The seizure disorder is characterised by a symptomatic generalised epilepsy with myoclonus, drop attacks, atypical absences and tonic-clonic seizures [121].

Table 1.5-1 Behavioural phenotypes of genetic disorders (*Continued*)

Disorder	Behavioural Phenotype
Prader-Willi Syndrome	Prader-Willi Syndrome is caused by numerous genetic mechanisms affecting the long part of chromosome 15 including parental deletion (70%), maternal disomy (25%) and unbalanced translocations and mutations of the imprinting centre (5%) [94, 112]. Most people with Prader-Willi Syndrome have a mild to moderate intellectual disability [112]. The behavioural phenotype includes neonatal hypotonia, feeding difficulties in early childhood followed by excessing eating and ultimately obesity, temper tantrums, aggression, skin picking, compulsive traits (e.g. hoarding, exactness), mood symptoms, irritability, depression, and major anxiety [112]. People with Prader-Willi Syndrome are particularly susceptible to irregularities in hypothalamic function related to growth, appetite, temperature control, and sleep [94].
Tuberous Sclerosis Complex	Tuberous Sclerosis Complex is an autosomal, dominant, genetic condition, resulting from mutations in TSC1, the gene on chromosome 9q34 and in TSC2, the gene on chromosome 16p13 [122, 123]. It is frequently responsible for instigating epilepsy, intellectual disability and autism [122, 123]. Indeed, epilepsy is believed to occur in 70-80% of people with Tuberous Sclerosis Complex, with involvement of all seizure subtypes [122, 123]. Onset is typically in childhood [123]. Epilepsy in Tuberous Sclerosis is believed to be due to the presence of cortical tubers, where abnormal activity in dysplastic neurons, giant cells and glial components results in epileptogenesis [123]. Seizures and epilepsy associated with Tuberous Sclerosis Complex is regularly refractory to drug treatment despite AED polytherapy [122, 123].
Velo-Cardio-Facial Syndrome	Velo-Cardio-Facial Syndrome results from a deletion at 22q11.2 and is also known as 22q11.2 Deletion Syndrome or DiGeorge Sequence, Conotruncal Anomalies Face Syndrome, CATCH 22 and Sedlackova Syndrome [94, 124]. It has an extensive phenotype with greater than 180 clinical features incorporating every organ and body system [124]. No single feature is distinctive in all cases; thus a diagnosis is made by deletion of DNA from chromosome 22 at the q11.2 band in the critical region [124]. Medical problems including congenital heart disease, immune disorder deficiencies, cleft palate, feeding issues, and developmental disorders present in the infancy years [124]. In adolescence, cognitive, behavioural, and learning disabilities are evident, with psychiatric disorders presenting in late adolescence and the adult years [124]. A UK study of 50 adults aged 17 years and above with Velo-Cardio-Facial Syndrome, found a 30% prevalence of psychotic disorder made up largely of schizophrenia (24% satisfying DMS-4 criteria for schizophrenia) [94, 125]. Indeed, the risk for severe psychiatric illness is believed to be 25 times greater for people with Velo-Cardio-Facial Syndrome compared to the general population [124].
Klinefelter Syndrome	Klinefelter Syndrome is the most commonly found sex chromosome disorder [126]. Affected males carry an extra X chromosome resulting in the karyotype 47, XXY [126-128]. Male hypogonadism, androgen deficiency, and impaired spermatogenesis are characteristic features of this syndrome [126]. Intellectual ability can range from normal intellectual functioning to cognitive deficits and intellectual disability [127]. A high prevalence of psychiatric disorders can be found in people with Klinefelter Syndrome, and it is a risk factor for psychosis [128].

Table 1.5-1 Behavioural phenotypes of genetic disorders (*Continued*)

Disorder	Behavioural Phenotype
Lesch-Nyhan Syndrome	Lesch-Nyhan Syndrome is a rare X-linked disorder resulting from a mutation in the purine salvage enzyme hypoxanthine-guanosine phosphoribosyl transferase (HPRT) [129, 130]. Characteristics of this syndrome include intellectual disability, dystonia, gout, aggressive behaviour and SIB. [129, 131]. Self-injurious behaviour traits include a partial or total damage of oral and perioral tissues and/or fingers with biting of fingers, hands, cheeks, lips, and persistent banging of head or limbs [132]. Epilepsy is believed to affect about 50% of children with Lesch-Nyhan Syndrome with microcephaly also common [133].
Cri-du-chat	Cri-du-chat is a French phrase, translated as 'cry of the cat', named after the cat-like cry of affected children [134]. The majority of cases result from de novo deletion of chromatin from the short arm (p) of chromosome 5, although 10-15% of cases are believed to occur due to unbalanced translocations [134] . Prevalence is believed to be 1 in 37,000 to 1 in 50,000 live births [134]. Characteristics of this syndrome include intellectual disability, craniofacial dysmorphisms, and behavioural issues including SIB and aggressive behaviour [134].
Rett Syndrome	Rett Syndrome is a developmental disorder, primarily seen in females, caused by mutations in the gene encoding methyl-CpG binding protein 2 (MeCP2) [135-137]. It is usually lethal in males and occurs in 1 in 10,000 to 1 in 23,000 girls worldwide [112, 136]. Motor developmental delay is often the initial presentation of this syndrome with sometimes a sudden onset of autistic features in late infancy to early childhood [138]. Syndrome progression results in patients losing use of their hands and developing stereotypic hand wringing and washing movements [135]. Clapping and flapping of the hands also presents in some individuals [135]. Patients can develop SIB, irritability, social withdrawal, and seizures [135]. The EEG of individuals is typically abnormal, with generalised slowing, rhythmic slow activity, epileptic-form activity like focal and generalised spikes, and sharp waves even in the absence of clinical seizures [55]. It is estimated that 50-80% of people with Rett Syndrome develop epilepsy [137]. A study of 602 people from The Rare Disease Consortium Research Network for Rett Syndrome project found seizures in Rett Syndrome to be common, with an age associated onset, varying by mutation, and related to increased clinical severity [137]. Epilepsy in Rett Syndrome often responds poorly to AEDs making it difficult to treat [55].

1.6 Medication use in people with intellectual disability

1.6.1 Polypharmacy

Understanding the prevalence of polypharmacy in a population is complicated by a variety of definitions of polypharmacy in studies, necessitating greater consistency to benefit comparison [139]. Polypharmacy has been defined as "*the concurrent use of multiple medications including both psychotropic and non-psychotropic drugs"* [139]. On a practical level, O'Dwyer et al. (2016) defined polypharmacy as use of five to nine medications, excessive polypharmacy as concurrent use of ten or more medications and no polypharmacy as individuals taking four or less medications [140]. O'Dwyer et al. (2016) studied 736 older adults with intellectual disability in the IDS-TILDA study in Ireland and found a 90% prevalence of medication use, with 31.5% of participants reporting polypharmacy and 20.1% reporting excessive polypharmacy [140]. They found that living in a residential institution and reporting a mental health or neurological condition was associated with polypharmacy and excessive polypharmacy, after adjusting for confounders [140].

A population-based survey study of people with an intellectual disability undertaken in the state of Victoria, Australia, analysed 897 people aged 18-82 and found that 20.9% of people with an intellectual disability were exposed to polypharmacy (defined as concurrent use of five or more prescribed medicines) [141]. They found polypharmacy to be significantly associated with the age groups 40-59 years and 60+ years, unemployment, inability to get help from friends if needed, and inability to get help from friends or family in an emergency. Interestingly, they also found that the prevalence of polypharmacy increased by 42% for every category increase in severity of intellectual disability [141].

A study in the older general population in Italy examined an outpatient pharmacy database of 887,165 people aged 65 years and over and found that 39.4% of people were exposed to at least one episode of polypharmacy in the study period [142]. They found the top three classes of medications involved in polypharmacy to be anti-thrombotics, drugs for peptic ulcer disease, gastro-oesophageal reflux disease, and angiotensin converting enzyme (ACE) inhibitors [142]. Conversely, O'Dwyer et al. (2016) in their intellectual disability study found the top three classes of medications involved in polypharmacy to be antipsychotics, antiepileptics and laxatives [140], illustrating the difference in prescribing between people with an intellectual disability and the general population.

High levels of AED polytherapy are also found in people with epilepsy and intellectual disability [143], with a greater prevalence of drug resistant epilepsy [51]. O'Dwyer et al. (2018) in an Irish retrospective cross-sectional study using IDS-TILDA Wave 1 data examined AED use in 205 older people with epilepsy and intellectual disability and found that half (50.3%) of participants who reported taking an AED were exposed to AED polytherapy [29]. In addition, 63 different polytherapy regimens were reported [29]. However, only three in ten participants taking AED polytherapy reported being seizure free for the previous two years [29]. A retrospective observational study in England by Ring et al. (2009) of 183 people with epilepsy and intellectual disability known to five adult services in one county, found that 59% of participants were taking AED polytherapy and 39.9% AED monotherapy [144]. The study found that 23% of participants were taking three or more AEDs [144]. Of those taking AED monotherapy, no differences were found in mean monthly seizure frequencies between different AEDs, and for those taking two AEDs, no specific combination was associated with a significantly lower seizure frequency [144]. Additionally, a Welsh general practice study by Matthews et al. (2008) of 318 adults with

intellectual disability in 40 general practices found that 58 people (18%) had a diagnosis of epilepsy [145]. Medication data was available for 57 of these participants and the study found that 5.3% took no regular AED, 42.1% took AED monotherapy and 52.7% AED polytherapy [145]. Participants with very poorly controlled seizures were found to be prescribed more AEDs at a significantly higher average dosage in terms of percentage of BNF maximum doses [145].

1.6.2 Medication use in older people

Prescribing suitable pharmacotherapy to older people involves weighing up the risks and benefits of their medications [146]. This is extremely important due to higher levels of frailty in the older population [146]. Frailty has been described as *"the condition that is characterised by the loss of functional reserve, physical decline, increased susceptibility to disease and higher risk of disability and mortality"* [146]. Indeed, in the intellectual disability population, older adults tend to be frail at a younger age, which could lead to increased drug sensitivity [147]. A Dutch cross-sectional study 'Healthy Ageing with Intellectual Disability' of 982 people, aged 50 years or over with intellectual disability found that people over the age of 50 had frailty scores similar to most elderly people in the general population over 75 years [148]. More severe intellectual disability was associated with higher frailty scores [148]. Factors contributing to increased risk of adverse drug reactions in older people include pharmacokinetic and pharmacodynamic ageing changes, increased comorbidity, and polypharmacy [146].

For people with intellectual disabilities, difficulties in swallowing, tooth loss, and dental complications may affect the oral consumption of medication [147]. An Irish cross-sectional study in the intellectual disability population by Mac Giolla Phadraig et al. (2015)

of 478 IDS-TILDA Wave 1 participants found that older people with intellectual disability are more likely to be edentulous compared to their non-intellectual disability peers (34.1% vs 14.9%), and that 61.3% of edentulous older people with intellectual disability were without dentures [149].

Geriatric patients are also understood to have impaired homeostasis with wide variability among individuals [150]. A significant age associated decrease in creatinine clearance is found in older people [150]. Moreover, hepatic metabolism of numerous drugs is reduced in older people. This results in increased bioavailability of drugs with substantial first pass effects and reduces the clearance of drugs metabolised in the liver [150]. Additionally, prodrug activation is decreased leading to reduced drug efficacy in the elderly [150].

Specifically with regards to AEDs, there is limited evidence of their safety, efficacy and tolerability in the older population [151]. Some AEDs with anti-cholinergic effects and enzyme inducing effects can have a negative impact on cognition [151]. This is particularly true of first generation AEDs, like carbamazepine [151]. AEDs are also associated with adverse effects on bone [151-153], particularly detrimental in older age. Phenytoin is reported to increase the catabolism of vitamin D, thus accelerating bone turnover [154, 155]. Valproic acid is known to interfere with osteoblasts [151, 154]. The narrow therapeutic index of some AEDs (carbamazepine, phenytoin), potential for drug-drug interactions with both concomitant AEDs and other co-prescribed medications, poorer cognitive function, effects on bone health, and greater levels of frailty, increase the complexity of prescribing AEDs in the older population [151].

Lower levels of epilepsy and antiepileptic drug use are found in the older general population compared to the older population of people with an intellectual disability [36,

38, 156]. An Irish retrospective comparative study by Peklar et al. (2017) contrasting ageing of people in the general population (n=8081) (using data from TILDA, The Irish Longitudinal Study on Ageing) with ageing of people with intellectual disability (n=238) (using data from IDS-TILDA), found that AEDs were more commonly prescribed to IDS-TILDA participants. Of the 20 most frequently reported classes of medication, AEDs were ranked fifth for IDS-TILDA and eighteenth for TILDA. Information on epilepsy prevalence was not collected in TILDA to allow comparison with IDS-TILDA [156].

1.6.3 Antiepileptic drug use in people with epilepsy and intellectual disability

It is said that people with an intellectual disability comprise almost a quarter of the population with epilepsy, and six in ten who have treatment resistant epilepsy [51]. A poor response to antiepileptic medication is found in people with epilepsy and intellectual disability [157]. This is not helped by the paucity of robust evidence on efficacy and safety in this population group, with data often extrapolated from randomised controlled trials in the general epilepsy population [51]. The UK SANAD randomised controlled trial [158] provided a comprehensive comparison of AEDs regarding side effect profile and quality of life in people in the general population, however, no similar trial was conducted in the population with intellectual disability [143]. A greater evidence base can be found for specific epileptic encephalopathies such as Lennox Gastaut Syndrome and Dravet Syndrome, which are associated with drug resistant epilepsy and drug sensitivity [51, 143, 159, 160]. However, two Cochrane reviews examining AED pharmacological interventions for epilepsy in people with intellectual disabilities highlighted the poor quality of evidence available [161, 162]. The most recent Cochrane review by Jackson et al. (2015) notes the wide variation across studies, with published studies found to use different AEDs and

report multiple outcomes [161]. This Cochrane review largely supports AED use for seizure reduction in people with refractory epilepsy and intellectual disability, and highlights how side effects appear similar to side effects experienced by people with epilepsy but without intellectual disability [161].

A White Paper by Kerr et al. (2014) identified four areas of concern in the delivery of care and support for people with epilepsy and intellectual disability including the "*development of guidelines for treatment, specifically best practice in the management of AEDs including rescue medication"* [163]. Consensus guidelines were also compiled by the working group of IASSIDD into the management of epilepsy in adults with intellectual disabilities [164]. The National Institute of Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) have also highlighted the challenges of prescribing in this population group with a limited evidence base [143, 157]. Greater levels of comorbidity and polypharmacy in this population group lead to increased opportunity for drug interactions and adverse events, necessitating a vigorous evidence based prescribing strategy [51].

A traffic light system for AEDs was created by the Faculty of Psychiatry of Intellectual Disability Working Group of the Royal College of Psychiatrists in the UK (2017) using available evidence on efficacy, side effects, and safety, to grade AEDs as follows [157]:

RED – only to be used in exceptional circumstances.

AMBER – used if benefit outweighs risk or as 2nd line

GREEN – used as 1st line.

A summary of the traffic light assignment of some common AEDs can be found in the following *Table* (*1.6-1*) (adapted from the Royal College of Psychiatrists UK (2017) [51]):

Table 1.6-1 Traffic light categorisation of AEDs (adapted from the Royal College of Psychiatrists UK [51])

Antiepileptic Drug	Positive Characteristics	Negative Characteristics
Lamotrigine **GREEN**	Well studied.	Potential interactions. Slow titration needed to achieve maintenance dose.
Sodium Valproate **GREEN** (**RED** if sexually active)	Used 1st line. Positive mood profile.	Weight gain (especially with co-prescribed neuroleptics). Risk of polycystic ovarian syndrome (PCOS). Limited evidence available in intellectual disability.
Levetiracetam **GREEN**	No interactions with commonly prescribed medications. Well studied in the general population.	More experience in intellectual disability is needed. Possible behavioural and psychiatric adverse effects.
Brivaracetam **AMBER**	No interactions with commonly prescribed medications.	Limited data available. Possible behavioural and psychiatric adverse effects.
Topiramate **AMBER**	Reasonable evidence in intellectual disability. Few interactions with the exception of oral contraceptives.	Weight loss. Possible impact on mood and behaviour.
Gabapentin **AMBER**		Little information available on efficacy or possible potential for harm.
Perampanel **AMBER**	No interactions with commonly prescribed medications. Considered alternative in treatment resistant epilepsy.	Potential behavioural, cognitive, and psychiatric adverse effects.
Lacosamide **AMBER**	Favourable profile.	Limited data available.
Carbamazepine **AMBER**	Long history of use as AED. Recognised 1st line treatment.	No evidence of efficacy in people with intellectual disability. Potential for multiple drug interactions. Hyponatraemia (especially with co-prescribed SSRIs and diuretics)
Phenytoin **RED**		Not suitable in intellectual disability. Potential for multiple drug interactions. Behavioural side effects. Requirement for regular blood monitoring.
Phenobarbital **RED**		Not suitable in intellectual disability. Potential for multiple drug interactions. Effects on cognition. Behavioural side effects. Requirement for regular blood monitoring.

The use of benzodiazepines as rescue treatment or add-on medication in treatment resistant epilepsy is supported by good quality evidence [51]. Midazolam is widely used in the community as a rescue medication for the treatment of acute status epilepticus and is administered in a convenient buccal preparation [51, 157]. Clobazam is used in short term regimens to treat clusters of seizures [157]. Benzodiazepines are limited by their adverse effects on cognition, potential for tolerance, and risk of contributing to an already high benzodiazepine load in this population group [51]. Clobazam is particularly useful in the treatment of atonic seizures (drop attacks) in Lennox Gastaut Syndrome, and due to structural differences is not believed to be as sedative as other benzodiazepines [51].

Carbamazepine prescribing in intellectual disability has a limited evidence base [51] with a Finnish double blind, randomised, controlled, cross-over study of 20 people with intellectual disability reporting improved efficacy when using slow release preparations compared to regular release [165]. Furthermore, a UK randomised, open label, parallel group, multicentre, add-on study of 109 people examining gabapentin and lamotrigine found both drugs effective for seizure control with no significant worsening of behaviour [166]. Similarly, Motte et al. (1997) in a double blind, placebo, controlled trial of lamotrigine in people with Lennox Gastaut Syndrome (n=169) found an improvement in seizure control with lamotrigine [167]. However, a UK retrospective case note analysis study of 51 people by Bhaumik et al. (1997) examining vigabatrin, gabapentin and lamotrigine, found vigabatrin to be associated with a higher risk of adverse effects and lamotrigine to be associated with increased seizures [168].

Levetiracetam has been shown to be effective in people with intellectual disability in a Scottish observational study of 64 people started on adjunctive levetiracetam [169] but it has not undergone a randomised controlled trial to date in this population [51].

Regarding perampanel, a UK multi-centre retrospective study (n=144) found it to be safe and well tolerated with improvements in seizure frequency [170]. However, caution is required with concomitant mental illness [170]. Phenytoin on the other hand is not recommended for people with intellectual disability unless benefit outweighs the risks [51]. It requires close therapeutic monitoring to avoid intoxication and phenytoin induced encephalopathy [171].

It has been reported that people with intellectual disability and drug resistant epilepsy may be more responsive to sodium valproate [51]. Positive findings for sodium valproate were also found in the UK SANAD study in the general population for difficult to treat seizures [158]. Concerning topiramate, a UK randomised, double-blind, placebo controlled study in 88 people with epilepsy and intellectual disability found reductions in seizure frequency [172]. However, adverse effects of sedation, weight loss, and word-finding difficulties have limited its use [51]. With regards to rufinamide, a US randomised, controlled trial of 138 people with Lennox Gastaut Syndrome found significant improvements in total seizure frequency and atonic attacks [173].

A poor evidence base for tolerability and efficacy in people with intellectual disability exists for zonisamide, pregabalin, brivaracetam, tiagabine, stiripentol, ethosuximide, eslicarbazepine, oxcarbazepine and retigabine [51].

The following table highlights some of the studies of AEDs in people with epilepsy and intellectual disability and the available evidence (*Table 1.6-2*). Electronic databases were searched including PubMed, Science Direct, Embase, Scopus, Web of Science and CINAHL and any relevant grey literature. Key words used included ‘AED’, ‘antiepileptic drugs’, ‘antiepileptic medication’, ‘epilepsy’, ‘intellectual disability’, ‘developmental disability’, ‘mental retardation’, ‘learning disability’, ‘seizures’, ‘AED monotherapy’, AED

polytherapy'. Repeated searches were undertaken with a combination of two or more words used each time, for example:

'intellectual disability' OR 'developmental disability' OR 'learning disability' AND antiepileptic drugs AND 'epilepsy'.

'intellectual disability' OR 'learning disabilities' AND 'antiepileptic drugs'

Titles and abstracts were used to exclude studies not relevant to the search topic. The full text of potentially relevant papers were screened for suitability or where the abstract did not provide sufficient information.

Table 1.6-2 Studies examining antiepileptic drugs in people with epilepsy and intellectual disability

Title, Journal, Author Year, Country	Aim	Population, Sample Size, Inclusion Criteria	Measures Used	Results
Antiepileptic drugs with mood stabilising properties and their relation with psychotropic drug use in institutionalized epilepsy patients with intellectual disability. ***Research in Developmental Disabilities*** Leunissen et al. (2011) The Netherlands [40]	To examine whether use of the mood stabilising AEDs (carbamazepine, lamotrigine and valproic acid) is associated with a different use of psychotropic drugs in institutionalised people with epilepsy and intellectual disability.	Retrospective, cohort study of adults with epilepsy and intellectual disability living in the long stay department of an epilepsy centre. n=246	Data extracted from Oracle database. AED load of mood stabilising AEDs calculated using PDD/DDD ratio. Psychotropic drugs categorised into four groups according to ATC index – antipsychotics, antidepressants, anxiolytics and others.	Study found a statistically lower use of antidepressants in people taking lamotrigine. A lower use of anxiolytics was found in people using AEDs with mood stabilising properties. Male patients were taking significantly more antipsychotics. An inverse relationship was found between drug load of mood stabilising AEDs and use of psychotropic drugs.
Levetiracetam for people with mental retardation and refractory epilepsy. ***Epilepsy & Behavior*** Kelly et al. (2004) Scotland [169]	To examine the effectiveness of adjunctive levetiracetam in people with intellectual disability and uncontrolled epilepsy.	Referrals to epilepsy clinic at Western Infirmary Glasgow with diagnosis of intellectual disability. n=67 Started on adjunctive levetiracetam after a 3-month baseline period.	Started on levetiracetam 250mg per day for two weeks then 250mg BD. Every 4-6 weeks, dose adjusted by 250-500mg depending on clinical response. Dose not altered if no seizure since last review. Reviewed until one of four endpoints. (1) seizure freedom for 6 months, (2) ≥50% reduction in seizure frequency (responders) over a 6-month period, (3) <50% reduction in seizure frequency (marginal effect) over 6 month period, (4) withdrawal due to lack of efficacy, adverse effects or both. Caregivers rated combined sleep, appetite, alertness, and behaviour scores as poor, reasonable or good.	38% of patient's seizure free (10 controlled on 250mg BD), 28% classified as responders, 12% received only marginal benefit and 22% discontinued levetiracetam (6 seizures worsened, 1 lack of efficacy and 7 adverse effects). Caregivers rated combined sleep, appetite, alertness, and behaviour as improved $p<0.001$.

Table 1.6-2 Studies examining antiepileptic drugs in people with epilepsy and intellectual disability (*Continued*)

Title, Journal, Author Year, Country	Aim	Population, Sample Size, Inclusion Criteria	Measures Used	Results
A randomised open-label study of gabapentin and lamotrigine in adults with learning disability and resistant epilepsy ***Seizure*** Crawford et al. (2001) UK [166]	To evaluate the efficacy and safety of gabapentin in patients with learning disabilities and resistant epilepsy, and compare with effects of lamotrigine regards efficacy, behaviour and mood.	Open label, randomised, parallel group multicenter add on study. n=109 39 people randomised to gabapentin and 44 people randomised to lamotrigine. Range of learning disabilities and severe partial epilepsy.	Initial baseline period of 8 weeks, doses increased to a max 3600mg of gabapentin and 400mg of lamotrigine. Seizures recorded in a diary and seizure frequencies per 28 days calculated. Mood, behaviour and dependency measured using: 1. The Key Carer Visual Analogue Scale to assess carer outcome. 2. Crichton Royal Behavioural Rating Scale. 3. Whelan and Speake Rating Scale. 4. Physician Global Rating Scale.	50% of participants taking gabapentin achieved a ≥50% reduction on seizure frequency compared to 48.6% with lamotrigine. Carer Visual Analogue Scale found significant improvements for the gabapentin treated patients in seizure severity, attention, general health, and sleeping pattern while for lamotrigine, seizure severity improved significantly.
Treatment of epilepsy in mentally retarded patients with a slow release carbamazepine preparation. ***Journal of Intellectual Disability Research*** Kaski et al. (1991) Finland [165]	To undertake a 24-hour trial comparing a slow release (SR) preparation given twice daily with a carbamazepine preparation given three times daily. To investigate how reduction of dosing frequency has on the control of epileptic seizures in patients with intractable epilepsy.	People in the care of the Vaalijala settlement for the 'mentally retarded' during years 1986 – 1987. Previously treated with carbamazepine and whose serum carbamazepine concentration had been in therapeutic levels for at least 2 months but people were still experiencing ≥4 seizures per month. n=20	8-week baseline period and two 10-week treatment periods. At the end of each period, 24-hour blood samples were taken for determination of serum carbamazepine and carbamazepine-10,11-epoxide. Seizure occurrence was monitored day and night by experienced nurses.	Bioavailability from both carbamazepine preparations was similar. The mean fluctuation of serum carbamazepine concentration was 16% smaller during SR dosing. Mean total number of seizures was approximately 4 per week and did not differ between the two treatments. However, during the last two weeks of the study period, the occurrence of seizures was significantly smaller with the SR preparation.

Table 1.6-2 Studies examining antiepileptic drugs in people with epilepsy and intellectual disability (*Continued*)

Title, Journal, Author Year, Country	Aim	Population, Sample Size, Inclusion Criteria	Measures Used	Results
A naturalistic study of the use of vigabatrin, lamotrigine and gabapentin in adults with learning disabilities. ***Seizure*** Bhaumik et al. (1997) UK [168]	To compare the efficacies, adverse events, and dropout rates for vigabatrin, lamotrigine and gabapentin.	Case lists of 4 consultant psychiatrists were examined. n=51	A retrospective case-note analysis undertaken examining age, sex, residence, degree of learning disability, cause of primary handicap, age of onset of epilepsy, prior AEDs prescribed, current AEDs, seizure frequency prior to and after add on therapy, any side effects reported, and drop out and reasons for drop out.	All AEDs had similar efficacies. Vigabatrin was associated with a higher incidence of behaviour problems. Behaviour problems also reported with other drugs. Lamotrigine caused increased seizures in 24% of patients, particularly at higher doses. Gabapentin was associated with fewer side effects.
Lamotrigine for generalised seizures associated with the Lennox Gastaut Syndrome. ***The New England Journal of Medicine.*** Motte et al. (1997) [167]	To examine the efficacy and tolerability of treatment of lamotrigine for seizures associated with Lennox Gastaut Syndrome.	Double blind, placebo controlled trial of lamotrigine with Lennox Gastaut syndrome. Participants had more than one type of predominantly generalised seizures including tonic-clonic, tonic, and major myoclonic and had seizures at least every other day, were younger than 11 years at onset of epilepsy, intellectual impairment or a clinical impression of intellectual deterioration and EEG showing pattern of slow spike and wave complexes. n=169	Four-week baseline period in which participants received placebo. Randomly assigned 169 participants (aged 3 to 25) to 16 weeks with lamotrigine (n=79) or placebo (n=90) in addition to their other antiepileptic medication.	Median frequency of all major seizures changed from baseline level of 16.4 and 13.5 per week with lamotrigine and placebo groups to 9.9 and 14.2 per week after 16 weeks' treatment. The study found that 33% of people taking lamotrigine and 16% of people taking placebo had a statistically significant reduction of at least 50% in the frequency of seizures. No significant differences in the incidence of adverse events was found between the groups. Colds or viral illness were more common in people taking lamotrigine.

Table 1.6-2 Studies examining antiepileptic drugs in people with epilepsy and intellectual disability (*Continued*)

Title, Journal, Author Year, Country	Aim	Population, Sample Size, Inclusion Criteria	Measures Used	Results
Efficacy of lamotrigine in institutionalized developmentally disabled patients with epilepsy: a retrospective evaluation. ***Seizure*** Gidal et al. (2000) USA [174]	To evaluate the efficacy of lamotrigine in developmentally disabled patients with epilepsy. To identify any adverse reactions from lamotrigine treatment and any discontinuation of treatment.	All participants had a diagnosis of intellectual disability (profound IQ<20), developmental disabilities and epilepsy, seizure type per ILAE criteria documented prior to evaluation. n=44	Medical/pharmacy records identified people receiving lamotrigine during 1995-1996. Retrospective and concurrent observation with each patient acting as their own control. Seizure frequency data obtained from standardised daily seizure records. Mean seizure frequency was compared between a two-month pre-lamotrigine baseline period and a two-month treatment period. A three-month lamotrigine titration phase occurred between baseline and treatment periods. Adverse effect data obtained from medical and nursing notes. Intent to treat analysis performed.	Mean lamotrigine dose of 272+/- 133mg per day. A significant reduction in seizure frequency was noted. In total, 32% had greater than 75% reduction in seizure frequency, 23% had 50-74% seizure reduction, 25% had less than 50% seizure reduction and 20% experienced an increase in seizure frequency.
Perampanel in the general population and in people with intellectual disability: differing responses. ***Seizure*** Shankar et al. (2017) UK [170]	To report clinically useful information on differences in response to perampanel adjunctive treatment for refractory epilepsy between intellectual disability sub-groups and the general population from the UK EP-ID research registers.	Pooled retrospective case notes of consented people with epilepsy with moderate-profound intellectual disability, mild intellectual disability and the general population. n=144	Information gathered on demographics, concomitant AEDs, starting and max dosage, exposure limits, adverse effects, dropout rates, seizure type, and frequency. Group differences were reported as odds ratios estimated from uni-variable logistic regression models.	Participants with a moderate to profound intellectual disability were less likely to come off perampanel compared to those with mild intellectual disability. 50% seizure improvement found in 11% of general population, 24% with mild intellectual disability and 26% with moderate to profound intellectual disability.

Table 1.6-2 Studies examining antiepileptic drugs in people with epilepsy and intellectual disability (*Continued*)

Title, Journal, Author Year, Country	Aim	Population, Sample Size, Inclusion Criteria	Measures Used	Results
A randomised, double blind placebo controlled trial of topiramate in adults with epilepsy and intellectual disability: impact on seizures, severity and quality of life. ***Epilepsy & Behavior*** Kerr et al. (2005) UK [172]	To evaluate the effect of topiramate as add-on therapy on seizure frequency and severity, adverse effects and quality of life in patients with epilepsy and intellectual disability.	Randomised, double blind, placebo controlled study. Age 12 years and older, weight at least 45kg. Diagnosis of epilepsy with a documented history of at least four seizures per month and have intellectual disability. On treatment with one to three other AEDs and to have an identified carer. n=88	Medical history, vital signs and body weights were recorded and physical and neurological examinations, hematology and biochemistry parameters assessed. Records of medication use and adverse events were examined. Occurrence of seizures were recorded on day cards and the total number of seizures overall and of each type were converted to monthly rates. Response was defined as a 50% reduction in seizure frequency. Behavioural scale questionnaires completed by carers. Three phases- four-weeks baseline, 18-weeks dose titration and 12-weeks maintenance.	Seizure frequency varied greatly. There was no significant difference in reduction in mean total seizure frequency or number of responders between the groups. Topiramate reduced seizure frequency >30% from baseline compared to 1% for placebo. Topiramate was well tolerated with body weight and blood pressure reduced. There was a trend towards significance for improvement in mean ELDQOL behaviour subscale for patients treated with topiramate.
Rufinamide for generalised seizures associated with Lennox-Gastaut Syndrome. ***Neurology*** Glauser et al. (2008). USA [173]	To evaluate the efficacy and tolerability of rufinamide adjunctive therapy in patients with Lennox Gastaut Syndrome.	Double-blind, randomised, placebo controlled trial in people with Lennox Gastaut Syndrome. Inclusion criteria: age 4-30 years with multiple seizure types and a minimum of 90 seizures in the month before baseline and recent history of slow spike and wave pattern on EEG. 74-rufinamide and 64-placebo. n=138	Seizures were identified and recorded by the patient's parents or guardians. Daily diaries of seizure frequency and adverse events were reviewed at each study visit (days 0,7,14,28,56,84). At each visit, patients had physical and neurological examination and blood samples taken. At the end of the double blind phase, the parents/guardians completed a global evaluation of seizure severity using a Likert scale.	Median % reduction in total seizure frequency was greater in the rufinamide therapy group compared to the placebo group. A significant reduction in tonic-atonic "drop attacks" seizure frequency with rufinamide (42.5% median % reduction) vs placebo (1.4% increase). The rufinamide group had a greater improvement in seizure severity and a higher 50% responder rate compared with placebo for total seizures and tonic-atonic seizures. Common adverse events were somnolence and vomiting.

Table 1.6-2 Studies examining antiepileptic drugs in people with epilepsy and intellectual disability (*Continued*)

Title, Journal, Author Year, Country	Aim	Population, Sample Size, Inclusion Criteria	Measures Used	Results
Epidemiology of epilepsy in older adults with an intellectual disability in Ireland: associations and service implications. ***American Journal on Intellectual and Developmental Disabilities*** McCarron et al. (2014) Ireland [28]	To estimate the prevalence of epilepsy in older adults with intellectual disability and to estimate the frequency of associated comorbid health conditions in people with and without epilepsy.	Data were drawn from the first Wave of IDS-TILDA. Inclusion criteria included age ≥40 years, registered on the NIDD and written consent to participate and/or family/guardian written agreement if required. n=753	A pre-interview questionnaire (PIQ) was sent to participants in advance of the face-to-face interview. The PIQ contained the questions relating to epilepsy diagnosis, comorbidity and medication data.	Epilepsy prevalence was found to be 30.7%. People with epilepsy were less likely to live with family, independently or in community settings. Refractory epilepsy rates were found to be high with over half of those with epilepsy still reporting experiencing seizures despite 89.5% of participants with epilepsy taking AEDs. Bivariate associations were found between epilepsy and joint disease, gastrointestinal disease and stroke. No association was found between epilepsy and mental health conditions. Among those with Down Syndrome, individuals with diagnosed dementia were 12.98 times more likely to have epilepsy.
Prevalence and patterns of anti-epileptic medication prescribing in the treatment of epilepsy in older adults with intellectual disabilities. ***Journal of Intellectual Disability Research*** O'Dwyer et al. (2018) Ireland [29]	To investigate the patterns and prevalence of AED prescribing in the management of epilepsy in an older population who have epilepsy and intellectual disability.	Data were drawn from the first Wave of IDS-TILDA. Inclusion criteria included age ≥40 years, registered on the NIDD and written consent to participate and/or family/guardian written agreement if required. Prescribing of AEDs in those with a doctor's diagnosis of epilepsy was the primary exposure of interest in the study. n=205	A pre-interview questionnaire (PIQ) was sent to participants in advance of the face-to-face interview. This PIQ contained the questions relating to epilepsy diagnosis, comorbidity and medication data. Participant exposure to AEDs was classified into AED monotherapy and AED polytherapy. Seizure frequency, review of epilepsy and which medical professional reviewed epilepsy was noted. Medications that may lower the seizure threshold as outlined in the Maudsley Prescribing Guidelines in Psychiatry were examined.	Of 205 participants with a diagnosis of epilepsy and use of AEDs, 50.3% were exposed to AED polytherapy and 63 different polytherapy regimens were reported. Valproic acid, carbamazepine and lamotrigine were the most frequently reported AEDs prescribed. Of those taking AED polytherapy, 29.5% reported being seizure free for the previous two years. The study found that 13.7% of participants were taking a concurrent psychotropic medication which was recommended to be avoided in epilepsy and 32.6% were taking a concurrent psychotropic medication where caution required was recommended.

Table 1.6-2 Studies examining antiepileptic drugs in people with epilepsy and intellectual disability (*Continued*)

Title, Journal, Author Year, Country	Aim	Population, Sample Size, Inclusion Criteria	Measures Used	Results
"Sometimes, it just stops me from doing anything", A qualitative exploration of epilepsy management in people with intellectual disabilities and their carers'. ***Epilepsy & Behavior*** Mengoni et al. (2016) UK [43]	To explore the impact and management of epilepsy in people with intellectual disability. Part of the WIELD Study.	Subgroup of people (n=15) from the WIELD Study (n=40) invited to take part in semi-structured interviews. WIELD inclusion criteria: diagnosis of intellectual disability and epilepsy, at least one seizure in the last year, meaningful verbal or non-verbal communication enabling the participant to engage with the picture booklet intervention and have a carer with sufficient English proficiency.	Interviews were created including an accessible version with simple questions and images for participants with intellectual disability. Purposeful sample was done to ensure a wide range of users and backgrounds were represented. Interviews were transcribed and analysed using thematic analysis. Interviews reported following COREQ (Consolidated Criteria for Reporting Qualitative Studies).	Three themes emerged - participant's characteristics, living with epilepsy, and epilepsy management and information. These indicated: 1. Much diversity regarding health profiles, communication abilities, severity and control of epilepsy and support needs. 2. Reduction in severity and frequency of seizures for many with AEDs. 3. Lifelong impact of epilepsy and seizures on participant's activities and quality of life. 4. Perceived burden of epilepsy and difficulty managing the condition for many participants. 5. High levels of satisfaction for epilepsy related services and care. 6. Lack of written accessible information about epilepsy.

Recommendations for prescribing AEDs to people with epilepsy and intellectual disability [51, 143, 157]:

1) Ensure a clear diagnosis of a seizure disorder is made prior to commencing treatment.
2) A holistic, person centred approach should be central to choosing appropriate treatment options.
3) Evaluations of seizure type and syndrome, together with patient and carer preference should be undertaken.
4) Be aware of potential side effects which may manifest as behavioural disturbances due to lack of ability to communicate these effects.
5) Start with a low dose of AED and titrate slowly. This starting dose may be lower than normally used in the general population and may take longer to reach a therapeutic level. Slow titration allows for identification of the therapeutic window and reduces the risk of adverse effects.
6) An overlap period should occur between the change of one AED to another to avoid the risk of seizures. Particular caution and monitoring when withdrawing AEDs.
7) A drug should not be dismissed for effectiveness until a therapeutic level has been reached. Side effects may limit this approach.
8) Regular review of AEDs should be undertaken (at least annually), particularly if changes are being made to therapy (three monthly reviews).

1.6.4 Psychotropic pharmacotherapy in people with intellectual disability

Psychotropic medications are frequently prescribed to treat psychiatric comorbidity in people with intellectual disability [175, 176]. It is said that people with intellectual disability encompass the most overmedicated group in society [177]. Additionally, it is reported that adverse effects of these medications are more common in people with intellectual disability than in the general population [178]. The support and opinions of primary care staff regarding pharmacotherapy in people with an intellectual disability is crucial to ensuring a successful transition from institutional care into the community [179]. However, concerns mount about the overuse of these medications together with widespread polypharmacy in this population group [178].

An Irish retrospective cross-sectional study by O'Dwyer et al. (2017) (n=736) examining psychotropic use in older adults with intellectual disability found a 59.1% prevalence of psychotropic use, with 66.2% of these reporting psychotropic polypharmacy [176]. Similar to other studies in this population group [178], O'Dwyer et al. (2017) found antipsychotics to be the most commonly reported psychotropic class with 43% of participants reporting use of this class of medication [176]. Additionally, they found that living in a residential institution and having a history of reporting a mental health condition or sleep problems was associated with psychotropic polypharmacy after adjusting for confounders [176]. Interestingly, participants with a diagnosis of epilepsy were found to be less likely to experience exposure to psychotropic polypharmacy [176]. The top three most frequently reported psychotropic agents in this study were the atypical antipsychotics, risperidone, olanzapine and the anxiolytic diazepam [176]. Regarding level of intellectual disability and reporting of psychotropic polypharmacy, 47% had a

severe/profound intellectual disability, 35.1% a moderate intellectual disability and 38.7% a mild intellectual disability [176].

A study of 300 people over the age of 18 years living in one Norwegian county who were receiving services from health or educational authorities found that 37.4% of people with an intellectual disability were using psychotropics, mainly antipsychotics [177]. They found that 25.9% of people were using one psychotropic, 9.2% using two psychotropics and 2.4% were using three psychotropics. This study discovered that 19.4% of participants used first generation antipsychotics (chlorpromazine, chlorprotixene, haloperidol, levopromazine, perphenazine, thioridazine or zuclopenthixol), 12.2% of participants used second generation antipsychotics (olanzapine, quetiapine or risperidone), 8.5% used SSRIs, 5.1% antiepileptics, 1.7% anxiolytics and 1.4% mood stabilisers [177]. The authors note that only 23.7% of all antipsychotics were indicated by a psychotic diagnosis [177]. A greater number of second-generation antipsychotics (41.7%) were indicated by a psychotic diagnosis compared to first-generation antipsychotics (12.3%) ($p<0.01$). The majority of prescriptions were written by GPs (62.3%) with 37.7% written by psychiatrists [177]. Interestingly, 73.7% of prescriptions written by psychiatrists were indicated by a diagnosis or symptom compared to 42.6% of prescriptions written by GPs [177]. Another interesting finding in this study is that 57.9% of antipsychotics prescribed by psychiatrists were second-generation antipsychotics in contrast to 25.5% of antipsychotics prescribed by GPs. GPs were found to prescribe a greater number of antidepressants compared to psychiatrists [177].

Another large UK population based cohort study by Sheehan et al. (2015) of 33,016 adults (211,793 person years of data) from 571 general practices who contributed data to the Health Improvement Network clinical database found a prevalence of 21% of mental

illness at the commencement of the study [175]. They also found a prevalence of 25% of challenging behaviour with nearly half (49%) of participants recording prescription of psychotropic drugs [175]. The rate of new prescribing of antipsychotics was found to be significantly higher in people with challenging behaviour, autism, dementia and older age after adjusting for comorbidity and sociodemographic factors. Similar to other studies in this population, the proportion of people with intellectual disability treated with psychotropic drugs greatly exceeds the proportion with recorded mental illness [175]. The authors found the most frequent class of drugs to be prescribed was anxiolytics/hypnotics followed by antidepressants, antipsychotics and mood stabilisers [175]. In contrast, they found a lower prevalence of drugs for dementia and ADHD. Interestingly, prescription of antipsychotics fell by 4% per year over the course of the study whilst prescription of antidepressants fell significantly in 2005 but returned to 1999 levels by 2013 [175]. Unsurprisingly, individuals with a history of challenging behaviour were twice as likely to receive a prescription for antipsychotics compared to those without a history of challenging behaviour after adjusting for neuropsychiatric diagnoses [175].

A British cross-sectional clinical audit study examining the quality of prescribing of antipsychotic medication to people with an intellectual disability in 54 mental health services in the UK (n=5654) found that 64% of participants were prescribed antipsychotic medication and 37% antidepressant medication [180]. Almost half (49%) of participants were found to have a schizophrenic spectrum or affective disorder diagnosis while another 36% of participants exhibited behaviours such as violence, aggression or self-injury, appropriate reasons for treatment according to NICE guidelines [180]. Despite a high compliance of use with evidence - based indicators for treatment, the authors found follow up in some services regarding screening for potential side effects, namely, body weight,

blood pressure, blood glucose and blood lipids to be poor [180]. Reasons for prescribing were found to be psychotic disorder (41%), general agitation and anxiety (41%), overt aggression (36%), threatening behaviour (29%), self-harm and SIB (19%), and obsessive behaviour (9%) [180]. Their multivariable analysis found an association between being prescribed an antipsychotic and age >25 years, cared for in a specialist inpatient setting and having a diagnosis of psychotic spectrum disorder, affective disorder, psychological development disorder or epilepsy [180].

Off-label prescribing is also an important consideration in psychotropic prescribing. The expression 'off-label prescribing' describes the use of a drug outside its marketing authorisation or product licence [181, 182]. A UK survey study examining off-label prescribing for 56 patients with mild intellectual disability and mental illness resident in a large psychiatric hospital, found that 67.9% were receiving one or more psychotropic drugs, and 46.4% were receiving at least one off-label psychotropic medication [181]. Off-label indications were found to include reduction of aggression, arousal and behavioural disturbance in 14 cases and mood stabilisation of affective disturbance in 13 cases [181]. Antipsychotics (17 cases) were the most commonly prescribed off-label psychotropic class [181]. This study also found that despite the off-label use being understood by the psychiatrist, the patient had only been informed of this off-label status in 6% (n=2) of the cases [181]. The psychiatrist determining that the patient lacked capacity to understand the concept was given as explanation for this in the study [181]. Another UK study examining retrospective case notes for 114 people found that 66% (n=75) of patients received licensed drugs for unlicensed applications, mainly for aggression, other challenging behaviour or agitation [182]. Risperidone (n=77) was the drug most frequently prescribed for an unlicensed indication, chiefly for aggression and agitation [182].

1.6.5 De-prescribing and STOMP (stopping the overuse of medication in people with learning disabilities and/or autism) in the UK

For many decades, concerns abound regarding the overuse of psychotropic medications, particularly antipsychotics in people with intellectual disabilities [183]. The Winterbourne View hospital report (2012) of an assessment unit for people with intellectual disability, autism or both who exhibited challenging behaviours in the UK highlighted concerns regarding the overuse of both antipsychotics and antidepressants [183, 184]. In addition, the 2013 Intellectual Disabilities Hospital Census from the Health and Social Care Information Centre in the UK found over two thirds (68.3%) of people (n=3250) with intellectual disability, autism or both who met inclusion criteria had been prescribed an antipsychotic prior to the census [183, 185]. Public Health England (2015) also estimated that every day between 30,000 and 35,000 adults with an intellectual disability were prescribed an antipsychotic, antidepressant or both in the absence of a diagnosed mental illness [186].

In July 2015, NHS England brought numerous stakeholders together to address this issue [183]. Overuse of psychotropic medications in people with dementia had previously been tackled using a 'call to action' approach which led to greater medication reviews and a reduction in inappropriate antipsychotic prescribing of 51.8% [183, 187]. A similar 'call to action' methodology was agreed for people with intellectual disability called 'STOMP' to reduce inappropriate prescribing and increase non-pharmacological interventions such as positive behavioural support, cognitive behavioural therapy, and addressing environmental triggers [188]. Lack of empowerment was found to be a predominant factor in difficulties in reducing overmedication, with GPs, community pharmacists and practices nurses expressing feelings that any change of medication was outside their expertise and

a task for specialists in the field [186]. A lack of influence on the prescribing process was also felt by family carers, professional carers, and other advocates who deemed it the responsibility of others [186].

To ensure success of the STOMP initiative, medication reviews were included in contractual arrangements, financial incentives were put in place, and thorough reviews were incorporated in inspection standards [186]. Some new reviews that were implemented in the UK included Care and Treatment Reviews (CTRs), The Annual Health Check, and The Learning Disabilities Mortality Review (LeDer) which examined deaths to identify whether over-medication was a contributory factor [186].

A systematic review by Sheehan and Hassiotis (2017) found that antipsychotics can be reduced or discontinued in many adults with intellectual disability who are prescribed them for challenging behaviours [189]. Improvements in weight reduction, metabolic parameters, and cognitive and adaptive function were found when antipsychotics were withdrawn [189]. A multicentre parallel group study in three care settings in the Netherlands by De Kuijper et al. (2014), examining the effect of controlled discontinuation of antipsychotics prescribed for challenging behaviours found that of 98 participants, 43 achieved complete discontinuation with seven resuming use at follow up three months later [190]. Mean behavioural ratings improved significantly for those who achieved complete discontinuation and at follow up for those who had not achieved complete discontinuation [190].

However, reducing or discontinuing antipsychotic medication can also be harmful [189]. Shankar et al. (2019) outline factors to be considered prior to any reduction intervention: 1. unmasking of a previously unrecognised mental health condition, 2.

misinterpreting concurrent physical, psychological or social changes, 3. inappropriate medication use and 4. multimorbidity leading to challenging behaviours [188].

1.6.6 Potential seizure threshold-lowering psychotropic co-medication in people with epilepsy

Some early studies found a reduction in seizure frequency with use of psychotropic medication [191, 192]. Pauig et al. (1961) investigating use of thioridazine hydrochloride in the treatment of behavioural disorder in people with epilepsy (n=100) found that seizure frequency reduced in 41%, coinciding with control of behavioural disorders which they credit to a reduction of hyperactivity and emotional disturbances [191]. Later, a US study by Gross et al. (2000) analysed retrospectively the impact of psychotropic drugs on seizure frequency in 57 patients seen consecutively at an epilepsy center [193]. The majority of patients were prescribed antidepressants (76%) with 14% taking TCAs, 55% taking SSRIs and 7% taking other types (bupropion and venlafaxine) [193]. In total, 12% of patients were prescribed antipsychotics. During psychotropic drug therapy, they found that seizure frequency decreased in 33% of patients, was unchanged in 44% and increased in 23% with the psychiatric conditions improving in greater than 90% of patients [193]. The authors highlight how treatment practices and methods employed in the study contributed to lower seizure risk [193]. They specifically highlight avoidance of highly epileptogenic psychotropic drugs and employment of a conservative approach to dosing. In addition, they note that changes in AED regimens during the study period do not account for their findings [193]. Furthermore, studies involving mirtazapine [194], citalopram [194-196], sertraline [197, 198] and fluoxetine [198] found positive effects on seizure control.

Both first and second generation antipsychotics have been implicated in raising seizure risk [199, 200]. With first generation antipsychotics, the greatest risk is associated with chlorpromazine [201]. It is generally believed that seizures are most likely to occur early in treatment with a pro-convulsive drug, at dosage changes and if the drug is abruptly withdrawn [202, 203]. However, a Japanese study by Okazaki et al. (2014) reported that the commencement of antipsychotics reduced seizure frequency [204]. They also found seizure outcomes to be significantly improved in those treated with antipsychotics compared to controls when examining the records of 150 epilepsy patients who had commenced antipsychotics matched with 309 epilepsy patients not taking antipsychotics [204].

With regards to lithium, the seizure impact of lithium has also been assessed in studies, albeit with conflicting results [205]. Erwin et al. (1973) in a study of 16 patients with epilepsy found at least a 25% reduction of seizures in 10 patients, four patients showed no significant change in seizure frequency, with one patient experiencing an increase in seizures [206]. A US open study by Shukla et al. (1988) found no deterioration of seizure frequency in active epilepsy and no induction of seizures in those in remission in a study of 8 patients [207]. In contrast, Jus et al. (1973) terminated their lithium study prematurely due to lithium adverse effects on EEG, seizures and behaviour [208].

1.7 Antiepileptic drugs and mental health

1.7.1 Psychotropic effects of antiepileptic drugs

The psychotropic effects of AEDs stem from a variety of factors including the AED's mechanism of action, specific underlying neurological condition and the individuals family or personal history of psychiatric disorders [209]. It is widely acknowledged that all AEDs

have the propensity to provoke either positive or negative psychiatric reactions in susceptible individuals [210]. AEDs have thus been classified into two “global” categories - sedating or GABAergic drugs, and activating or anti-glutamatergic drugs [211]. Sedating drugs are typified by fatigue, cognitive slowing, weight gain, anxiolytic, and anti-manic effects and include AEDs such as benzodiazepines, barbiturates, valproate, gabapentin, tiagabine, and vigabatrin. On the other hand, activating drugs are typified by weight loss and probable antidepressant and anxiolytic effects and include AEDs such as lamotrigine and felbamate [211]. Topiramate is believed to have a mixed profile [211]. Mula et al. (2009) highlight how epilepsy itself complicates matters and psychotropic effects are linked to both ‘direct’ and ‘indirect’ mechanisms [212]:

Table 1.7-1 Direct and indirect mechanisms of psychotropic effects of AEDs (Adapted from Mula and Monaco (2009) [212])

Drug related DIRECT effects	**Non-drug related INDIRECT effects**
▪ AED mechanism of action (GABA or glutamate) ▪ Polytherapy ▪ Drug toxicity ▪ Drug withdrawal	**Epilepsy effects** ▪ Forced normalisation phenomenon ▪ Release phenomenon ▪ Post-ictal syndromes ▪ Hippocampal sclerosis **Patient effects** ▪ Psychiatric history ▪ Familial psychiatric history

The phenomenon of forced normalisation or post ictal psychosis could result from AED changes on seizure control without links to a particular AED [212]. Other factors such as epilepsy severity or limbic system abnormalities may also have a role [212].

1.7.2 Forced normalisation phenomenon

This concept dates back to the work of Heinrich Landolt in 1953 who described patients whose abnormal EEGs improved or 'normalised' while they were psychotic [213]. He described this as *"the phenomenon characterized by the fact that with the occurrence of psychotic states, the EEG becomes more normal, or entirely normal as compared with previous and subsequent EEG findings"* [213]. Of the 107 patients with psychoses studied by Landolt, 44% exhibited forced normalisation. In further work, Tellenbach coined the term 'alternative psychosis' to described the phenomenon of the reciprocal relationship between abnormal mental states and seizures that did not rely on EEG findings [212, 213].

1.7.3 GABA (Gamma Aminobutyric Acid) transmission

Results from preclinical and clinical studies have demonstrated that an increase in glutamate and/or a decrease in GABA increases the likelihood of seizures in GABA neurotransmission in the brain [214]. $GABA_A$ receptors are ligand-gated chloride ion channels and are the major type of receptor for the inhibitory neurotransmitter GABA [215]. Several AEDs are known to facilitate GABAergic neurotransmission by interacting with $GABA_A$ receptors or altering enzymatic and transporter activity linked to GABA [209]. Benzodiazepines are one such class, with sedative and anxiolytic effects. In addition, the primary mechanism of action for barbiturates, vigabatrin, stiripentol and tiagabine is augmentation of GABAergic neurotransmission [209]. GABAergic effects are also seen with valproate and topiramate [209].

1.7.4 Glutamate transmission

Glutamate is the principal excitatory neurotransmitter in the brain acting through iono-tropic (NMDA, AMPA and kainite) and metabotropic receptors [214]. It has a function in the initiation, speed and maintenance of epileptic activity [214]. An increased plasma level of glutamate in individuals with epilepsy, and continued increases of extracellular glutamate levels during seizures in the epileptogenic hippocampus have been reported in studies [214, 216, 217]. Indeed, glutamatergic neurotransmission inhibition is the primary or secondary mechanism of action for some AEDs, especially lamotrigine, felbamate and topiramate [209]. Perucca et al. (2013) also highlight how glutamate levels are raised in the plasma of individuals with mood disorders, and how psychotropic drugs are known to alter the binding profile of glutamate receptors and agents involved in glutamatergic neurotransmission leading to positive mood and behavioural outcomes [209].

1.7.5 Voltage-gated sodium (Na+) channels

A number of AEDs act principally by sodium channel blockade including phenytoin, carbamazepine, oxcarbamazepine, eslicarbazepine acetate, lacosamide and rufinamide [209]. Lamotrigine, felbamate, topiramate and zonisamide also utilise voltage-gated sodium channel blockade as their mechanism of action [209].

1.7.6 Voltage-gated calcium (Ca2+) channels

Voltage-gated calcium channels are multimeric proteins which encompass five subunits ($\alpha 1$, $\alpha 2$, β, γ, δ) and can be categorised as high voltage activated channels (L-,R-, P/Q-, N-type) and low voltage activated channels (T-type) [209]. Inhibition of voltage-gated calcium channels likely leads to reduction in excitatory neurotransmission, potentially leading to

positive mood and behavioural effects [209]. Ethosuximide, pregabalin, lamotrigine and zonisamide use this mechanism of action [209].

1.7.7 Antiepileptic drugs and adverse psychiatric effects

Understanding whether a particular AED is responsible for an adverse effect may be determined by withdrawing the drug, then reintroducing it with close observation [218], but this method has ethical implications [212], especially in a population of adults with intellectual disability. Some psychiatric and behavioural effects of individual AEDs are discussed in *Table 1.7-2.*

Table 1.7-2 Behavioural and psychiatric effects of AEDs

Antiepileptic Drug	Behavioural and Psychiatric Effects
Barbiturates	The barbiturates are known to facilitate GABAergic neurotransmission by positive allosteric modulation of $GABA_A$ receptors [209]. They are also associated with a higher risk of adverse psychiatric effects [209]. Adverse behavioural disturbances associated with phenobarbital are widely accepted [219]. A US comparative study by Brent et al. (1987) examining treatment and major depressive disorder in children with epilepsy, with comparison of phenobarbital (n=15) and carbamazepine (n=24) groups, found phenobarbital patients had a much higher prevalence of major depressive disorder (40%) and suicidal ideation (47%) compared to the carbamazepine group [220]. Both groups were similar in demographic, seizure associated, and family environmental variables [220]. A Mexican cross-sectional study by Lopez-Gomez et al. (2005) of 241 people with epilepsy found primidone use (OR 4.08, 95% CI 2.09-7.98, p<0.001) to be associated with increased risk of depression [221]. Barbiturates are known to impair cognition, reduce motivation, dampen mood, and instigate hyperactivity, irritability and aggressive behaviour [222].
Levetiracetam	The mechanism of action of levetiracetam is believed to be related to its binding to the synaptic vesicle protein SV2A, with resulting neurotransmitter release inhibition from the end terminals [209]. Levetiracetam has been known to incite aggressive behaviour and irritability in both adults and children [223]. A UK study of 517 patients treated with levetiracetam found that 10.1% of patients experienced adverse psychiatric effects, 2.5% developed depression, 3.5% aggressive behaviour, 2.3% emotional lability, 1.2% psychotic symptoms, and 0.6% other behavioural problems including anger, hostile behaviour, agitation, and personality changes [224]. Risk factors for acquiring psychiatric adverse events included a history of febrile convulsions, a history of status epilepticus, and a prior psychiatric history [224]. The influence of the titration schedule on behavioural adverse effects has been examined in studies of levetiracetam. A US case control study of patients treated with levetiracetam at MINCEP between January 2000 and February 2002 examined behaviours that may require discontinuation and found that only titration of levetiracetam to maximum doses was statistically significant for levetiracetam stoppage due to behavioural reasons [225].
Valproic acid	Valproic acid is known to raise GABA levels in the brain by a number of possible mechanisms including inhibition of GABA transaminase, inhibition of succinic semi-aldehyde dehydrogenase, and activation of glutamic acid decarboxylase [209]. Other mechanisms of action include inhibition of glutamatergic neurotransmission, inhibition of T type calcium currents, and blockade of voltage-gated sodium channels [209]. Valproic acid is an effective mood stabiliser in the treatment of bipolar disorder [222]. It has also been shown to have a beneficial effect on mood in patients with epilepsy [222], intellectual disabilities [226], schizoaffective disorder [227], panic disorder [228] and borderline personality disorder [229]. Regarding adverse effects, valproic acid can cause sedation and rarely irritability, depression, cognitive impairment, hyperactivity, and aggressive/destructive behaviour [222].
Lamotrigine	Lamotrigine's mode of action involves blockage of voltage dependent sodium channels, stabilisation of neuronal membranes, and a decrease in the release of excitatory neurotransmitters including glutamate and aspartate [230]. It has been shown to have a beneficial effect on mood [210]. However, in people with an intellectual disability and epilepsy, lamotrigine has been reported to incite behavioural problems which may restrict its use [209, 231]. In an Australian survey study of nineteen people with epilepsy and intellectual disability who showed a tendency to exhibit aggressive behaviour after taking lamotrigine by Beran et al. (1998), nine people were found to display aggressive behaviour including five patients who had to discontinue use due to unprovoked aggression [231]. Four patients were found to have behavioural problems other than aggression and the behaviour was reported to be improved in one individual with lamotrigine [231].

Table 1.7-2 Behavioural and psychiatric effects of AEDs (*Continued*)

Antiepileptic Drug	Behavioural and Psychiatric Effects
Carbamazepine	Carbamazepine is a sodium channel blocking AED, also approved by the FDA for the treatment of Bipolar I acute manic and mixed episodes [209, 232]. A review by De Leon (2001) presented the effectiveness of carbamazepine in stabilising mood in bipolar disorder [233]. However, carbamazepine may induce behavioural problems [222]. A study by Friedman et al. (1992) evaluating the incidence of carbamazepine associated behavioural adverse effects in 65 people with intellectual disability aged 8-67 years, found that 9.2% of patients with intellectual disabilities treated with carbamazepine for mood disorders exhibited behavioural effects [234]. The incidence of behavioural side effects was not associated with age, sex or serum carbamazepine level [234]. Carbamazepine associated behavioural affects typically present in individuals with existing behavioural problems [222]. Two randomised controlled trials in epilepsy in old age found that carbamazepine was associated with high rates of discontinuation due to adverse effects compared with lamotrigine and gabapentin [45, 235, 236].
Phenytoin	Phenytoin is known to bind to mammalian voltage-gated sodium (Na+) channels and prolong their inactivation [209]. It has a cognitive and behavioural profile resembling carbamazepine [222]. A toxic plasma concentration of phenytoin has been associated with agitated psychosis, delirium, lethargy, ataxia, ophthalmoplegia, involuntary movements, and paradoxical seizures [209, 210, 222, 237, 238]. A chronic encephalopathy associated with phenytoin has been termed 'dilantin dementia' [223]. A US double blind, placebo controlled, parallel groups study (n=29) examined the behavioural effects of three anticonvulsants in impulsive aggressive men [239]. Participants were randomly allocated to one of four 6-week treatments: phenytoin (n=7), carbamazepine (n=7), valproate (n=7) and placebo (n=8). A global severity index, the 'average aggression score' from the Overt aggression scale was utilised to measure efficacy [239]. A significant reduction in impulsive aggression was found for all three anticonvulsants compared with placebo. The treatment effect of carbamazepine was slightly behind when compared to phenytoin and valproate [239].
Topiramate	The mechanism of action of topiramate is multifactorial including increasing GABAergic neurotransmission, inhibiting voltage-gated sodium and calcium channels, kainite/α- amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA) type glutamate and carbonic anhydrase [209]. Topiramate has been associated with negative effects on mood and behaviour in people with epilepsy [209]. A UK study evaluating the prevalence of psychiatric adverse events using case records of 431 patients taking topiramate found that psychiatric adverse effects occurred in 23.9% of patients [240]. The study found that 10.7% of patients developed an affective disorder, 3.7% a psychotic disorder, 5.6% aggressive behaviour with or without irritability and 3.9% developed other behavioural abnormalities including agitated behaviour, anger, hostility, and anxiety [240]. Patients developing psychiatric adverse events were identified to have the following risk factors: family psychiatric history, family history of epilepsy, personal history of febrile convulsions, psychiatric history, diagnosis of symptomatic epilepsy, left hemisphere damage, left temporal EEG epileptic focus, high starting doses, and a fast titration schedule [240]. Another UK case record study of 94 patients receiving topiramate found a high incidence of side effects leading to withdrawal of the drug in 41% of patients [241]. The incidence of psychotic symptoms was significantly higher for patients receiving topiramate (12%) compared with gabapentin (0.5%) and lamotrigine (0.7%) ($p<0.001$) [241]. 'Abnormal thinking' involving difficulty in finding words and mental slowing occurred in 31% of people. Seven patients were admitted to hospital as a result of psychotic symptoms or depression [241].

Table 1.7-2 Behavioural and psychiatric effects of AEDs (*Continued*)

Antiepileptic Drug	Behavioural and Psychiatric Effects
Felbamate	Due to its haematological and hepatic toxicity, the use of felbamate is restricted [223]. It is used in Lennox Gastaut Syndrome where treatment with other AEDs is hampered by resistance [223]. It is known to possess stimulant properties triggering insomnia, anxiety and irritability [222]. A US double blind, placebo controlled, parallel monotherapy trial by Theodore et al. (1995) of 40 patients whose seizures were uncontrolled by standard AEDs found that of the 21 people taking felbamate, 6 withdrew due to side effects including anxiety, sleeping difficulties, abdominal discomfort, acute psychosis, and oro-buccal dyskinesia [242]. Behavioural problems linked to agitation may also occur in children with intellectual disabilities [223].
Vigabatrin	Vigabatrin works by irreversibly inhibiting GABA transaminase, the enzyme that breaks GABA into succinic acid semi-aldehyde [209], increasing GABA levels in the CNS [222]. Adverse effects of vigabatrin include mood and behavioural changes [209]. A meta-analysis of double blind, placebo controlled trials of vigabatrin as add on therapy for treatment refractory, partial epilepsy found that vigabatrin was associated with a higher incidence versus placebo of depression (12.1% vs 3.5%, $p<0.001$) and psychosis (2.5% vs 0.3%, $p=0.028$) [243]. Psychosis was found to be temporary and responded to a reduction or discontinuation of vigabatrin or to neuroleptic treatment [243]. Depression due to vigabatrin is associated with a prior history of depressive illness [244]. Psychiatric effects in children, especially in those with intellectual disabilities, are excitation and agitation, aggression and hyperkinesia, similar to that seen with barbiturates [223]. A review of the literature of psychotic and severe behavioural reactions with vigabatrin by Ferrie et al. (1996) found an incidence of severe abnormal behaviour of 3.4% in adults and 6% in children [245]. Potential risk reduction measures include slow introduction and titration, limiting dosage to the dose necessary for seizure control, careful withdrawal, and monitoring especially in those on polytherapy regimens or with psychiatric history [245].
Zonisamide	The mechanism of action of zonisamide primarily involves blocking of voltage-gated sodium (Na+) channels and inactivation of voltage-gated T type calcium (Ca2+) channels [209]. It is known to bind to the GABA-benzodiazepine receptor complex, raising GABA brain levels, lowering extracellular glutamate release, and inhibiting carbonic anhydrase [209]. Extensively used in Japan since 1989, greater than 2 million patient years of exposure have accumulated for zonisamide [246]. While zonisamide may aid the treatment of mania in patients with bipolar and schizo-affective disorders [222], it is also linked to substantial psychiatric adverse effects including psychoses. A US case-control study of patients at MINCEP Epilepsy Care (between March 2000 – September 2008) (n=544) measured the incidence of psychiatric and cognitive adverse events and found that 6.9% of participants suffered adverse events severe enough to be associated with discontinuation of zonisamide [247]. Psychiatric adverse events reported included depression, aggressive behaviour, psychosis, and irritability [247].
Lacosamide	Lacosamide enhances the slow inactivation of voltage-gated sodium channels without disturbing the fast inactivation of voltage-gated sodium channels [209, 248]. A UK based epilepsy database register study (n=232) compared lacosamide response for the intellectual disability population (n=76) with the general population (n=156) and found no difference in outcomes between the groups [248]. The authors highlighted that a slower titration of lacosamide in the first three months was associated with a greater study retention rate and lower behavioural side effects compared to other comparable studies in Europe [248]. On the other hand, a Dutch retrospective study of 132 adults living in three specialised care facilities found that 62.9% of participants suffered adverse effects related to use of lacosamide [249]. When the adverse effects were classified, 51.5% of participants experienced behavioural adverse effects and 33.3% of participants experienced somatic adverse effects [249]. Behavioural side effects were associated with cessation of lacosamide [249].

Table 1.7-2 Behavioural and psychiatric effects of AEDs (*Continued*)

Antiepileptic Drug	Behavioural and Psychiatric Effects
Perampanel	Perampanel is a non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor antagonist [250]. It is one of the newest AEDs and is associated with behavioural disturbances in studies [250, 251]. A German retrospective observational single-centre study examining the efficacy of perampanel in patients with drug resistant epilepsy and intellectual disability found that behavioural changes were documented in 15 of 27 patients at all doses (2-10mg) [251]. Aggression was the most commonly reported adverse effect and one of the main reasons for discontinuation of the drug [251]. Another retrospective study of medical records at a tertiary epilepsy centre in the Netherlands (n=62), found that 40.3% of patients experienced behavioural adverse effects, with aggression, agitated and disruptive behaviour, and mood symptoms being the most common [250]. Interestingly, the study found that pre-existing behavioural issues or polypharmacy did not predict the incidence of additional behavioural adverse effects [250]. In contrast, a UK study by Shankar et al. (2017) examined retrospective case notes of 144 people with epilepsy and found that people with severe intellectual disability had better retention and efficacy than people with mild intellectual disability or the general population [170]. The authors note that titration and mental or behavioural issues can influence retention and advise caution when a history of mental health problems is present [170].
Gabapentin	Gabapentin binds to the α2-δ subunit of voltage-gated calcium channels modulating calcium currents [209]. It has been reported that gabapentin can induce behavioural problems including aggression, oppositional behaviour, and hyperactivity in children and people with severe intellectual disabilities [209, 223, 252, 253]. Parents considered tantrums, aggression directed towards others, hyperactivity, and defiance as the most troublesome behaviours in children studied [253]. In contrast, a UK open label, randomised, parallel group, multicentre add on study by Crawford et al. (2001) comparing gabapentin with lamotrigine in 109 people aged 12 years and older with epilepsy and intellectual disability found positive effects on behaviour [166].

1.8 Antiepileptic drugs and adverse effects

1.8.1 Bone health

Burke et al. (2019) have highlighted the substantial prevalence of poor bone health in Irish people with intellectual disabilities in their observational cross-sectional study of 575 Wave 2 IDS-TILDA participants who completed quantitative ultrasound measurement on one or both feet [152]. They found that 74% of participants had overall poorer bone health, with 33.2% indicating evidence of osteopenia and 41% osteoporosis [152]. For decades, AED use has been associated with bone disorders and increased fracture risk [254]. The burden of disability and death associated with fractures is high [255]. Prevalence rates of 50% and greater have been reported for clinical or subclinical bone disorders in people taking long term AEDs [254, 256]. Osteoporosis affects both genders with women more susceptible due to lower muscle mass, variable oestrogen levels, and menopause [153, 257]. For women with an intellectual disability, especially those with Down Syndrome, late menarche and early menopause also increase the risk [153]. In addition, hypogonadism resulting in reduced oestrogen and testosterone levels is common among males with Down Syndrome [153]. A systematic review and meta-analysis assessing the risk of fractures in patients receiving AEDs found a robust association between AEDs and fracture risk, especially for enzyme inducing AEDs [258]. Phenobarbital, topiramate, and phenytoin were found to be associated with an increased fracture risk [258]. Compared to AED monotherapy, polytherapy with AEDs showed an increased risk of fractures [258].

1.8.2 Cognition/memory

Cognitive dysfunction is a frequently observed phenomenon in people with epilepsy [259], and represents one of the least tolerated side effects of antiepileptic pharmacotherapy

[260]. Neuropsychological functions most influenced by AEDs include memory, sedation, psychomotor speed, attention, distractibility, and mood [259, 261]. Side effects of antiepileptic drug therapy can have a greater negative impact on quality of life than the frequency of epileptic seizures [262]. Elderly people are also more vulnerable to cognitive side effects due to pharmacokinetic and pharmacodynamic factors [261]. Multiple factors contribute to cognitive effects in epilepsy, including the seizure type, etiology of the seizures, age of onset of epilepsy, seizure frequency, severity, presence of cerebral lesions, intra-ictal and inter-ictal physiologic dysfunction as a result of seizures, hereditary, and psychosocial factors [261]. Older AEDs (phenobarbital, phenytoin, carbamazepine, and valproate) especially can have harmful effects on cognition [259]. Topiramate is the newest AED most associated with negative effects on cognition [259].

The risk of significant cognitive adverse effects is known to increase with higher drug dosages and with AED polytherapy [261]. A UK longitudinal study by Thompson et al. (1983) of 28 people with a diagnosis of epilepsy and an IQ in the range of 64-130, explored the relationship between AED serum concentrations and cognitive adverse effects [263]. Patients were tested on two occasions, with a three-month period between tests. Half of the patients had the dose of the AED increased and the other half had the dose decreased following the first test [263]. More serious cognitive impairment was seen with high serum concentrations [263]. Polytherapy also contributes to pharmacodynamic interactions causing cognitive side effects, with the additive cognitive effects of multiple drugs [259]. Early studies found a beneficial effect on cognition of moving from polytherapy to monotherapy regimens [259]. However, it is worth noting that polytherapy regimens are often indicative of chronic drug resistant epileptic syndromes with prior cognitive deterioration, and thus individuals are more susceptible to adverse effects of AEDs [259].

Generalised tonic-clonic seizures are also associated with greater cognitive impairment than focal seizures [259].

1.9 Drug load of antiepileptic drugs (AED load)

Use of AED polytherapy and high doses with rapid titration is associated with greater adverse cognitive and behavioural effects [264, 265]. Total drug load has been defined as *"the amount of drug exposure for a certain indication"* [266]. Total drug load can be defined as the sum of the prescribed daily dose (PDD) divided by the defined daily dose (DDD) [40, 266, 267]. Polytherapy might be less acceptable than monotherapy due to a higher drug load [268]. The PDD/DDD ratio is the ratio of prescribed daily dose to defined daily dose (DDD) [40]. The DDD is the assumed average maintenance daily dose, for a drug taken for its main indication in adults (e.g., epilepsy) [40]. The PDD is the actual prescribed daily dose. A PDD/DDD ratio can be used as a measure of drug load [40].

$$total\ drug\ load = \sum_i \frac{PDD_i}{DDD_i}$$

Several studies in the general epilepsy population have examined AED load using this method. A Dutch cohort study by Lammers et al. (1995) examined 289 outpatients of tertiary epilepsy centres and found that 71-100% of people taking AED polytherapy with an AED load >2 had neurological adverse effects [269]. In addition, they found that 100% of people with an AED load >4 had neurological adverse effects [269]. The severity of neurological adverse effects increased with increasing dose but peaked about 3.5 PDD/DDD ratios [269]. A German cross-sectional study of 834 people with a diagnosis of epilepsy by Witt et al. (2015) found a considerable adverse effect on cognition, especially executive functions with a higher AED load [270]. In contrast, an Italian study of 809 people

with drug refractory epilepsy by Canevini et al. (2010) found that adverse effects did not correlate with AED load, but they found that patients on AED polytherapy had higher AED loads than patients on AED monotherapy [271]. Chen et al. (2017) in a US study examining the medical records of 4085 patients newly started on an AED regimen, found that the average AED load of patients when they experienced psychiatric and behavioural side effects (PBSE) (2.02±1.51) did not differ significantly from the average AED load of patients when they did not experience PBSE [272].

Studies in the intellectual disability population examining AED load (PDD/DDD) are scarce. A Dutch retrospective cohort study of 246 people with intellectual disability and epilepsy in a long stay department of an epilepsy centre by Leunissen et al. (2011) found an inverse relationship between drug load of mood stabilising AEDs (carbamazepine and/or valproic acid and/or lamotrigine) and use of psychotropic drugs [40]. Another cross-sectional Dutch study by Snoeijen-Schouwenaars et al. (2018) of 189 people with intellectual disability and epilepsy found that lower levels of anxiety were significantly associated with a high drug load of mood stabilising AEDs and a high seizure frequency [89]. AED load is examined further in *Chapters 4 and 6* of this thesis. The following table summarises previous AED load (PDD/DDD) research in this area (*Table 1.9-1*).

Electronic databases were searched including PubMed, Science Direct, Embase, Scopus, Web of Science and CINAHL and any relevant grey literature. Key words included 'AED load', 'antiepileptic drug load', 'drug load'. Titles and abstracts were used to exclude studies not relevant to the search topic. The full text of potentially relevant papers were screened for suitability or where the abstract did not provide sufficient information.

Table 1.9-1 Studies of AED load in the literature

Title	Inclusion criteria	Data collection method	n	Drug load thresholds/ Measures used	Summary/Comments/Findings
Antiepileptic drugs with mood stabilizing properties and their relation with psychotropic drug use in institutionalized epilepsy patients with intellectual disability. ***Research in Developmental Disabilities*** Leunissen et al. (2011) The Netherlands **[40]**	A history of epilepsy demonstrated by the active use of AEDs. In absence of AED use, the diagnosis "epilepsy" was verified in the electronic patient files. Diagnosis of epilepsy according to AAMR definition (AAIDD 2012) 18 years and older.	Retrospective cohort study at long stay department of an epilepsy center in the Netherlands. Data extracted from Oracle database containing electronic patient files - use of AEDs, use of psychotropic drugs, the PDD/DDD of carbamazepine, lamotrigine and valproic acid.	n=246	Five groups measuring only drug load for mood stabilizing AEDs – carbamazepine, lamotrigine and valproic acid measured against numbers of psychotropic drugs. A - 0 (no AED load) B - 0.01-0.99 C - 1.00-1.99 D - 2.00-2.99 E - >3	Higher drug loads of mood stabilising AEDs correspond with less use of psychotropic drugs. Statistically significant lower use of antidepressants with lamotrigine use. Less prescriptions of anxiolytics in patients using AEDs with mood stabilising properties. Inverse relationship between the drug load of carbamazepine and/or valproic acid and/or lamotrigine and use of psychotropic drugs.
Monotherapy *vs*. Polytherapy for epilepsy: a multicenter double-blind randomized study ***Epilepsia*** Deckers et al. (2001) The Netherlands [267]	Adult patients with untreated generalised tonic-clonic, complex partial and/or simple partial seizures. An accurate history including adequate neuro-physiologic data for a firm diagnosis. Seizures were defined according to the International classification of epileptic seizures. Age 24 and older.	130 patients with untreated generalised tonic clonic and/or partial seizures were randomised to equal drug loads of either monotherapy (400mg carbamazepine per day) or polytherapy (200mg carbamazepine plus 300mg valproic acid per day). Started on maintenance dose of 0.4 PDD/DDD which was titrated in three steps with weekly intervals.	n=130	Outcome measured by seizure counts, clinimetric epilepsy scales and neuropsychological tests at baseline, at 2 and 12 months and irregularly between 2 and 12 months.	No statistical differences were found between the two treatments in the reduction of seizure frequencies, in overall neurotoxicity, or in overall systemic toxicity. The frequencies and clinimetric scores of some adverse effects did differ- more monotherapy patients remained sedated and more polytherapy patients gained weight. Fewer polytherapy patients withdrew because of adverse effects (14% vs 22%) but not significantly different. Neuropsychological assessment did not show significant difference either.

Table 1.9-1 Studies of AED load in the literature (*Continued)*

Title	Inclusion criteria	Data collection method	n	Drug load thresholds/ Measures used	Summary/Comments/Findings
Adverse cognitive effects of antiepileptic pharmacotherapy: Each additional drug matters ***European Neuropsychopharmacology*** Witt et al. (2015) Germany [270]	Diagnosis of epilepsy according to the guidelines of the German Neurological Society. Chronological age of at least 16 years (pre-determined by the age range of the cognitive tests)	Used a brief cognitive assessment using Epi-track plus - assess response inhibition, visuo-motor speed, mental flexibility, visual motor planning, verbal fluency and working memory.	n=834	Total drug load quantified in two ways- 1) Number of concurrent AEDs 2) Drug load total PDD/DDD Number of AEDs and PDD/DDD investigated against cognitive & clinical variables reflecting disease severity.	Cognitive measures showed higher inverse correlations with the number of AEDs than with the total DDD. Each additional drug in polytherapy resulted in significantly lower performance in executive function. Adverse effect of a higher drug load on cognition, especially on executive functions. Combination of AEDs with favorable cognitive profiles may attenuate the negative effect of the total drug load. Average PDD/DDD was 2.7 +/- 1.7.
Psychiatric and behavioral side effects of antiepileptic drugs in adults with epilepsy. ***Epilepsy & Behavior*** Chen et al. (2017) USA [272]	Aged 18 and over. Medical records on Columbia and Yale database. Newly started on one or more AEDs between January 1st 2000 and January 1st 2015 and followed up for at least one year.	Columbia and Yale AED database project reviewed records of demographics, medical history, AED use, and side effects. Psychiatric & behavioural side effects (PBSE) determined by patient or physician reported - depressive moods, psychosis, anxiety, suicidal thoughts, irritability, aggression, and tantrum.	n=4085	AED drug ratios (PDD/DDD) were summed to get the total AED load for each patient. Then they calculated a mean AED load for regimens with no PBSE and regimens with PBSE. Means of both groups were compared.	The average AED load of patients when they experienced psychiatric and behavioural side effects (PBSE) (2.02 ± 1.51) was not significantly different from the average AED load of patients when they did not experience PBSE (2.07 ± 1.34)

Table 1.9-1 Studies of AED load in the literature *(Continued)*

Title	Inclusion criteria	Data collection method	n	Drug load thresholds/ Measures used	Summary/Comments/Findings
Monotherapy or polytherapy for epilepsy revisited: a quantitative assessment. ***Epilepsia*** Lammers et al. (1995) The Netherlands [269]	Patients aged ≥15 years whose seizures could be defined accurately according to the International Classification of the International League against Epilepsy (ILAE). Patients with factors that were believed to complicate the evaluation of whether a clinimetric approach has added value over present management were excluded - progressive brain disorders, obvious non-compliance with drug treatment or seizure registration, pseudoseizures and severe mental retardation.	Recruited cohort of patients from the outpatients of the special centers for epilepsy in the Netherlands and outpatients of the Dept. of Neurology, Nijmegen University, Netherlands. Severity of adverse effects was assessed by using the neurotoxicity index and the systemic toxicity index.	n=289	AED monotherapy and AED polytherapy stratified according to the PDD/DDD ratio. Data from all patients receiving monotherapy (n=161) and also from patients receiving polytherapy with a PDD/DDD ratio in the same range (n=128) were examined. Therefore, 289 patients entered the main arm of the study. All patients with a PDD/DDD above 2 (n=134) were in the polytherapy group. The polytherapy group as a whole (n=262) was also studied separately in comparisons of patients receiving polytherapy with a PDD/DDD ratio of ≤2 and >2. The patients were stratified according to PDD/DDD ratio with intervals of 0.33 PDD/DDD ratio and prevalence and severity of adverse effects (AE) studied in each stratum.	Prevalence of neurological adverse effects for individuals with similar PDD/DDD ratios was 50–80% for AED monotherapy patients and 50–82% for AED polytherapy patients. The prevalence of neurological adverse effects for patients taking AED polytherapy with a PDD/DDD ratio >2.0 was 71–100%. All patients with a PDD/DDD ratio >4.0 had neurological adverse effects. The severity of neurological adverse effects also increased with dose, but appeared to peak at ~3.5 PDD/DDD ratio.

Table 1.9-1 Studies of AED load in the literature (*Continued*)

Title	Inclusion criteria	Data collection method	n	Drug load thresholds/ Measures used	Summary/Comments/Findings
Relationship between adverse effects of antiepileptic drugs, number of co-prescribed drugs, and drug load in a large cohort of consecutive patients with drug-refractory epilepsy ***Epilepsia*** Canevini et al. (2010) Italy [271]	Established diagnosis of epilepsy. Drug refractoriness defined as persistence of seizures after adequate treatment with one or more appropriate AEDs at maximally tolerated doses, excluding treatments where idiosyncratic reactions prevented titration to usually effective doses. At least one seizure during the previous six months while at steady state on the current AED regimen. Written informed consent.	Protocol involved a baseline evaluation and a prospective follow up evaluation aimed at assessing health outcomes in relation to treatment changes over an 18-month period. Evaluation of demographic data, epilepsy history, comorbidities, current drug regimens and depressed mood as assessed by the Beck Depression Inventory. AEDs were identified through an unstructured interview and for patients aged 16 and over, by the adverse event profile (AEP) questionnaire.	n=809	Enrolled all eligible patients of any age who attended consecutively 11 tertiary referral centers in different regions of Italy. Drug load calculated per PDD/DDD ratio. Compared drug loads between monotherapy and polytherapy groups. Investigated number of spontaneous reported adverse effects and AED load. Compared adverse event profile scores in people taking one AED, two AED…	Adverse events did not differ between monotherapy and polytherapy patients, and did not correlate with AED load. Patients on polytherapy had higher drug loads (PDD/ DDD ratios) than patients on monotherapy

Table 1.9-1 Studies of AED load in the literature (*Continued*)

Title	Inclusion criteria	Data collection method	n	Drug load thresholds/ Measures used	Summary/Comments/Findings
Mood, anxiety and perceived quality of life in adults with epilepsy and intellectual disability. ***Acta Neurologica Scandinavica*** Snoeijen-Schouwenaars, F.M. et al. (2018) The Netherlands [89]	Age ≥18 years Diagnosis of epilepsy according to the ILAE clinical definition. Diagnosis of intellectual disability according to DSM-V or current adaptive functioning at level of intellectual disability as measured by the individuals' psychologist.	Mood and anxiety were measured using the Dutch version of the Anxiety, Depression, and Mood Scale (ADAMS). Self-reported quality of life was measured using the intellectual disability quality of life questionnaire. (IDQOL-16).	n=189	The drug load (PDD/DDD) of mood stabilising AEDs was measured (lamotrigine, carbamazepine, valproic acid). PDD/DDD ratio also calculated for benzodiazepines that were prescribed as AEDs - clobazam, clonazepam, diazepam and dipotassium clorazepate.	No epilepsy characteristics were related to depressive symptoms. Intellectual disability characteristics were significantly associated with depressive and anxiety symptoms. Lower levels of anxiety were significantly associated with a high drug load of mood stabilising AEDs (carbamazepine, valproic acid and lamotrigine) and a high seizure frequency.

1.10 Interactions between psychotropic drugs and AEDs

1.10.1 Drug interactions

Clinically important drug interactions have been defined as *"events in which the safety or effectiveness of a drug is modified by a second substance. The second substance may be a concomitantly prescribed drug, an over-the-counter medication, or some other substance such as food, alcohol, a herbal supplement, or tobacco smoke"* [273, 274]. Serious adverse effects, some potentially fatal can arise from drug interactions [273]. A French prospective study of 1000 elderly, hospitalised patients in the geriatric unit of a University hospital, found that adverse events arising from drug interactions were responsible for the hospitalisation of 11.5% of patients exposed to a drug-drug Interaction (DDI) [275]. They also found the number of side effects secondary to DDIs relating to psychotropic drugs (28%) was significantly higher than the number of side effects secondary to DDIs involving cardiovascular drugs (14%) ($p<0.001$) [275].

Certain patient populations have a greater predisposition to DDIs than others [273]. Population groups most predisposed to this issue include the elderly with modified drug metabolism and high rates of polypharmacy as a result of comorbidity, HIV patients with complex pharmacotherapy regimens, patients with reduced liver and kidney function, and those with chronic disease [273]. Certainly, people with intellectual disability are also exposed to a number of these risk factors due to high levels of comorbidity, polypharmacy and premature ageing [60, 140, 147].

Two types of interactions occur between drugs, namely pharmacokinetic and pharmacodynamic. These have been defined as follows [276]:

Pharmacokinetic interactions occur when *"one drug interferes with the disposition of another, alters the concentration of the drug at the site of action. These interactions are associated with a change in plasma concentration of either the drug or its metabolite or both"* [276].

Pharmacodynamic interactions occur *"between drugs that have similar or opposing pharmacologic mechanisms of action. These interactions take place at the cellular level where the drugs act and are not associated with any change in the plasma concentration of either drug"* [276].

The Cytochrome P450 (CYP) enzyme system and uridine glucuronyl transferases (UGTs) play a major role in drug metabolism [277]. Cytochrome P450 enzymes form a substantial part of the mixed-function oxidase system and are situated in the smooth endoplasmic reticulum of the cells of most tissues with the highest concentrations found in the liver [276]. Isoenzymes sharing ≥40% sequence homology are classified as families and are assigned the same primary position number [273]. Subfamilies that share ≥55% sequence homology are assigned the secondary position number with the tertiary position number allocated to a specific gene designation [273].

Isoenzymes involved in antidepressant drug interactions include CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 [273]. Uridine glucuronyl transferases work by catalysing glucuronidation [278]. Two families of these enzymes exist, UGT1 and UGT2 which are each composed of eight isoenzymes [278]. Both cytochrome P450 mediated reactions and glucuronidation are liable to inhibition and induction [278]. Inhibiting a CYP450 pathway can decelerate the metabolism of an active drug, increasing plasma levels,

and the risk of adverse effects [273]. On the other hand, inducing a CYP450 pathway accelerates the metabolism of the active drug, reducing plasma levels and potential drug efficacy [273].

Few pharmacokinetic studies exist in the intellectual disability population. Requirement for blood samples to analyse serum concentrations may be a limiting factor in this type of study due to difficulties in getting informed consent. A 20-year review of participation in intellectual disability studies by Cleaver et al. (2010) found that studies with greater invasiveness with data collection, particularly those requiring blood samples or physical tests reported lower levels of participation than other less invasive studies [279]. Moreover, a review of the challenges of finding the most effective treatment for pain in intellectually disabled children by Valkenburg et al. (2015) found that children with intellectual disability were more at risk of medication side effects, and that pharmacodynamics can be altered in various groups of children with intellectual disability [280], necessitating greater caution. The authors of this review note that new sampling methods and opportunistic screening may improve the feasibility of pediatric pharmacokinetic studies [280].

A recent UK cross-sectional study by McMahon et al. (2021) examining the prevalence of potential DDIs in 217 adults with intellectual disability, found that potential DDIs of clinical significance were common, with a total of 519 potential DDIs of clinical significance identified [281]. In total, 105 participants were exposed to at least one potential DDI of clinical significance [281]. This study showed that every prescribed drug led to a 0.87 (95%CI 0.72-1.0) increase in having a potential DDI of clinical significance [281].

Results from pharmacokinetic studies in the general population are often extrapolated into the intellectually disabled population. The following sections in this Chapter examine interactions between psychotropic medication and AEDs arising from studies conducted in the general population due to a lack of suitable studies in people with intellectual disability. However, the body may process a drug differently in people with intellectual disability due to differences in physical stature leading to variations in volumes of distribution, changes in electrolytes and modifications of renal and hepatic capacity [147]. Therefore, it is important to highlight that the response to individual drugs may differ between the intellectual disability and general populations [147].

1.10.2 Interactions between antidepressants and AEDs

Enzyme inducing AEDs, particularly carbamazepine, phenytoin and the barbiturates induce the metabolism and decrease the plasma concentration of many concomitantly prescribed antidepressants (*Table 1.10-1*) [282, 283]. They are believed to be inducers of numerous drug metabolizing enzymes including CYP-1A2,2A6,2B6,2C9,2C19,3A4 and UGTs-1A1, 2B7, 2B15 [284]. Valproic acid is believed to have broad spectrum enzyme inhibition potential involving CYP-2C9, 2C19, 3A4 and UGTs- 1A4 and 2B7 [284].

Table 1.10-1 Antidepressant drugs (adapted from Mula (2008) [285])

Antidepressant class	Antidepressant name
Tricyclic Antidepressants (TCA)	Amitriptyline Nortriptyline Clomipramine Imipramine Desipramine Trimipramine Maprotiline Amoxapine Doxepin
Monoamine Oxidase Inhibitors (MAOIs)	Phenelzine Tranylcypromine Isocarboxazid
Reversible Inhibitors of Monoamine Oxidase A (RIMAs)	Moclobemide
Selective Serotonin Reuptake Inhibitors (SSRIs)	Citalopram Escitalopram Fluoxetine Paroxetine Sertraline Fluvoxamine
Norepinephrine and Dopamine Reuptake Inhibitor (NDRIs)	Bupropion
Selective Noradrenergic Reuptake Inhibitor (NRI)	Reboxetine
Serotonin and Norepinephrine Reuptake Inhibitor (SNRIs)	Venlafaxine Duloxetine
Serotonin 2 Antagonists/Serotonin Reuptake Inhibitors (SARIs)	Trazodone
Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs)	Mirtazapine Mianserin

Tricyclic Antidepressants (TCAs)

Amitriptyline, clomipramine and imipramine are largely metabolised by CYP1A2, 2D6 and 3A4 [277]. Nortriptyline and desipramine, the active metabolites of amitriptyline and imipramine are metabolized by CYP2D6 [277]. Valproic acid might inhibit the metabolism of amitriptyline, nortriptyline and clomipramine [282]. Valproic acid has been associated with a 50-60% increase in the plasma concentrations of amitriptyline and nortriptyline potentially leading to supra-therapeutic plasma levels and worsening of seizure control [282, 286, 287]. An interaction between valproic acid and clomipramine could also result in increased plasma levels of clomipramine raising the risk of seizure [283]. A case study

highlighted how one patient with epilepsy that was well controlled on valproic acid, suffered prolonged status epilepticus following co-prescription of 75mg clomipramine [288]. Regarding the effect of TCAs on AEDs, a review by Houghton et al. (1975) highlighted how nortriptyline can produce a small increase in serum phenytoin concentrations which is unlikely to be of clinical importance [289]. Another UK case report study by Perucca et al. (1977) found an increase in serum phenytoin levels in two patients with epilepsy aged 29 and 34 years, who were resident in an epilepsy centre following administration of the antidepressant imipramine but the phenytoin serum levels returned to normal following withdrawal of the antidepressant [290].

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs undergo phase 1 oxidation via one or multiple CYP450 pathways [273]. With the exception of sertraline, all SSRIs are metabolised by CYP2D6 [285]. Paroxetine is primarily metabolised by this isoenzyme making it especially prone to drug interactions [273, 285]. SSRIs metabolised by two CYP450 isoenzymes include citalopram (3A4, 2C19), fluoxetine (2D6,2C9) and fluvoxamine (2D6,1A2) [273]. Those metabolised by three CYP450 isoenzymes include escitalopram (2D6, 2C19, 3A4) and sertraline (2C9, 2C19, 3A4) [273]. A lower risk of drug interactions is found for drugs metabolised through multiple pathways due to additional pathways accessible if one CYP450 isoenzyme is inhibited [273]. Fluvoxamine is a strong inhibitor of CYP1A2, CYP2C9 and CYP2C19, with a moderate effect on CYP3A4 and a low effect on CYP2D6 [273, 285]. Fluoxetine and paroxetine are inhibitors of CYP2D6 with high potency and CYP1A2 with low potency [273, 274, 285]. Fluoxetine is also known to inhibit CYP2C9 moderately and CYP2C19 with low potency [273]. A number of reports exist of plasma phenytoin concentrations increasing to toxic levels following

fluoxetine administration, with cause attributed to inhibition of CYP2C9, which contributes to the metabolism of phenytoin [283]. In vitro and in vivo studies show a moderate inhibitory activity of norfluoxetine, the major metabolite of fluoxetine on CYP2D6 and CYP3A4 [285]. Sertraline is believed to weakly inhibit CYP-1A2, 2C9, 2C19 and 2D6 [273, 274, 285], however, this is not believed to be of clinical significance [285]. The SSRI citalopram and its s-enantiomer escitalopram are recognised to be less likely to cause drug interactions due to weak inhibitory effects on CYP2D6 [273, 274, 285].

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) & others

The SNRIs venlafaxine and duloxetine are both metabolized by two isoenzymes (venlafaxine (CYP2D6, CYP3A4), duloxetine (CYP2D6, CYP1A2)) [273]. Duloxetine inhibits CYP2D6 with moderate to high potency, whereas venlafaxine inhibits with low to negligible potency [273]. Venlafaxine and duloxetine both exhibit greater inhibition of serotonin reuptake than norepinephrine reuptake, leading to a greater risk of serotonin syndrome when in combination with other serotonin augmenting drugs [273]. Accordingly, both venlafaxine and duloxetine are contraindicated in conjunction with monoamine oxidase inhibitors (MAOIs). A similar reaction can be found with SSRI-MAOI drug combinations [273]. Regarding other antidepressants, bupropion is metabolised by CYP2B6, and is a moderate to potent inhibitor of CYP2D6 [273]. It has been known to increase the plasma level of venlafaxine and other CYP450 substrates when used in combination [273]. Mirtazapine is oxidised by numerous CYP450 isoenzymes (CYP1A2, CYP2D6, CYP3A4) and it inhibits CYP2D6 with low to negligible potency leading to low risk of adverse drug interactions [273].

1.10.3 Interactions between antipsychotics and AEDs

Table 1.10-2 Antipsychotic drugs (adapted from Mula (2016) [284])

Antipsychotic class	Antipsychotic name
First generation antipsychotics (Typical Antipsychotics)	
	Chlorpromazine
	Trifluoperazine
	Haloperidol
	Fluphenazine
	Loxapine
	Perphenazine
	Pimozide
	Prochlorperazine
	Zuclopenthixol
	Flupenthixol
	Benperidol
Second generation antipsychotics (Atypical Antipsychotics)	
	Olanzapine
	Clozapine
	Aripiprazole
	Asenapine
	Quetiapine
	Risperidone
	Ziprasidone
	Paliperidone
	Sulpride
	Amisulpride

Typical & atypical antipsychotics

Enzyme inducing AEDs have been shown to reduce the plasma concentration of numerous antipsychotics (*Table 1.10-2*), both first and second generation antipsychotics, including chlorpromazine, mesoridazine (active metabolite of thioridazine), clozapine, haloperidol, olanzapine, risperidone, ziprasidone, and quetiapine [282, 284]. Carbamazepine, for example, is a potent inducer of different CYP450 isoenzymes including CYP1A2 and CYP3A4 [283]. This can result in a substantial decrease in the plasma concentrations of many antipsychotics [283]. In case reports and pharmacokinetic studies, the combination of carbamazepine and haloperidol resulted in substantial decreases in the plasma haloperidol

concentration [283, 291, 292]. Carbamazepine has also been shown to reduce the plasma concentration of clozapine which is metabolized by CYP1A2 and CYP3A4 [283, 293]. Decreases in the plasma concentration of olanzapine and risperidone with concomitant carbamazepine have also been reported [283, 294-296]. Newer generation antipsychotics are typically weak in vitro inhibitors of CYPs, thus they are not anticipated to influence the metabolism of co-administered AEDs [283].

1.11 Aims and objectives of thesis

1.11.1 Aim of thesis

The overall aim of this thesis is to examine the characteristics of participants with intellectual disability reporting a diagnosis of epilepsy and mental health disorders, and the patterns of their medication use with regards to psychotropic drugs.

1.11.2 Objectives of thesis

a) To examine demographic and clinical factors relating to the prevalence of epilepsy and use of antiepileptic drugs (AEDs) in a nationally representative sample of older adults with intellectual disability and epilepsy in Ireland.

b) To investigate AED therapy in people with epilepsy and intellectual disability using three drug utilisation research methods - monotherapy/polytherapy, AED load $<2/\geq 2$ and numerical AED load.

c) To examine the use of AEDs and co-prescribed psychotropic medications with the potential to lower the seizure threshold, and assess the impact on seizure frequency.

d) To determine the relationship between challenging behaviour and use of antiepileptic drugs and AED load in people with epilepsy.

e) To investigate the demographic characteristics of older adults with intellectual disability reporting a mental health disorder, and investigate the patterns and use of psychotropic medication.

1.11.3 Data used in thesis

This thesis uses IDS-TILDA Wave 3 data to examine epilepsy and mental health problems in people with intellectual disability. Epilepsy has also been examined in Wave 1 of this study [28, 29]. However, owing to the fact that only three Waves of data have been collected (at three yearly intervals) during the time of this PhD research analysis, this study utilises data solely from the third Wave, and thus can be better described as a cross-sectional study. The narrow time frame of data collected to date, different characteristics examined from earlier waves and difficulties in acquiring complete medication dosage data in the first Wave demand further Waves of data to be completed prior to any meaningful longitudinal analysis being undertaken. Further detail on the data used can be found in *Chapter 2*.

1.11.4 Thesis structure

Chapter 2 of this thesis details the methodology used in succeeding Chapters, providing additional detail regarding the study design and methods employed. Reference to sections of this Chapter can be found throughout the thesis to avoid repetition.

The topic of epilepsy is introduced in ***Chapter 3*** with a focus on epilepsy prevalence and use of antiepileptic drugs (AEDs) in people with a dual diagnosis of epilepsy and intellectual disability. Owing to the significant comorbidity associated with an epilepsy diagnosis, this Chapter also examines physical and psychiatric comorbidity using bivariate analysis, comparing participants with and without an epilepsy diagnosis. Furthermore, the prevalence of psychotropic medication is introduced, a theme explored throughout this thesis.

Chapter 4 delves further into patterns of AED use with evaluation of three AED utilisation methods – monotherapy/polytherapy, categorised AED load $<2/\geq 2$ and numerical AED load. A series of bivariate and non-parametric tests were undertaken to examine these methods with regards to demographic and clinical characteristics of participants with epilepsy and intellectual disability.

Chapter 5 examines AED use, seizure frequency and effect of psychotropic medication with the potential to lower the seizure threshold in participants with epilepsy and intellectual disability. Psychotropic medication were categorised according to seizure risk – low/moderate/high risk. Binary logistic regression was utilised to identify factors

associated with seizure frequency. This Chapter is based on a publication in the *Journal of Applied Research in Intellectual Disabilities*.

Chapter 6 expands on the concept of AED load and examines the relationship between AED load and challenging behaviours – self-injurious behaviour (SIB), aggressive/destructive behaviour and stereotyped behaviour in older adults with epilepsy and intellectual disability. Behaviours were assessed using the Behaviour Problems Inventory Short Form (BPI-S). Non-parametric tests and binary logistic regression were performed to determine the relationship between AED load and challenging behaviours. This Chapter is based on a publication in the Journal *Epilepsy & Behavior*.

Chapter 7 focuses on the central theme of psychotropic pharmacotherapy, this time in all participants with intellectual disability in the IDS-TILDA study. It investigates the prevalence and factors associated with reporting a mental health disorder, psychotropic pharmacotherapy and psychotropic polypharmacy. The prevalence of psychotropic medication in those exhibiting challenging behaviour with regards to reporting a mental health disorder is examined. Binary logistic regression was undertaken to identify factors associated with reporting psychotropic polypharmacy, with a diagnosis of epilepsy included as a potential predictor in the model.

Chapter 8 presents a thorough discussion of the main findings of this thesis, the limitations identified and recommendations and implications for practice. It is hoped that this thesis assists in reducing the scarcity of epilepsy research in people with intellectual disability, aiding policy development and contributing to evidence based practice.

Chapter 2

Methodology

2.1 Introduction

Increased life expectancy of people with an intellectual disability is a tremendous societal achievement. However, it is laden with challenges, in particular, a lack of information on health and ageing in this population group in order to inform health and social policy. The IDS-TILDA study was borne out of a desire to address these challenges, and it became the first study in Europe with the ability to compare ageing between general and intellectual disability populations by co-ordinating with TILDA, the longitudinal study of ageing in the general population in Ireland [30] . The IDS-TILDA study includes participants of all age groups ≥40 years, male and female, with all levels of intellectual disability and living in all types of residential settings [30].

To create the original Wave 1 sample, 1800 'pins' (participant identifiers) were randomly selected by the National Intellectual Disability Database of Ireland (NIDD) according to inclusion/exclusion criteria [30]. A response rate of 45-50% was expected, consistent with sampling reported in social studies [30, 297]. A response rate of 46% was achieved [30]. The NIDD then released the pin numbers of potential participants to the Regional Disability Database Administrator (RDDA) who verified the pins, and ensured the individual concerned was currently registered on the NIDD. To preserve confidentiality in all aspects of this process, IDS-TILDA provided the RDDA with invitation packs and they posted the packs to potential participants [30].

The original sample showed that 24% of participants had a mild intellectual disability, 46% a moderate intellectual disability, 24% a severe intellectual disability, 5% a profound intellectual disability, and approximately 5% had an unverified level of intellectual disability [30]. In 50% of cases, the cause of intellectual disability was unknown. In cases where cause of intellectual disability could be identified, 20% reported having

Down Syndrome and 17.3% reported multiple causes including trauma at birth, cerebral palsy, autism and road traffic accidents [30]. A further 12.7% reported that they did not know [30].

2.1.1 Representativeness of the IDS-TILDA sample

Comparisons of participants in the original Wave 1 sample proved largely representative of the population of people registered on the 2008 NIDD, with some discrepancies with regards to age, gender and type of residence [30, 298]. *Table 2.1-1* [20] allows comparison between the IDS-TILDA sample and the NIDD. A greater proportion of people aged <50 years were registered on the 2008 NIDD (46.9%) compared to 38.2% of Wave 1 participants. With regards to gender, there was a higher prevalence of males (50.8%) registered on the 2008 NIDD compared to females (49.2%). This is in contrast to the IDS-TILDA Wave 1 sample which had a higher prevalence of females (55.5%). In addition, a greater proportion of people registered on the 2008 NIDD lived in independent/family settings (35.1%) compared to 17.1% of Wave 1 participants. Moreover, a greater proportion of Wave 1 participants (47.3%) lived in residential/campus settings compared to 34.4% of people registered on the 2008 NIDD.

Data in this thesis are drawn from **Wave 3** (2016/2017). Ageing over the 10 years between Wave 1 and Wave 3 had an impact on the representativeness of the sample in Wave 3. As expected, the number of people aged <50 years in Wave 3 decreased to 11.8% due to ageing, a third of the 35.8% of people aged <50 years registered on the 2017 NIDD. This ageing led to an increase in the 50-64 year age group in Wave 3 (62.6%), higher than the 45.2% of people aged 50-64 years registered on the 2017 NIDD. Similar to Wave 1, a greater proportion of males were registered on the 2017 NIDD (52.3%), with a greater

proportion of females (55.8%) in Wave 3 of the study. A greater proportion of people with a mild intellectual disability were registered on the 2017 NIDD (30.0%) compared with the Wave 3 sample (24.8%), whereas a greater proportion of people with a severe/profound intellectual disability (29.1%) were found in the Wave 3 sample compared with 23.0% of people registered on the 2017 NIDD. A higher proportion of people registered on the 2017 NIDD (42.3%) were living in independent/family settings compared to 15.6% of the Wave 3 sample. On the other hand, 44.0% of Wave 3 participants lived in residential/campus settings compared to 24.0% of people registered on the 2017 NIDD. Therefore, compared to the 2017 NIDD register, the Wave 3 sample has fewer participants aged <50 years, greater numbers aged 50-64 years and 65+ years, a higher prevalence of females, fewer participants with a mild intellectual disability and greater numbers of participants with a severe/profound intellectual disability, less people living in independent/family settings and greater numbers of participants living in residential/campus settings.

Table 2.1-1 Representativeness of sample – comparisons of demographic data from the NIDD and the IDS-TILDA sample who responded [20]

Demographic characteristic	NIDD 2008	IDS-TILDA Wave 1 (2009/2010)	IDS-TILDA Wave 2 (2013/2014)	NIDD 2017	IDS-TILDA Wave 3 (2016/2017)
Total	8470	753	708	10589	609
	n (%)	n (%)	n (%)	n (%)	n (%)
Age					
<50 years	3970 (46.9)	288 (38.2)	197 (28.1)	3792 (35.8)	72 (11.8)
50-64 years	3482 (41.1)	343 (45.6)	356 (50.8)	4786 (45.2)	381 (62.6)
65+ years	1018 (12.0)	122 (16.2)	148 (21.1)	2001 (19.0)	156 (25.6)
Missing	-	-	8 (1.1)	-	-
Gender					
Male	4305 (50.8)	335 (44.5)	312 (44.1)	5548 (52.3)	269 (44.2)
Female	4165 (49.2)	418 (55.5)	396 (55.9)	5041 (47.6)	340 (55.8)
Level of intellectual disability					
Mild	2341 (27.6)	167 (24.0)	158 (24.2)	3175 (30.0)	139 (24.8)
Moderate	3756 (44.3)	323 (46.5)	304 (46.5)	4868 (46.0)	259 (46.2)
Severe/profound	2209 (26.1)	205 (29.5)	192 (29.4)	2444 (23.0)	163 (29.1)
Missing/not verified	164 (1.9)	58 (7.7)	54 (7.6)	102 (0.9)	48 (7.9)
Type of Residence					
Independent/family	2976 (35.1)	129 (17.1)	115 (16.3)	4469 (42.3)	95 (15.6)
Community group home	2496 (29.5)	268 (35.6)	307 (43.5)	3564 (33.7)	246 (40.4)
Residential/campus	2957 (34.4)	356 (47.3)	284 (40.2)	2531 (24.0)	268 (44.0)

2.1.2 Sample refreshment in Wave 4

A sample refresh was undertaken in Wave 4 (2019/2020) in order to address participant attrition, make the sample more representative of the NIDD register and to replace the deficit of participants in the 40-49 age group due to ageing of the sample. This was undertaken by drawing an age stratified random sample in batches from the NIDD. The work was undertaken by the Health Research Board (HRB). A total of 1510 pins were selected and the service providers were contacted by the HRB. Invitation packs were sent to service providers by IDS-TILDA. The pins were subsequently matched by the service providers. If an individual was interested, they made contact with IDS-TILDA directly. In total, 739 people took part in Wave 4 of this study (2019/2020) [299]. A summary table of demographic characteristics of participants in Wave 4 can be found below (*Table 2.1-2*). However, the author (RM) was not involved with data collection or any analysis of data pertaining to Wave 4 of this study.

Table 2.1-2 Demographic characteristics of Wave 4 participants n=739 [299]

Demographic characteristic	**Wave 4 participant n (%)**
Gender	
Male	344 (46.5)
Female	395 (53.5)
Age	
<50 years	135 (18.3)
50-64 years	407 (55.1)
65+ years	197 (26.7)
Level of intellectual disability	n=689
Mild	204 (29.6)
Moderate	293 (42.5)
Severe/profound	192 (27.9)
Type of residence	n=730
Independent/family	126 (17.3)
Community group home	358 (49.0)
Residential/campus setting	246 (33.7)

2.2 Study design

2.2.1 Wave 3

For Wave 3 (August 2016-February 2017), all participants who had taken part in Waves 1 and 2 and who agreed to be contacted again were invited for interview. To reduce the burden on participants, information previously given in the physical health section was 'fed forward' from previous Waves and confirmed or updated in Wave 3 [300]. A comprehensive training programme was undertaken by 24 field researchers on 8-10th August 2016, with six field researchers returning from previous Waves [300]. Caseload assignment took place in early September 2016. Three objective measures were included in Wave 3, including weight, waist size and mid upper arm circumference (MUAC) [300]. Specific training was provided to field researchers in carrying out these measurements. Waist size and MUAC were used to calculate BMI. MUAC is an alternative method to calculate BMI for people immobile and unable to stand independently on the scales [300].

The response rate for participants alive at Wave 2 (n=638) was 95.5% (609/638) [300]. In total, 70.7% of attrition was due to deaths, 28.3% withdrew and 1.0% were lost to follow up. The response rate for Wave 3 (based on 708 Wave 2 participants) was not significantly different for men (86.2%) and women (85.9%) [300]. A significant decrease in response rate was found for age groups (based on age at Wave 1) – 91.4% of participants aged <50, 85.8% aged 50-64 years, and 72.6% aged 65+ years [300]. A pre-interview questionnaire (PIQ) was returned by 97.5% (n=594) of Wave 3 participants. Owing to changes in policy regarding housing and supports, a number of new questions were asked of participants in Wave 3 including whether moving residence was part of a participants' personal plan, reasons for multiple moves, where they occurred and personal outcomes of moves, ownership and tenure of accommodation, whether a participant had a key to their

own home, choice, person centred planning and access to housing and tenancy options [300].

Issues emerging from Waves 1 and 2 led to the addition of a number of additional scales in Wave 3. The following table outlines these scales (*Table 2.2-1*):

Table 2.2-1 Additional scales added in Wave 3 (Adapted from IDS-TILDA Wave 3 Report [300])

Scale	Rational
Physical activity The Rapid Assessment of Physical Activity (RAPA) (9-item self-report questionnaire) [301].	Measures level and intensity of physical activity for aerobic exercise, strength and flexibility.
Life satisfaction The Satisfaction with Life Scale (SWLS) is a 5-item self-report scale rated on a 6-point scale. The Purpose in Life Questionnaire is a 7-item subscale from The Ryff Psychological Wellbeing Scale, rated on a 6-point scale [302].	The scales measure global life satisfaction and purpose in life allowing comparisons with TILDA, Health and Retirement Study (HRS) and English Longitudinal Study of Ageing (ELSA).
Personal well-being and social connectedness Closeness sub-scale of the Friendship Qualities Scale. (5-item scale with responses on a 5-point rating scale) [303]. Intimacy sub-scale of the McGill Friendship Questionnaire. (5-item scale with responses on an 8-point rating scale) [304]. Quality of life sub-scale from the Personal Wellbeing Index - Intellectual Disability Version. (8-item scale with responses on an 11-point rating scale) [305].	The scales regarding social connectedness, friendship and personal well-being were added to better understand the quality of life and relationships for older adults with intellectual disability.
Mental health 20-item Glasgow Depression Scale – Learning disability (GDS-LD) and 27-item Glasgow Anxiety Scale – Learning Disability (GAS-LD) [306, 307].	High prevalence of mental health problems in Waves 1 and 2 required further investigation.
Behaviours that challenge The Behaviour Problems Inventory- short form (BPI-S) was used to measure the frequency and severity of a range of self-injurious, aggressive and stereotyped behaviours. (30-item questionnaire) [95].	Preliminary questions in Wave 2 indicated a high prevalence of behaviours that challenge/challenging behaviour in cohort.
Dementia Dementia Screening Questionnaire for individuals with Intellectual disability (DSQID) (43-item questionnaire rated on a 4-point scale [308].	Increased risk of developing dementia in people with Down Syndrome was confirmed in Wave 2.

2.2.2 Longitudinal observational study

These studies involve repeating observations over time and can be used to study trends in drug utilisation to identify patterns or changes over a period of time [309]. Studies involve examining the same cohort over time (closed cohort) or repeated cross-sectional studies with new cohorts (open/dynamic cohort) [309]. The IDS-TILDA study is an example of a closed cohort longitudinal observational study.

2.2.3 Cross-sectional study

These studies can describe the observation, for example, the utilisation of drugs, in a given population at a given point in time [309]. Drug prescribing, dispensing and consumption data can be collected with demographic utilisation patterns analysed [309]. It is essential to note the lack of a causal effect relationship in these studies as information is not available regarding whether the factor of interest precedes or follows the effect [309].

2.2.4 Patient reported medication data

IDS-TILDA is a self-report study [30, 300]. However, due to difficulties in ability and understanding in more severe levels of intellectual disability, much of the medication data and other clinical variables would have been confirmed by a proxy, be it a family member, carer, nurse, or health professional who would have known the participant a minimum of six months. Regardless, patient reported data is incredibly valuable in gaining insight in drug utilisation studies, especially in relation to medication adherence; barriers to use; identification of adverse effects; beliefs regarding health and medication use; information on consumption of prescription and over-the-counter (OTC) medications/herbal drugs; and other information not necessarily ascertained by medical and dispensing records [310].

Nevertheless, patient self-reported data is not without its difficulties. Recall bias, misinformation, misinterpretation and non-response are just some of the difficulties that can be encountered [310-313]. Thus the use of proxy respondents is a necessity for many studies, particularly of older people, and indeed for studies of people with intellectual disability to validate and improve the quality of the data acquired [310]. With use of proxy data, two important risks of potential bias are the *'proxy effect'* with the proxy under-reporting due to a lack of knowledge and information, and '*the saliency principle'* where a proxy over-reports issues the proxy themselves deem to be most relevant [310]. The following table illustrates the breakdown of the sections of interest in this thesis by answering style in the CAPI interview (self-report/proxy report or combination of both) (*Table 2.2-2*). No data was available for a similar breakdown for the pre-interview questionnaire (PIQ).

Table 2.2-2 Answering style of sections of interest in this thesis

Section of interest	**Self-report only**	**Proxy only**	**Combination of self-report and proxy**
Epilepsy questions	20.8%	48.5%	30.7%
Mental health questions 1. Diagnosis questions			
Hallucinations	14.3%	28.6%	57.1%
Anxiety	11.8%	31.8%	56.4%
Depression	16.8%	30.5%	52.6%
Emotional problems	14.5%	27.7%	57.8%
Schizophrenia	18.2%	22.7%	59.1%
Psychosis	4.8%	23.8%	71.4%
Mood swings	11.0%	31.9%	57.1%
Manic depression	18.2%	27.3%	54.5%
PTSD	0%	0%	0%
Other	4.0%	32.0%	64.0%
2. Getting treatment/who provides treatment questions	11.8%	30.0%	58.3%
Behavioural questions (informant questionnaire) (BPI-S in PIQ)	0%	100%	0%

2.2.5 TILDA study

The IDS-TILDA study runs in parallel and complements The Irish Longitudinal Study on Ageing (TILDA) [314]. The goal of TILDA is to *"make Ireland the best place in the world to grow old"* [314]. TILDA collates information on all aspects of health, economic, and social circumstances from people aged 50 years and older, every two years via self-completion questionnaires (SCQ), computer assisted personal interviews (CAPI) and health assessments (HA) [315, 316]. TILDA was born out of the necessity to have a longitudinal study on ageing in Ireland in response to the growing ageing global population, and the profound impact this ageing will have on society [315, 316]. According to data from the United Nations (World Population Prospects; the 2019 revision), by 2050, an estimated one in six people in the world will be aged 65 years and older, increased from one in eleven in 2019 [317].

The principal objectives of the TILDA study include: a) to provide an integrated and representative database covering the key domains of the lives of older adults, comprising health, income, living conditions, social contact, accommodation, environment and family circumstances; b) to give older people a voice within the national conversation through documenting and publicising their concerns, experiences and expectations; c) to provide comprehensive base-line data on older people in Ireland; d) to link with and learn from best international studies in this field; e) to collaborate with other cutting-edge research initiatives in Ireland; e) to build an understanding that ageing affects more than the old; f) to build capacity in ageing research in Ireland [315].

The sampling framework used in TILDA is the RANSOM system based on the Geodirectory, developed by the Economic and Social Research Institute (ESRI) of Ireland [315, 316]. This differs to IDS-TILDA which uses the NIDD database due to large numbers

of people with an intellectual disability living in residential settings [30]. The TILDA study does not address ageing of people with an intellectual disability, which led to the conception of IDS-TILDA which was designed to address the lack of ageing research and longitudinal studies of older people with an intellectual disability, in a bid to help inform national policy and give a voice to people with intellectual disability.

2.2.6 IDS-TILDA underpinning conceptual framework (Figure 2.2-1)

The conceptual framework illustrates the range of data collected by IDS-TILDA across physical health, cognitive, psychological, behavioural, healthcare and social categories. Sections of relevance to this thesis are highlighted in red.

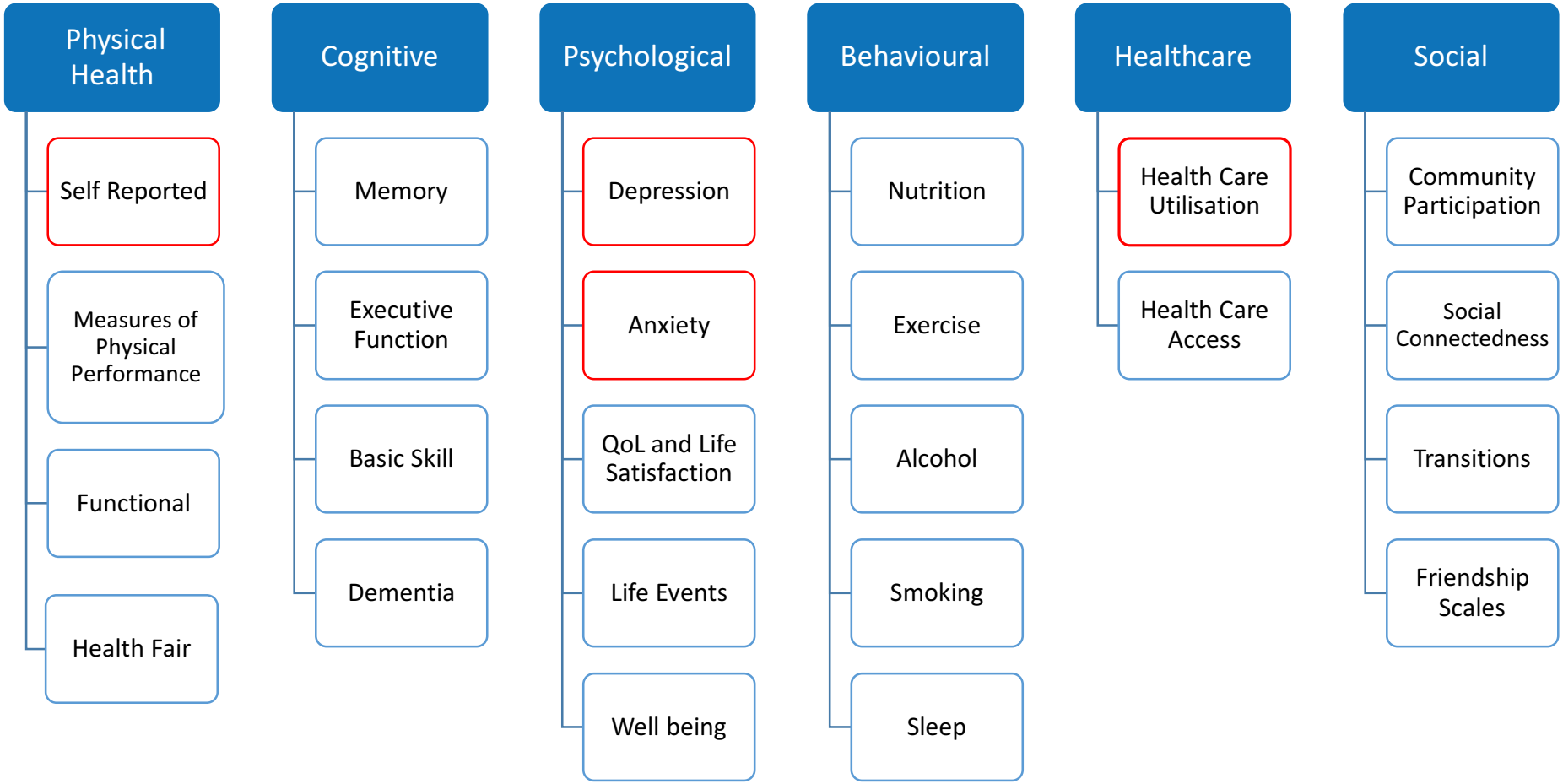


Figure 2.2-1 IDS-TILDA conceptual framework

2.2.7 IDS-TILDA ethos

The IDS-TILDA Wave 1 report underlines the study ethos *"The underpinning ethos of promoting the inclusion and participation of people with an intellectual disability guided the design of the study, as did maximising comparability with The Irish Longitudinal Study on Ageing (TILDA) and other European and International studies on ageing. In addition, the study included measures and topics that are particularly and uniquely relevant to people with intellectual disability"* [30].

2.2.8 IDS-TILDA team & International Scientific Advisory Committee

The IDS-TILDA team consists of a multidisciplinary group of experts, encompassing the specialities of intellectual disability nursing, psychiatry, psychology, sociology, pharmacology, statistics, dentistry and economics who are involved in research, supervision, teaching and advocacy. Supervisory activities range from undergraduate summer research projects, undergraduate thesis projects, master thesis projects, MD thesis projects, PhD thesis projects to Post-Doctoral research fellowships. An International Scientific Advisory Committee was formed to oversee the study. Each member of the committee was chosen for their extensive expertise in the field of intellectual disability research and in working with people with an intellectual disability [30].

2.2.9 Inclusion of people with intellectual disability in the study

People with an intellectual disability were involved in every stage of the development, design, implementation and evaluation of the study. This is very important as the study is fully committed to the principle of *"nothing about us, without us"* [30]. Enormous contributions have been made by people with an intellectual disability in the design of pictorial explanations of material including consent forms and questionnaires with the goal

of increasing the accessibility of the study. People with an intellectual disability also contribute to the training of fieldworkers prior to data collection with valuable advice at the training sessions and assessment of individual fieldworkers in order to maintain high standards of respect and inclusivity.

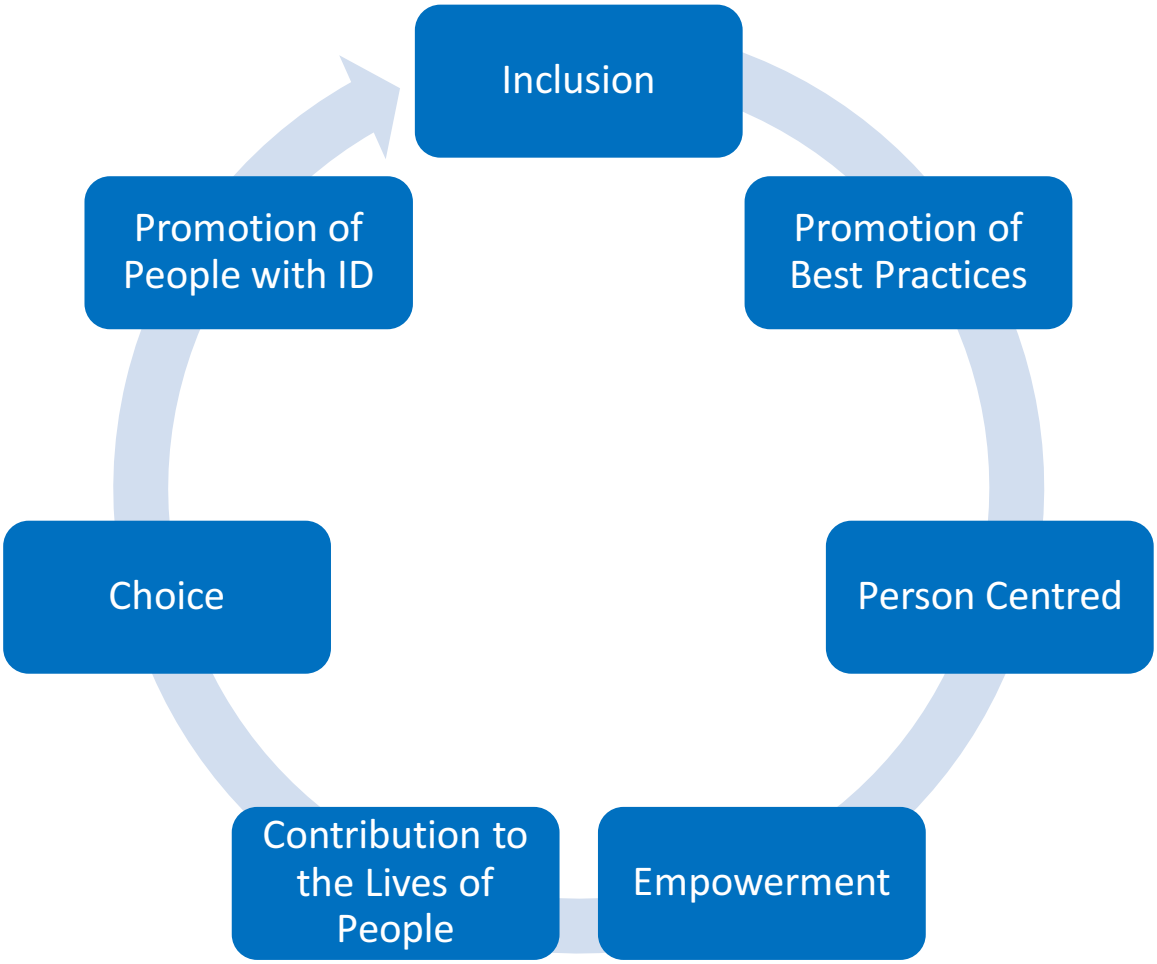


Figure 2.2-2 IDS-TILDA values framework

2.3 Study recruitment process

2.3.1 Participants

At Wave 1, a total of 753 people (*figure 2.3-1*) aged between 41 and 90 years with an intellectual disability were recruited following consent and protocol completion, representing 8.9% of people aged 40 years and over who were registered on the 2008 NIDD database [28]. Where an individual was not in a position to provide consent, a family member or guardian could sign a letter of agreement for their relative to participate. A comparison of demographics by McCarron et al (2011) showed the IDS-TILDA sample to be representative of this population group [30], as previously outlined. Participants live independently/with family, in community group homes, or in residential/campus settings. Residential/campus settings were defined as living arrangements where 10 or more people share a single living unit or where the living arrangements are campus based, i.e., there are a cluster of living units. Community group homes are in a community setting with staff support for small groups of people with intellectual disabilities. Independent/family settings means living independently or living with family in the community.

For this study, the number of people taking part in Wave 3 was 609 with 44.2% male and 55.8% female. The age range for Wave 3 was 48 to 95 years with a mean of 59.1 years (SD: 8.81) [300]. Level of intellectual disability is associated with intelligence quotient scores [318] - mild (50-69), moderate (35-49), severe (20-34) and profound (<20). Case notes for each participant, where possible confirmed the correct classification. Overall in Wave 3, 24.8% had a mild intellectual disability, 46.2% a moderate intellectual disability and 29.1% a severe/profound intellectual disability [300].

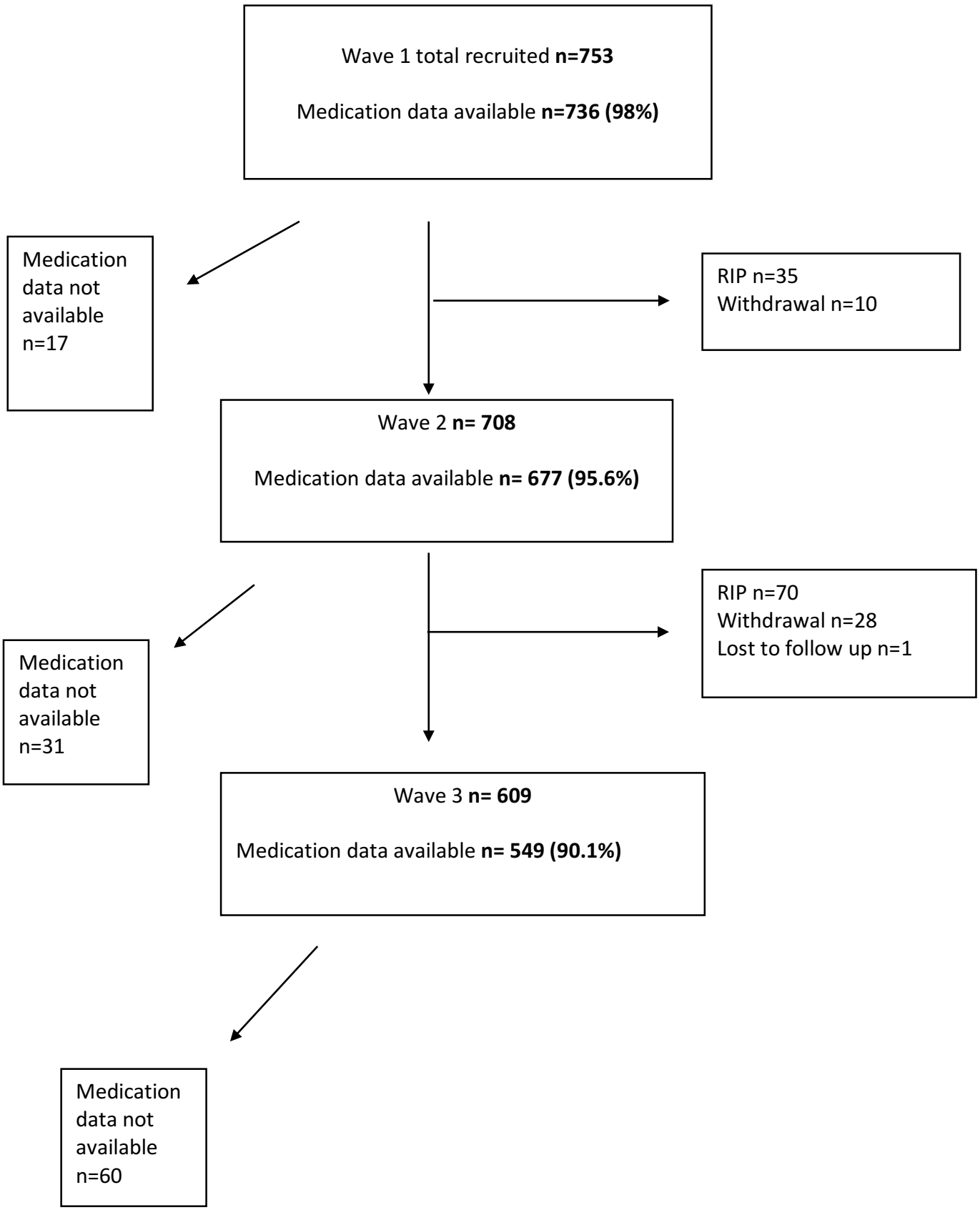


Figure 2.3-1 Flow chart of participation in the IDS-TILDA Study

2.4 Ethical approval, consent & GDPR

The IDS-TILDA study received ethics approval from the Faculty of Health Sciences, Ethics Committee at Trinity College Dublin and all 138 intellectual disability service providers. Ethics approval was granted by the Faculty of Health Sciences, Ethics Committee at Trinity College Dublin on 10th July 2008. A copy of this letter can be found in *Appendix 1* of this thesis. People with an intellectual disability who were to receive invitation packs were associated with 138 intellectual disability service providers, and local and/or regional ethical approval was sought and received from each provider over an 18-month period, prior to the sending of invitation packs [30]. A local letter of support for the study was then requested from the service provider and included in the invitation packs once ethical approval was received [30].

2.4.1 Consent

IDS-TILDA strives to get informed consent from participants. Accessible information booklets and consent forms are produced and every field researcher is trained in the process of gaining consent. The cover of the accessible information booklet can be found in *Appendix 6* and the consent form in *Appendix 7*. A system of 'process consent' is implemented in the study, whereby participants' consent is not assumed throughout the entire interview process and is instead reviewed at multiple stages to ensure participants are willing participants and understand they have the right to withdraw at any stage.

2.4.2 Assisted Decision-Making (Capacity) Act 2015

Since 2015, the Assisted Decision-Making (Capacity) Act 2015 has changed how consent is viewed in Ireland. Since this legislation was enacted, it is now presumed in law that an

individual can provide consent unless it is proven otherwise. This legislation established new roles and regulations that will appoint people to support an individual to make decisions, co-decision makers and if necessary, for decisions to be made on a person's behalf [319]. Regarding people with intellectual disability, it is not always possible for informed consent to be obtained, so proxy respondents have been invited to participate on behalf of the person. This, however, is not allowed under the General Data Protection Regulation (GDPR) [320] and the Health Research Regulations, 2018 (HRR) [321]. This means that data collected previously where no consent was given or sought would have to be destroyed.

The only exception to seeking re-consent (or indeed collecting data from an individual who cannot consent) is to get a waiver from the Health Research Consent Declaration Committee (HRCDC) [322] for any data supplied in the past or future by people unable to consent. The HRCDC issued a conditional declaration to IDS-TILDA on the 17th October 2019 which is valid until October 31st 2021 and 5 years thereafter (until October 31st 2026), or upon confirmation that the data has been rendered anonymised or destroyed or whichever comes first [319].

To find a permanent solution to this problem, the HRCDC wrote to the Department of Health in Ireland advising that they change the Health Research Regulations (HRR) with the following [323]: *"An amendment aimed at finding a workable basis for the processing of personal data for health research where an adult lacks capacity to consent. The Department is of the view that the requirement for explicit consent in the case of someone who lacks capacity to consent means that the very people who might benefit from particular research studies will not be able to allow their personal data to be used for such research and that is not consistent with public policy and the values underpinning a patient*

centered health system. An amendment has therefore been prepared reflecting the core principles set out in the Assisted Decision-Making (Capacity) Act 2015 and the HSE National Consent Policy".

The IDS-TILDA study fully complies with the requirements of the General Data Protection Regulation (GDPR). In addition, researchers were required to undertake a GDPR learning module using the Trinity College Dublin Blackboard Learning system which was completed by the author (RM).

2.4.3 Access to data and data protection

In order to access variables, a researcher is required to submit a request to the study Data Controller detailing the reasons why the data is required. Access to data is granted following review. A strict access protocol is in place to ensure that no researcher has access to the complete dataset or any identifying variables. Participants are given anonymised pins. Any identifiable personal data is only accessible to the Principal Investigator (PI), the Project Manager and the Senior Executive Officer. In addition, access to the data is possible only via a secure computer drive using designated encrypted "hot desks" in the IDS-TILDA study office, in the School of Nursing and Midwifery. No data could be removed from these computers or transferred to personal computers. All variables utilised in this study can be found in *Appendix 8*.

2.4.4 Confidentiality and sharing of information

Confidentiality is of paramount importance. The researcher is obliged not to disclose any information regarding the participants' involvement in the study. All PIQs and other sensitive documentation is kept in a secure location in the possession of the field researcher at all times. No disclosure of personal information is allowed to any third party.

If a participant were to disclose to a field researcher that they were suffering abuse or at risk in any way, a protocol was in place to deal with this, whereby the Principal Investigator (PI) would be immediately contacted.

2.4.5 Avoidance of participant identification in reporting, non-reporting of small groups

As some groups in this thesis have small numbers of participants, and thus a participant may be easily identifiable, all groups with a value <5 will be removed from a table and listed as a table footnote. Where a subgroup has a value <5, it will be denoted as <5 or removed from a table, if necessary to ensure confidentiality and participant anonymisation.

2.4.6 Garda vetting

All field researchers undergo Garda (police) vetting to ensure that they have no criminal record. This is especially important when dealing with a vulnerable group of people.

2.4.7 Data breach

The following figure outlines the protocol to be followed in the event of a data breach in the IDS-TILDA study (*Figure 2.4-1*).

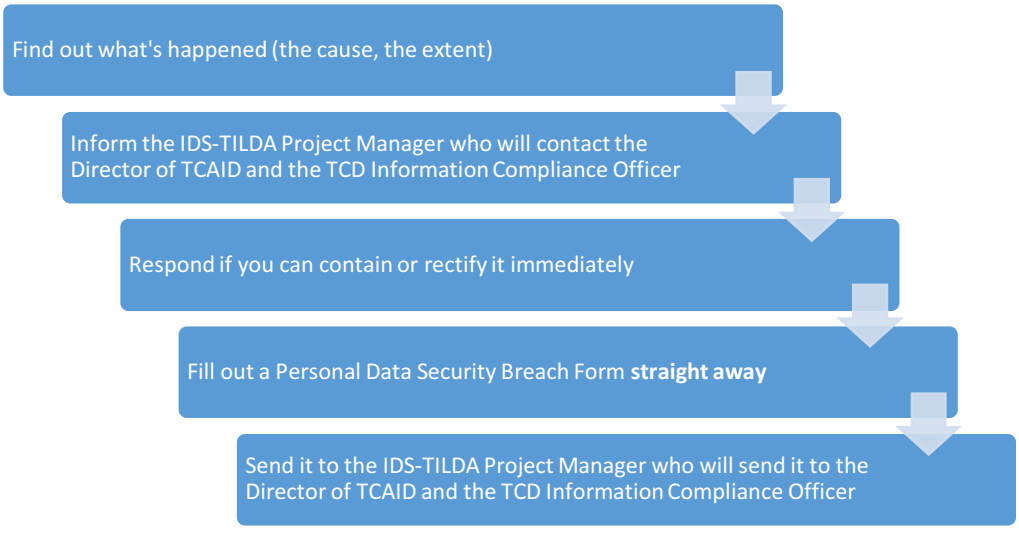


Figure 2.4-1 IDS-TILDA protocol in event of data breach

2.5 Data collection

2.5.1 PIQ Pre-Interview Questionnaire

A pre-interview questionnaire (PIQ) was sent to each participant one week before the interview took place. This allowed participants to prepare and locate any information that may be required (for example, medication data). This also helped to enhance the reliability of the data. Participants were asked in the Wave 3 PIQ: (a) how they spend their free time; (b) what they like to eat and drink; (c) their weight; (d) the exercise they do; (e) how physically active they are; (f) medical tests and screening undertaken (including men only/women only section); (g) health service utilisation; (h) how happy they are with the health services; (i) if they have received information on health; (j) medications taken (medication record); (k) sources of income; (l) transport; and (m) how they felt about filling out the questionnaire. Some memory and challenging behaviour (BPI-S) questions to be completed by the carer/key worker/support person were also part of the PIQ. The medication section (*Appendix 2*) included instructions on how to fill out the medication record *"We would like to record all medications that you take on a regular basis, take every day or every week. This will include prescription and non-prescription medications, over-the-counter medicines, vitamins, herbal and alternative medicines. Please write down all medications/tablets you take and how often you take them."*

A total of 594 (97.5%) participants in Wave 3 (n=609) returned a completed PIQ. Overall, 90.4% of participants who returned a PIQ reported that they were supported in filling out the questionnaire, with 1.7% reporting no help and 7.9% not answering this question. When asked about the relationship to the person supporting them with the questionnaire, 1.5% reported a parent, 5.2% a sibling, 76.6% a key worker/support worker, 0.5% a friend, 5.6% other and 10.6% did not answer. When asked about how long they

knew the person supporting them, 6.6% reported less than 6 months, 5.6% reported between 6 months and a year, 74.6% said they knew the person by more than a year and 13.3% did not respond to this question.

2.5.2 CAPI Computer Assisted Personal Interviewing

CAPI (Computer Assisted Personal Interviewing) interviews were completed by field workers, utilising small laptops, who had completed a comprehensive course and were experienced in the care of people with intellectual disability. Advantages included the automatic rerouting of questions and detection of inadmissible replies. Participants reported that they found CAPI less intimidating compared with a large paper based questionnaire [30]. Different interviewing styles were proposed to participants depending on their level of intellectual disability and capacity to communicate. These included a respondent only interview conducted only with the participant, a proxy interview completed with a family member or carer very familiar with the person, or an interview with the participant and supported by a family member or carer. A combination of these approaches was utilised by a small number of participants. To act as a proxy, the individual was required to know the person with intellectual disability for a minimum of six months. Some questions were self-report and only the participant with intellectual disability could answer, while other questions could be completed by the person, carer or staff. At the time of interview, some PIQ entries including medication data were confirmed to improve accuracy.

2.5.3 Participant welfare

The welfare of the participants throughout the data collection period was of utmost importance. Field researchers attempted to organise interviews at the most convenient time for the participant and/or proxy, even on weekends. The interview location was selected to ensure the participant was in familiar surroundings and of their choosing, usually their place of residence. If the participant and/or proxy were unable to complete the interview in one sitting, they were offered the option of the field researcher returning on another occasion. If the participant found the interview difficult and long, they were offered the option of taking regular breaks or defer the interview to another day.

2.6 Missing medication data analysis

For Wave 3, medication data was available for 549 (90.1%) participants. Of the 60 participants missing medication data, four (6.7%) participants refused to provide this data. 15 (25%) participants and/or proxies did not return the PIQ which contained the medication record detailing the participants' medication usage. Medication data was not available for the remaining 41 (68.3%) participants. PIQs were not systematically checked for missing data once returned to the office in Wave 3. A lack of awareness from field researchers regarding difficulties arising from missing data and time constraints of carers/participants are some of the likely factors contributing to this problem. Following this, a change in protocol was made and all PIQs in Wave 4 of this study are now thoroughly checked on return to the project manager to ensure all sections are answered, to reduce the incidence of missing data in future Waves of this study. Field researchers are contacted if any missing data is discovered and timely attempts to retrieve this data are made if possible.

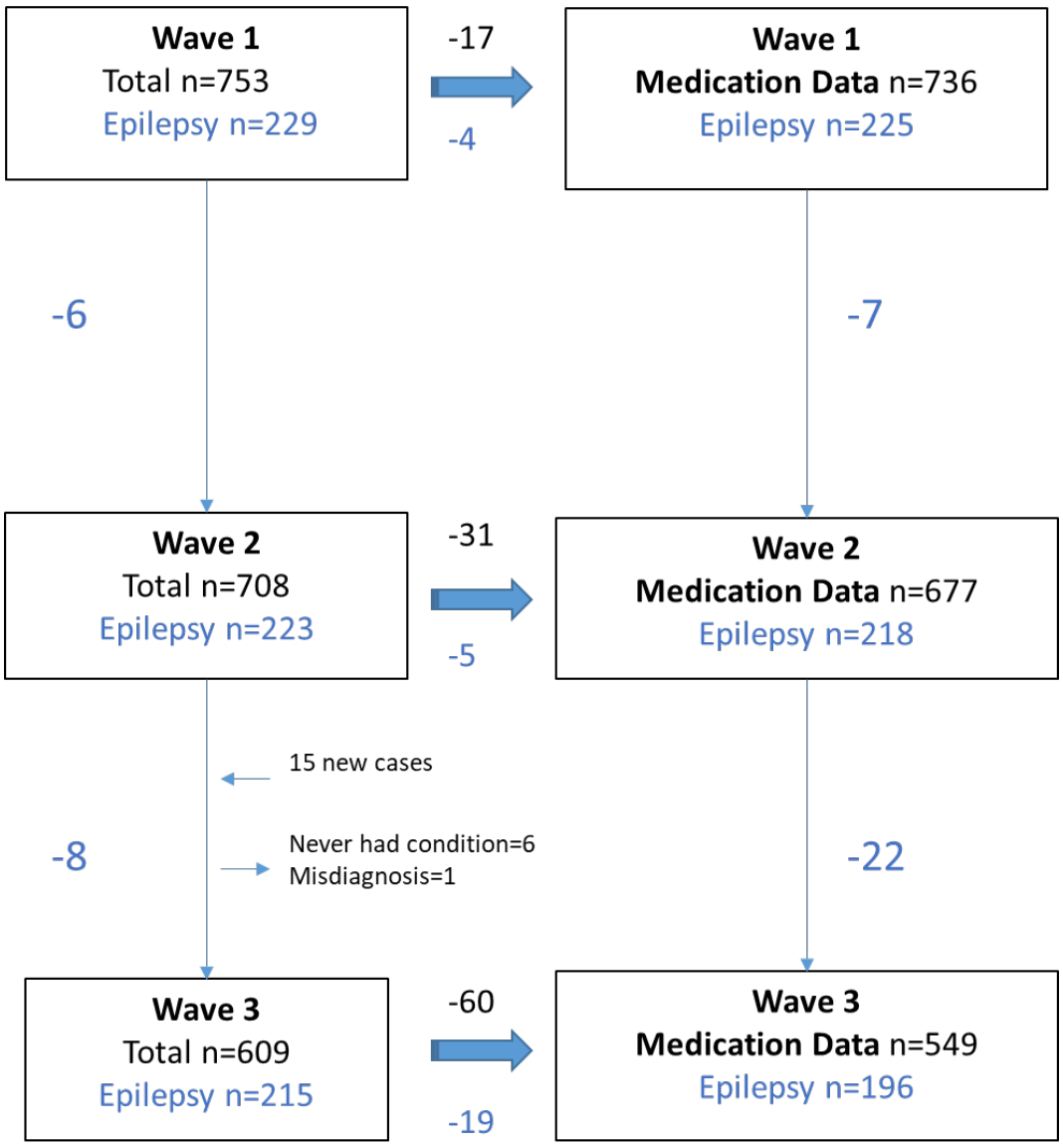


Figure 2.6-1 Flow chart of missing data over Wave 1-Wave 3

The following tables illustrate the demographic characteristics of those with medication data, those without medication data and those who refused to provide this data in Wave 3 of IDS-TILDA (*Tables 2.6-1 - 2.6-4*):

Table 2.6-1 Medication availability and gender (n=609)

Medication data available	Male n=269 n (%)	Female n=340 n (%)	Total n=609 n (%)
Yes	236 (87.7)	313 (92.1)	549 (90.1)
No	30 (11.2)	26 (7.6)	56 (9.2)
Refused to answer	3 (1.1)	1 (0.3)	4 (0.7)

Table 2.6-2 Medication availability and age (n=609)

Medication data available	<50 years n=72 n (%)	50-64 years n=381 n (%)	65+ years n=156 n (%)	Total n=609 n (%)
Yes	64 (88.9)	346 (90.8)	139 (89.1)	549 (90.1)
No	8 (11.1)	32 (8.4)	16 (10.3)	56 (9.2)
Refused to answer	0 (0)	3 (0.8)	1 (0.6)	4 (0.7)

Table 2.6-3 Medication availability and type of residence (n=609)

Medication data available	Independent/ family n=95 n (%)	Community group home n=246 n (%)	Residential/ campus n=268 n (%)	Total n=609 n (%)
Yes	78 (82.1)	223 (90.7)	248 (92.5)	549 (90.1)
No	15 (15.8)	23 (9.3)	18 (6.7)	56 (9.2)
Refused to answer	2 (2.1)	0 (0)	2 (0.7)	4 (0.7)

Table 2.6-4 Medication availability and level of intellectual disability (n=609)

Medication data available	Mild n=139 n (%)	Moderate n=259 n (%)	Severe/profound n=163 n (%)	Unknown n=48 n (%)	Total n=609 n (%)
Yes	122 (87.8)	231 (89.2)	154 (94.5)	42 (87.5)	549 (90.1)
No	16 (11.5)	25 (9.7)	9 (5.5)	6 (12.5)	56 (9.2)
Refused to answer	1 (0.7)	3 (1.2)	0 (0)	0 (0)	4 (0.7)

2.7 Cleaning of the medication data

"If drug utilisation studies are to be reliable, they will have to adhere to strict methodological standards, the most basic of which continue to be the use of a common drug classification system and of an international unit of measurement" D. Capella 1993 [324, 325] .

All medication data were checked by trained interviewers at the time of interview. Medications were coded using the World Health Organisation (WHO) Anatomical Therapeutic Chemical Classification (ATC) System by two pharmacists JO'C and HA. Supplements and herbal medicines were excluded from the definition of a medicine. All PIQ medication entries and ATC Codes input into the statistics software SPSS were independently reviewed and confirmed by the author (RM).

2.7.1 ATC classification system

The ATC classification system was designed in the 1970s by Norwegian researchers in partnership with the Drug Utilization Research Group (DURG) [324]. The WHO recommended the system in the early 1980s as the International standard for drug utilisation studies, and the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC) [326] was founded in 1982 [324]. The centre is based in the Norwegian Institute of Public Health, working in collaboration with an international expert group - the International Working Group for Drug Statistics Methodology - chosen by the WHO in Geneva [324]. This group is responsible for approving any new ATC codes, new DDDs

(defined daily doses) and any changes to the system [324]. The DDD is the average maintenance dose for a named indication [40, 327].

The ATC system utilises a hierarchical structure consisting of five levels [324, 328]. Level one consists of 14 main anatomical/pharmacological groups which are subsequently divided into pharmacological or therapeutic subgroups giving level two [324]. Levels three and four consist of chemical, pharmacological or therapeutic subgroups whilst the fifth and final level is the chemical substance [324]. The International Non-Proprietary Name (INN) is the preferred nomenclature system for the chemical substance. A significant benefit of the ATC/DDD system is that it allows for standardisation of drugs and allows for comparison of drug use across regions, jurisdictions and health care settings enabling examination of pharmacoepidemiological trends [324, 327].

As there is only one ATC code per medicinal product (defined by route of administration and strength), medicines are classified according to their main therapeutic use [328]. Medicinal products are liable to have multiple ATC codes for various routes of administration (e.g. systemic, local administration) with different therapeutic uses [324]. If confusion arises as to the main therapeutic use, due to differences in use in different jurisdictions, the decision is granted by the International Working Group for Drug Statistics Methodology, following consultation of literature and consensus as to the most prevalent indication across jurisdictions [324].

For combination products, ATC codes differ from those of the individual ingredients [324]. Following the protocol for single ingredient products, the determining factor is the main therapeutic use [324]. The principle ingredient is identified and the combination product is given a fifth level code in the fourth level of the principle ingredient, thus

different combination products sharing the same main principle ingredient are assigned the same ATC code [324].

2.7.2 DDD Defined daily dose

The DDD has been described as *"the assumed average maintenance dose per day for a drug used for its main indication in adults"* [326]. The DDD is a static unit of measurement with one DDD assigned per ATC code and route of administration [327]. It is assigned following review of recommended doses in various countries [327]. Different cultural and ethnical traditions, national and international guidelines and therapy conventions can account for variations in drug use, thus the DDD in no way reflects the recommended prescribed daily dose in any given country [327]. Maintenance of the DDDs in the ATC/DDD system is the responsibility of the WHOCC [328] and approval for individual DDDs made by the WHO International Working Group for Drug Statistics Methodology. DDDs are assigned to both single substances and combination products [328].

DDDs for individual substances are in the ATC/DDD index [328], whilst DDDs for combination products are found in a separate list. DDDs are not available for a number of products including vaccines, topical products, anaesthetics, contrast media, antineoplastic agents and allergen extracts due to wide variation in doses [327]. Applications for missing DDDs must be made to the WHOCC, and the ATC/DDD index is published once yearly. DDDs are presented per amount of active ingredient, for example, g, mg, mcg, mmol and U (unit) [327, 328]. The average maintenance dose is typically used to enhance pharmaco-epidemiological studies in the community by providing a more realistic picture of drug use [329]. In some cases (for example, antibiotics), severity is considered and thus the DDD for

antibiotics is based on use in moderately/severe infections [327]. As dosages are liable to change, a review of assigned DDDs occurs three years after assignment [327].

2.7.3 PDD Prescribed daily dose

The PDD is the actual daily amount of a drug that is prescribed to patients. It is worth noting that PDDs do not definitively reflect drug consumption as individual patient compliance with pharmacotherapy can be variable [327]. However, with regards to intellectual disability populations, particularly in residential or community group home settings with nursing supervision, medication adherence would be expected to be high.

2.8 Reported diagnosis of epilepsy

In Wave 1**,** each participant/proxy was asked in the PIQ if the individual with intellectual disability was ever diagnosed by a doctor/relevant health professional with epilepsy [29]. A diagnosis of epilepsy was then confirmed in person during the face to face interview. In subsequent Waves (2 and 3) of the study, each participant/proxy was asked *'since your last interview, has a doctor ever told you that you have epilepsy?'*. This allowed for the creation of a variable for prevalence. Once a condition was confirmed, accuracy was further checked with the question: *'When were you first told by a Doctor that you had epilepsy?'* If a case of epilepsy was uncertain, the participant/proxy was invited to confirm the diagnosis with any additional information written in a free text box in the CAPI. Diagnosis data was not available for one (0.2%) participant with medication data.

2.9 Concurrent medications that may lower the seizure threshold

The prescribing of co-medications that are listed as having the potential to lower the seizure threshold, or contraindicated for use in people with epilepsy was examined. In *Chapter 5*, psychotropic drugs were categorised by potential seizure threshold-lowering risk using the Maudsley Prescribing Guidelines in Psychiatry 2018, 13th Edition [330]. The following tables (*Table 2.9-1*: Antidepressants & Lithium and *Table 2.9-2*: Antipsychotics) illustrate the evidence available using two versions of the Maudsley Prescribing Guidelines in Psychiatry (2015 & 2018) and the Summary of Product Characteristics (SmPC) of individual drugs [330, 331].

Table 2.9-1 Overview of common potential seizure threshold-lowering antidepressant & lithium medications using the SmPC of individual drugs and two versions of the Maudsley Prescribing Guidelines in Psychiatry 2015 & 2018 (Adapted from [330, 331])

Antidepressant	Maudsley 2015	Maudsley 2018	SmPC
Selective Serotonin Reuptake Inhibitors (SSRI)	Good Choice: SSRIs may be anticonvulsant at therapeutic doses [199, 332] and help protect against hypoxic damage [333]. No obvious difference between drugs [334] except citalopram [335]. Care required: **Citalopram** as pro-convulsive in overdose [335, 336].	Low Risk: Recommended in people with epilepsy [265, 337]. SSRIs may be anticonvulsant at therapeutic doses [338] and pro-convulsant in overdose [339]. The preferred SSRI with lowest risk of interaction include citalopram/escitalopram followed by sertraline [265, 337, 340, 341]. Escitalopram is preferred over **citalopram** as lower risk of seizures in overdose [342]. Others have a low risk of seizures (e.g. Fluoxetine [342]) but possible drug interactions with anticonvulsants requiring caution [265, 337].	Seizures are a potential risk with antidepressant drugs. For all SSRI's: - SSRI should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored and discontinued (D/C) if increase in seizure activity. - SSRI should be D/C if a patient develops seizures for the first time or if there is an increase in seizure frequency. -Fluoxetine should be introduced cautiously in patients with a history of seizures. [343-347]
Mirtazapine	Good Choice [348, 349]	Low Risk: Recommended in people with epilepsy [337, 340]. It is not known to be pro-convulsant [199].	Mirtazapine should be introduced cautiously in patients who have a history of seizures. Treatment should be D/C in any patient who develops seizures, or where there is an increase in seizure frequency [350].
Agomelatine	Care required: very limited data and clinical experience [331].	Probably Low Risk: Use with caution - it is not known to be pro-convulsive and is anticonvulsive in animal models [342].	- [351]
Duloxetine	Care required: Very limited data and clinical experience [352].	Probably Low Risk: Use with caution - Limited data. Has been recommended for use in people with epilepsy [337, 353]. The risk of seizure is likely negligible [342].	Use with caution in patients with a history of seizures. [354]

Table 2.9-1 Overview of common potential seizure threshold-lowering antidepressant & lithium medications using the SmPC of individual drugs and two versions of the Maudsley Prescribing Guidelines in Psychiatry 2015 & 2018 (Adapted from [330, 331]) (*Continued)*

Antidepressant	Maudsley 2015	Maudsley 2018	SmPC
Mono Amine Oxidase Inhibitors (MAOI) Moclobemide	- Good Choice: It is not known to be pro-convulsive [355].	Probably Low Risk: Use with caution - they are not known to be pro-convulsive at therapeutic doses [342]. Low risk of seizure expected in overdose [356]. Probably Low Risk: Use with caution- it is not known to be pro-convulsive, anticonvulsive in animal models [342].	e.g. Phenelzine: Nardil should be used only with great caution in agitated patients or those who have cardiovascular disease, epilepsy, blood dyscrasias, porphyria or diabetes; and in patients taking diuretics. Used with caution in people with epilepsy. [357]
Reboxetine	Care required: Very limited data and clinical experience [331].	Probably Low Risk: Use with caution - a small open-label study suggests no problems in people with epilepsy [194].	Not tested in convulsive disorders in clinical studies and rare cases of seizures reported in clinical studies - given under close supervision in people with a history of convulsive disorders and D/C if seizures develop [358].
Vortioxetine	Care required: Very Limited data and clinical experience [331].	Probably Low Risk: Use with caution - it is not known to be pro-convulsive but there is no experience in people with epilepsy [342].	Introduce cautiously in patients with a history of seizures or in patients with unstable epilepsy. Treatment D/C in any patient who develops seizures or increase in seizure frequency [359].
Trazodone	-	Moderate Risk: Care Required- The limited data available suggest some risk of seizures [342, 360].	Careful dosing and regular monitoring required in epilepsy, specifically abrupt increases or decreases in dosage should be avoided [361].
Venlafaxine	Care Required: Pro-convulsive in overdose [205].	Moderate Risk: Care Required - Shown to be effective in people with epilepsy [353], been recommended [337] but mixed evidence on seizure risk [342].	Convulsions may occur with venlafaxine. Venlafaxine should be introduced carefully in people with a history of convulsions and closely monitored. Treatment D/C if seizures develop [362].
Amoxapine	**Avoid:** Most TCA's are epileptogenic, especially at higher doses. Ideally be avoided completely [337, 363].	**Higher Risk**: AVOID - Numerous reports of seizures at therapeutic doses [360].	*SPC not available. (Not licenced in Ireland)
Bupropion	**Avoid:** Epileptogenic. Ideally be avoided completely [199].	**Higher Risk**: AVOID - Dose associated risk of seizures especially with instant release formulations. The risk is reduced with slow release formulations at doses under 300mg/day [342].	Contraindicated in patients with a seizure disorder or any history of seizures. [364]

Table 2.9-1 Overview of common potential seizure threshold-lowering antidepressant & lithium medications using the SmPC of individual drugs and two versions of the Maudsley Prescribing Guidelines in Psychiatry 2015 & 2018 (Adapted from [330, 331]) *(Continued)*

Antidepressant	Maudsley 2015	Maudsley 2018	SmPC
Maprotiline	-	**Higher Risk**: AVOID - Numerous reports of seizures at therapeutic doses [360].	*SPC not available. (Not licenced in Ireland)
Tri-cyclic Antidepressants (TCAs)	**Avoid:** Most TCA'S are epileptogenic, especially at higher doses [363, 365, 366].	**Higher Risk**: AVOID - Most TCA'S are epileptogenic, especially at higher doses- chiefly clomipramine and amitriptyline [199, 284, 360]. Doxepin has a possible lower risk from results of one small study. The SNRI's preferred over TCA'S in epileptics.	TCAs known to lower convulsion threshold. Clomipramine SPC: Extreme caution in epilepsy. Occurrence of seizures dose dependent. Amitriptyline SPC: Caution in patients with convulsive disorders. Doxepin SPC: Use with caution in patients with a history of epilepsy. [367, 368]
Lithium	Care Required: Low pro-convulsive effect at therapeutic doses. Greater pro-convulsive activity in overdose [369].	Moderate Risk: Care Required - Low risk of seizures [342]. It is anticonvulsant in animal models. Limited data showing increases or decreases in seizure frequency in people with epilepsy [342]. To treat bipolar disorder, advised to try anticonvulsant mood stabilisers [370].	Risk of convulsions may be increased with co-administration of lithium with drugs that lower the epileptic threshold or in epileptic patients. [371]

TCA: Tri-cyclic antidepressant. SNRI: Serotonin Noradrenaline Reuptake Inhibitor.

Table 2.9-2 Overview of common potential seizure threshold-lowering antipsychotic medications using the SmPC of individual drugs and two versions of the Maudsley Prescribing Guidelines in Psychiatry 2015 & 2018 (Adapted from [330, 331])

Antipsychotic	Maudsley 2015	Maudsley 2018	SmPC
Amisulpride/Sulpiride	Good choice: Low pro-convulsant effect. Few reports of suspected drug related seizures [200]. No known interactions with anticonvulsants. [372-374]	Low Risk: Good Choice - Considered safe in people with epilepsy [375]. Seizures uncommon in overdose [376]. It is excreted in kidneys so low risk of pharmacokinetic interactions with anticonvulsants.	Sulpiride: Dolmatil induces slight EEG modifications. Neuroleptics may lower the epileptogenic threshold and some cases of convulsions have been reported with Sulpiride. Cases of convulsions, sometimes in patients with no previous history, have been reported [377]. Amisulpride: Amisulpride may lower the seizure threshold. Therefore, patients with a history of epilepsy should be closely monitored during amisulpride therapy [378].
Aripiprazole	Care Required: Very limited data and clinical experience. Seizures have been rarely reported [379, 380].	Low Risk: Good Choice - It rarely lowers the seizure threshold [381]. The incidence of seizures is similar to placebo in randomised controlled trials (RCT) [199].	In clinical trials, uncommon cases of seizure were reported during treatment with aripiprazole. Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures [382].
Ziprasidone	-	Low Risk: Good Choice - It rarely lowers the seizure threshold [381]. The incidence of seizures is similar to placebo in (RCT) [199].	Caution is recommended when treating patients with a history of seizures [383].
High potency FGA (first generation antipsychotics) e.g. Fluphenazine, haloperidol, Trifluoperazine, Flupenthixol	Good Choice: Low pro-convulsant effect. Carbamazepine increases the metabolism of some antipsychotics and larger doses of an antipsychotic may be required. [369, 384, 385]	Low Risk: Good Choice - Have a low risk of lowering the seizure threshold [381].	Haloperidol SPC: It has been reported that seizures can be triggered by haloperidol. Caution is advised in patients suffering from epilepsy and in conditions predisposing to seizures (e.g., alcohol withdrawal and brain damage). Trifluoperazine SPC: Since phenothiazines may lower the convulsive threshold, patients with epilepsy should be treated with caution[386].

Table 2.9-2 Overview of common potential seizure threshold-lowering antipsychotic medications using the SmPC of individual drugs and two versions of the Maudsley Prescribing Guidelines in Psychiatry 2015 & 2018 (Adapted from [330, 331]) (*Continued)*

Antipsychotic	Maudsley 2015	Maudsley 2018	SmPC
Risperidone	Care Required: Doubts about safety in epilepsy. [199]	Low Risk: Good Choice - Has a rare to low risk of lowering the seizure threshold [381]. The incidence of seizures similar to placebo in RCT [199]. Recommended in people with epilepsy [340]. There is evidence of safety in a case series of adolescents with epilepsy [387].	Should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold [388].
Asenapine	**Avoid if possible**: Not believed to affect seizure threshold but experience is limited [331].	Probably Low Risk: Use with caution - Seizure rate comparable to placebo in RCT. Data and clinical experience of use in people with epilepsy is extremely limited [330].	In clinical trials, cases of seizure were occasionally reported during treatment with asenapine. Therefore, Sycrest should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures [389].
Olanzapine	Care Required: Doubts about safety in epilepsy [199]. Olanzapine may affect the EEG [390] and myoclonic seizures have been reported [391, 392]. Olanzapine is associated with higher rates of drug related seizure [200].	Moderate Risk: Care Required - Associated with seizures in RCT [199]. Olanzapine causes more EEG abnormalities than quetiapine [376]. Overall likely low risk of lowering the seizure threshold [381] and olanzapine has been recommended by some for use in people with epilepsy [340].	Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur uncommonly in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported [393].
Quetiapine	Care Required: Doubts about safety in epilepsy [199]. Seizures rarely reported [394] but found to have anticonvulsant activity in ECT [372]. Quetiapine is associated with higher rates of drug related seizure [200].	Moderate Risk: Care Required - Associated with seizures in RCTs [199]. Overall likely low risk of lowering the seizure threshold [381].	In controlled clinical trials, there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. No data is available about the incidence of seizures in patients with a history of seizure disorder. As with other antipsychotics, caution is recommended when treating patients with a history of seizures [395].

Table 2.9-2 Overview of common potential seizure threshold-lowering antipsychotic medications using the SmPC of individual drugs and two versions of the Maudsley Prescribing Guidelines in Psychiatry 2015 & 2018 (Adapted from [330, 331])(*Continued*)

Antipsychotic	Maudsley 2015	Maudsley 2018	SmPC
Clozapine	**Avoid if possible**: Clozapine is very epileptogenic. It has been shown that approximately 5% of people who receive more than 600mg/day develop seizures. Valproic acid or lamotrigine are the anticonvulsants of choice as they have a lower incidence of leucopenia than carbamazepine. [396-398]	**Higher Risk**: Care Required - Clozapine is believed to be the most epileptogenic antipsychotic [340]. Successfully used in people with epilepsy that are stable on anticonvulsants without worsening seizures [399] and in epilepsy that is resistant to treatment [400]. Should not be used with carbamazepine due to risk of blood dyscrasias and reduced clozapine levels. Valproate or lamotrigine are preferred anticonvulsants.	Patients with a history of epilepsy should be closely observed during Clozapine therapy since dose-related convulsions have been reported. In such cases, the dose should be reduced and, if necessary, an anti-convulsant treatment should be initiated. [401]
Low potency First generation antipsychotics (FGAs) e.g. Chlorpromazine	**Avoid**: One of the most epileptogenic of the older drugs. Ideally best avoided completely [396].	**Higher Risk**: AVOID - Best avoided in people with epilepsy [339]. Doses of chlorpromazine above 1G/day have a 9% incidence of seizures.	Since chlorpromazine may lower the seizure threshold. Treatment must be discontinued if seizures occur. [402]
Loxapine	**Avoid**: One of the most epileptogenic of the older drugs. Ideally best avoided completely [331].	**Higher Risk**: AVOID - Highest rate of seizures among the first generation antipsychotics [33].	Loxapine should be used with caution in patients with a history of seizure disorders since it lowers the seizure threshold. Seizures have been reported in patients receiving oral loxapine at antipsychotic dose levels, and may occur in epileptic patients even with maintenance of routine anticonvulsant drug therapy. [403]
Depot Antipsychotics	**Avoid**: None of the depot preparations available are thought to be epileptogenic [331]. However: -the kinetics of depots are complex and seizure may be delayed. If seizures do occur, the drug is not easily withdrawn. Use with extreme care.	**Higher Risk**: AVOID - None of the depot preparations available thought to be epileptogenic [330]. However: - the kinetics of depots are complex - seizure may be delayed.	Zuclopenthixol SPC: Like other antipsychotics, zuclopenthixol decanoate should be used with caution in patients with organic brain syndrome, convulsions and advanced hepatic disease [404]

2.10 Reported diagnosis of other comorbid mental health disorders

In Wave 3, participants were asked in the CAPI, *"has a doctor ever diagnosed you with an emotional/psychiatric disorder?".* Participants were then asked in the CAPI *"what type of emotional, nervous or psychiatric problems do/does you/he/she have?"* The following options were given in the CAPI: Hallucinations, anxiety, depression, emotional problems, schizophrenia, psychosis, mood swings, manic depression, post-traumatic stress disorder (PTSD), something else, unclear response, don't know, refused to answer.

For the purposes of analysis, three categories of mental health disorder were created by grouping the above mental health conditions. Psychotic disorder includes psychosis, hallucinations, and schizophrenia. Mood disorder includes depression, manic depression, mood swings and emotional problems and anxiety disorder includes anxiety and post-traumatic stress disorder (PTSD). Responses for unclear response, don't know and refused to answer were excluded from the analysis. Responses for something else included primarily behavioural problems (dealt with separately - see section 2.11), autism, OCD, inappropriate sexual behaviours and personality disorders.

2.11 Challenging behaviours

The Behaviour Problems Inventory - Short Form (BPI-S), an informant based questionnaire, was used to assess challenging behaviours [95]. This instrument examines three subtypes of challenging behaviours; self-injurious behaviour (SIB) (8 items), aggressive/destructive behaviour (10 items) and stereotyped behaviour (12 items) [405] (*Table 2.11-1*). A study investigating reliability and factorial validity of the BPI-S found acceptable reliability regarding internal consistency, inter-rater agreement and test-retest reliability [405]. The carer/key worker/support person who knew the person with intellectual disability very

well (minimum of 6 months) completed this questionnaire. This data was collected via the PIQ, giving the informant time to fill out the information required prior to the CAPI interview.

Broad definitions of each type of behaviour were given in the PIQ as follows:

i. *"Self-injurious behaviour (SIB) - causes damage to the person's own body; i.e., damage has either already occurred, or expected."*
ii. *"Aggressive or destructive behaviours are deliberate overt attacks directed towards other individuals or property."*
iii. *"Stereotyped behaviours look unusual, strange or inappropriate to the average person. They are voluntary acts that occur repeatedly in the same way over and over again, and they are characteristic for that person. However, they do not cause physical damage."*

Individuals providing this data were instructed to indicate behaviours observed in the person with intellectual disability during the previous two months by circling the number in the appropriate boxes indicating how often a described behaviour typically occurs and how serious a problem the behaviour is. If the behaviour did not occur during the previous two months and therefore, posed no problem, they were instructed to check "never/no problem". If the behaviour had occurred, they were asked to rate the approximate frequency of its occurrence and its severity. Each level of severity (mild/moderate/severe) was clearly defined. They were not required to provide a severity level for stereotyped behaviour and no scale/severity definition was provided. For the purposes of this thesis, a positive response to frequency indicated the presence of challenging behaviour. This

allowed for the creation of a variable (YES/NO) for individual types of challenging behaviour which were then grouped into SIB, aggressive/destructive and stereotyped behaviour per BPI-S [95] and then grouped into overall presence of challenging behaviour. All new variables were created by the author (RM).

Table 2.11-1 Categories of challenging behaviours [95]

Behaviour category	***Type of behaviour***
Self-injurious behaviour (SIB)	
	Self-biting
	Head hitting
	Body hitting
	Self-scratching
	Pica
	Objects in nose
	Hair pulling
	Teeth grinding
Aggressive/destructive behaviour	
	Hitting others
	Kicking others
	Pushing others
	Biting others
	Grabbing & pulling others
	Scratching others
	Pinching others
	Verbally abusive with others
	Destroying things (e.g. rips clothes, throws chairs, smashes tables)
	Bullying (being mean or cruel e.g. grabbing toys/food from others)
Stereotyped behaviour	
	Rocking & repetitive body movements
	Sniffing objects, own body
	Waving & shaking arms
	Manipulating (e.g. twirling, spinning)

Table 2.11-1 Categories of challenging behaviours [95] (*Continued*)

Behaviour category	***Type of behaviour***
Stereotyped behaviour (*Continued*)	Repetitive hand and/or finger
	Yelling & screaming
	Pacing, Jumping, bouncing, running
	Rubbing self
	Gazing at hands or objects
	Bizarre movements/postures
	Clapping hands
	Grimacing

2.12 Statistical analysis

The author (RM) undertook all analyses of Wave 3 data in this thesis. A list of all individuals and contributions to this thesis can be found in section *2.14* of this Chapter. Statistical advice was obtained from the study statistician (RC/RL) and MO'D, where necessary. The study statistician (RL) reviewed statistical analysis in manuscripts prior to journal submission to ensure accuracy (*Chapter 5 and 6*). No analyses were undertaken by the study statistician. All variables required from the master IDS-TILDA Wave 3 data set were requested from the data controller (RC), following the study protocol. All cleaning of these variables was done by the author (RM). All new variables created were produced by the author (RM). A list of all variables used in this thesis can be found in *Appendix 8*. All statistical analyses were carried out using the Statistical Package for Social Sciences, version 25.0 (SPSS Inc., Chicago, IL, USA). Antiepileptic drug load was calculated by RM using Microsoft Excel and the final AED load variable input into SPSS for further analysis. A series of descriptive, bivariate, and multivariate analyses were performed incorporating both parametric and non-parametric tests. Descriptive statistics were used to describe the characteristics of the population being studied and include case (n) numbers and

percentages. The alpha level (α) was set at 0.05 meaning $p<0.05$ for statistical significance. Bonferroni correction was applied to some Chi-Square/Fisher's Exact Tests when multiple tests on categorical variables were undertaken and when used, is highlighted in this thesis. *Figure 2.12-1* gives a summary of statistical analysis methods used in this thesis. Sections 2.12 and 2.13 of this Chapter give further information on statistical methods used.

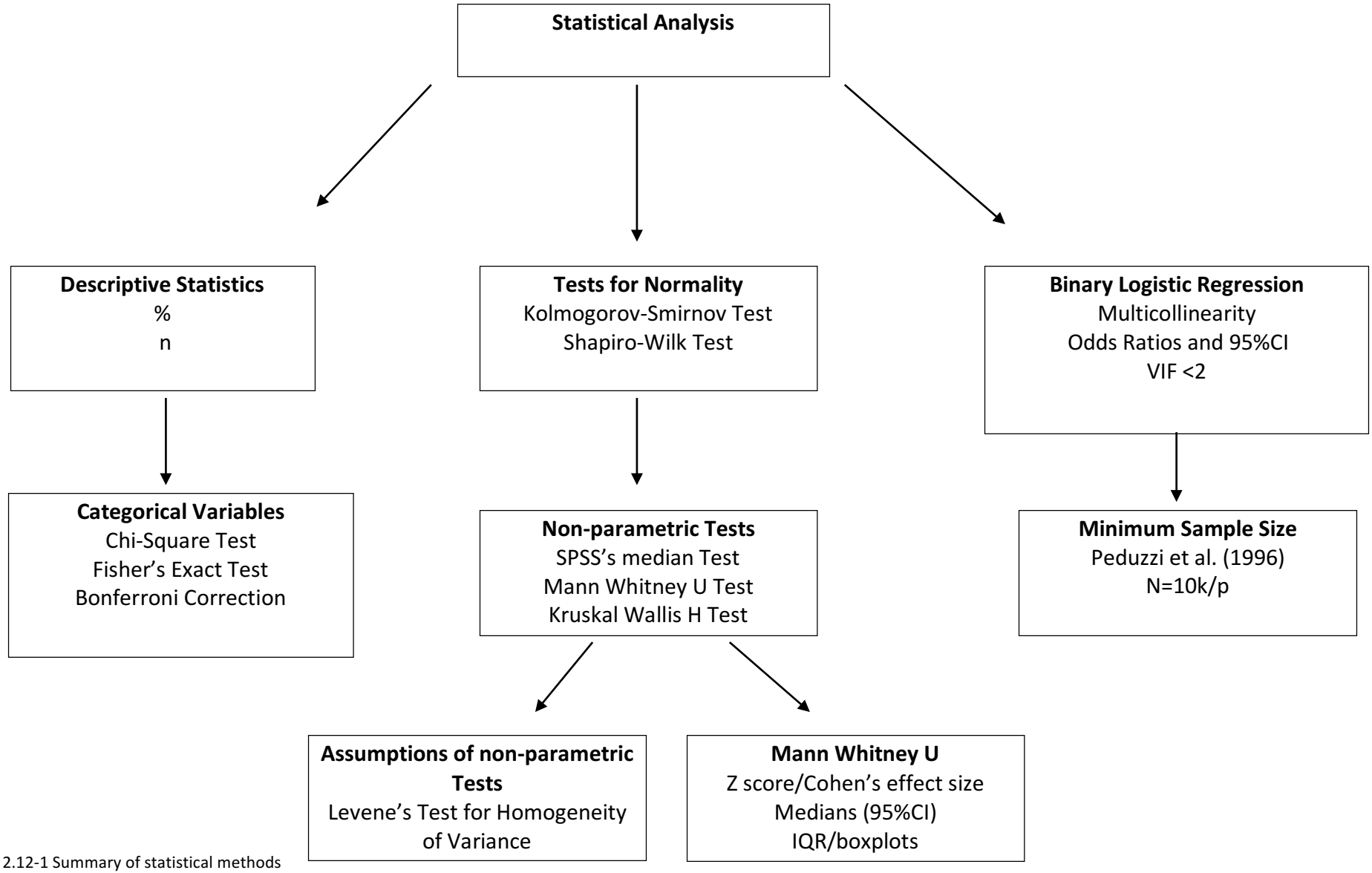


Figure 2.12-1 Summary of statistical methods

2.12.1 Chi-Square (χ^2) test & Fisher's Exact test

Cross tabulations for bivariate associations between variables was undertaken. The Chi-Square (χ^2) test for independence was utilised to test for a significant association between categorical variables. Fisher's Exact test was used to test for a significant association between variables where the sample size in subgroups was small (n<5). The Fisher's Exact test requires a 2x2 matrix of cells, therefore, this test was not possible to do in the case of some variables (for example, type of residence with three groups- Independent/family, community group home, residential/campus setting).

2.12.2 Bonferroni correction

To control for problems associated with multiple comparisons for categorical variables, thereby increasing the likelihood of Type I error (rejecting the null hypothesis when it is true and the false discovery rate), a Bonferroni correction was applied to bivariate Chi Square/Fisher's Exact tests where appropriate [406]. If Bonferroni correction was utilised, this is recorded in the footnote to the table concerned.

2.12.3 Binary logistic regression

Binary logistic regression allows association of categorical variables when the dependent variable has two possible outcomes [407]. This was performed to identify factors associated with demographic and clinical characteristics in some of the studies *(Chapters 5-7)*. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were reported. Some variables with small groups were collapsed with other variables to prevent reduction of power in the analyses.

In *Chapter 5,* binary logistic regression was performed to identify factors associated with seizure frequency. Demographic variables included in the model were gender, age, level of intellectual disability and place of residence. Clinical variables with significance $p<0.10$ at bivariate level relating to regular AED medication (type of therapy) and seizures (type of seizures) were included in the model along with the variable - medications categorised by seizure risk - which is of interest in this study.

In *Chapter 6*, three binary logistic regressions were performed to identify factors associated with exhibiting (a) SIB, (b) aggressive/destructive behaviour and (c) stereotyped behaviour. Demographic variables included in each of the models were age, level of intellectual disability and place of residence. AED load was included in the models as this was of interest in the study and following positive associations found in non-parametric tests undertaken. Other variables could not be included due to small sample sizes in regression.

In *Chapter 7*, binary logistic regression was performed to identify factors associated with exposure to psychotropic inter-class polypharmacy. Demographic variables included in the model were gender, age, level of intellectual disability and place of residence. Clinical variables associated with mental health with significance $p<0.01$ at bivariate level (mental health diagnosis, exhibit challenging behaviour) and diagnosis of epilepsy (highly prevalent in this cohort) were included.

2.12.4 Multicollinearity

Variance inflation factor (VIF) was used to test for multicollinearity between independent variables [407]. A stringent cutoff threshold (<2) was employed to rule out multicollinearity

between variables in each binary logistic regression analysis, thus contributing to the strength of all studies.

2.12.5 Sample size

To determine the sample size for each logistic regression, we followed the guidelines of Peduzzi et. al. (1996) for a minimum required number of cases for the study. Here it is suggested to use N=10k/p where k is the number of covariates (independent variables), p is the smallest of the proportions of negative or positive cases in the population and k/p is the number of events per variable [408].

2.13 AED load data (PDD/DDD)

The Kolmogorov-Smirnov test and Shapiro Wilk test were used to assess if the AED load (PDD/DDD) variable was normally distributed. Medians and Interquartile Ranges (IQR) are presented for the AED load data as this data was not normally distributed. Non-parametric tests (Mann Whitney U and Kruskal Wallis H) were used to analyse the numerical AED load data. Spearman's Correlation was used to measure the strength and direction of association between AED load (PDD/DDD) and number of AEDs. Box plots of AED load with regards to demographic characteristics (gender; age; type of residence; level of intellectual disability; cause of intellectual disability) were completed using data visualisation software (Tableau). The numerical AED load variable was also transformed into a categorical variable <2, ≥ 2 for further analysis (adapted from Lammers et al. (1995)) [409]. Antiepileptic drug load was analysed in *Chapters 4 and 6* of this thesis. Further tables regarding AED load data can be found in *Appendices 11-19*.

2.13.1 Comparison of medians across groups

SPSS's Median test (formally called Mood's Median test) tests the null hypothesis that the medians in each group are the same. The test calculates a pooled median from all the data and then uses a Chi-Square (χ^2) test to compare each groups proportions below the pooled median. If the two groups have similar medians, a similar proportion of subjects will be above and below the pooled median. SPSS's median test can be found in *Appendices* 11-14 and 16 to this thesis.

2.13.2 Levene's test for homogeneity of variance

Levene's test for homogeneity of variance checks that the variances are equal for all samples when the data come from a non-normal distribution. If the p value (Levene test) is significant, then the null hypothesis is rejected which means the assumption of equal distributions between the two groups is not satisfied [410]. Therefore, implications arise when interpreting p values from non-parametric tests holding this assumption. Tables are highlighted ** where groups fail to satisfy the assumption of equal distributions. Levene's test was utilised in *Chapters 4 and 6.* Further information can be found in *Appendices 17-19* of thesis.

2.13.3 Mann Whitney U test

The Mann Whitney U test was used to evaluate whether there was a difference in the dependent variable (AED load) between two independent groups (for example, gender) [407, 411]. It compares the distribution of the dependent variable, and determines whether or not it is the same for the two groups and consequently, from the same population. Assumptions for undertaking a Mann Whitney U Test are that the two groups

are independent and that the dependent variable is ordinal or numerical [411]. However, to report the difference between groups as medians, the shape of the distributions of the dependent variable by group must be similar. If the shape of the distributions is not similar, differences in the mean ranks rather than medians can be summarised. The Levine test above was used to test the homogeneity of variance assumption. The Mann Whitney U test was utilised in *Chapters 4* and *6* of this thesis. Further tables can be found in *Appendices 15 and 35-37.*

2.13.4 Mann Whitney U Z score

For the Mann Whitney U test, the U value is calculated using a formula that compares the summed ranks of the two groups and takes into account sample size [411]. To calculate the p value, SPSS converts the value of U to a Z score. The Z score is then converted into a p value in the same way as for the Z test [411].

2.13.5 Cohen's effect size

An effect size is a way of quantifying the size of the difference between two groups [407]. It can be calculated by dividing the absolute (positive) standardised test statistic Z by the square root of N ($Z/\sqrt{N}$) [411]. Cohen's effect size estimates were used to interpret the meaning of the r score in *Chapter 4* - small effect=0.1, moderate effect=0.3 and large effect=0.5+ [411].

2.13.6 Kruskal-Wallis H test

The Kruskal-Wallis test is the non-parametric test equivalent to the one- way ANOVA, and an extension of the Mann-Whitney U test [407]. It allows comparison of more than two

independent groups (e.g. place of residence where there are three categories: those living in residential settings, community group homes or independently/with family). The Kruskal Wallis test assumes that observations in each group come from populations with the same shape of distribution - see Levine above. The Kruskal-Wallis test ranks the scores for the whole sample and then compares the mean rank for each group [407]. If Kruskal-Wallis shows a significant value, this suggests a difference between at least one pair of groups [412]. To determine which groups, Dunn's post hoc tests were carried out on each pair of groups [412]. SPSS then makes an adjustment to the p-value as multiple tests are being carried out. The Bonferroni adjustment is to multiply each Dunn's p value by the total number of tests being carried out. The Kruskal Wallis test gives you a Chi-Square (χ^2) result [412]. Kruskal Wallis H test is utilised in *Chapter 4*.

2.14 Contributors to thesis

The following tables outline the contributions all individuals made to the studies included in this thesis:

Table 2.14-1 List of individual contributions to the thesis

Chapter/Study	Contributors
Data collection and review	The author (RM) conducted 50 Wave 3 interviews alongside other field researchers. Two pharmacists JO'C and HA input all medication data from the PIQs into SPSS statistical software. The author (RM) then performed a quality control role by reviewing all PIQs and double checking medication data entered into the statistics software SPSS.
Variables used in study	**Carroll, R:** supplied all requested variables from the Wave 3 master data set following study protocols.
Chapter 3 Epilepsy prevalence and use of antiepileptic drugs Monaghan, R., O'Dwyer, M., Henman, M.C.	**Monaghan. R:** Overall study concept and design. Conducted literature review. Requested all required variables from data manager. Categorisation of mental health disorders. Data extraction and production of variables. Conducted statistical tests. Interpreted results. Wrote first draft of Chapter. Assembled co-authors revisions of Chapter. **O'Dwyer, M:** Contributed to overall study concept and design. Categorisation of mental health disorders. Proposed statistical methods. Revision of Chapter. **Henman, M.C:** Contributed to overall study concept and design. Categorisation of mental health disorders. Proposed statistical methods. Revision of Chapter.
Chapter 4 Evaluation of antiepileptic drug utilisation methods Monaghan, R., O'Dwyer, M., Henman, M.C.	**Monaghan. R:** Overall study concept and design. Conducted literature review. Requested all required variables from data manager. Data extraction and production of variables. Calculated prescribed daily dose of AEDs (PDD) and retrieved DDDs. Calculated AED load PDD/DDD. Developed seizure frequency categories. Categorisation of mental health disorders. Conducted statistical tests. Interpreted results. Wrote first draft of Chapter. Assembled co-authors revisions of Chapter. **O'Dwyer, M:** Contributed to overall study concept and design. Categorisation of mental health disorders. Development of seizure frequency categories. Proposed statistical methods. Revision of Chapter. **Henman, M.C.:** Contributed to overall study concept and design. Categorisation of mental health disorders. Development of seizure frequency categories. Proposed statistical methods. Revision of Chapter.

Table 2.14-1 List of individual contributions to the thesis (*Continued*)

Chapter/Study	Contributors
Chapter 5 Monaghan, R., O'Dwyer, M., Luus, R., Mulryan, N., McCallion, P., McCarron, M., Henman, M.C. Antiepileptic drugs, occurrence of seizures and effect of co-administration of potential seizure threshold-lowering psychotropic drugs in adults with intellectual disability who have epilepsy.	**Monaghan, R**: Overall study concept and design. Conducted literature review. Requested all required variables from data manager. Data extraction and production of variables. Developed categorisation for potential seizure threshold-lowering medication. Conducted statistical tests. Interpreted results. Developed seizure frequency categories. Categorisation of mental health disorders. Wrote first draft of manuscript. Assembled co-authors revisions of manuscript. Submission of manuscript to the *Journal of Applied Research in Intellectual Disabilities*. Management of revisions from peer reviewers. **O'Dwyer, M:** Contributed to overall study concept and design. Categorisation of mental health disorders. Developed seizure frequency categories. Developed categorisation for potential seizure threshold-lowering medication. Proposed statistical methods. Revision of all drafts of manuscript. Aided in Journal selection. **Luus, R:** Reviewed statistical analysis undertaken by R.M. Revision of all drafts of manuscript. **Mulryan, N:** Contributed to overall study concept and design. Revision of all drafts of manuscript. **McCallion, P:** Contributed to overall study concept and design. Revision of all drafts of manuscript. Aided in Journal selection. **McCarron, M**: Contributed to overall study concept and design. Revision of all drafts of manuscript. Aided in Journal selection. **Henman, M.C:** Contributed to overall study concept and design. Categorisation of mental health disorders. Developed seizure frequency categories. Developed categorisation for potential seizure threshold-lowering medication. Proposed statistical methods. Revision of all drafts of manuscript. Aided in Journal selection.

Table 2.14-1 List of individual contributions to the thesis (*Continued*)

Chapter/Study	Contributors
Chapter 6 Monaghan, R., O'Dwyer, M., Luus, R., Mulryan, N., McCallion, P., McCarron, M., Henman, M.C. The relationship between antiepileptic drug load and challenging behaviours in older adults with intellectual disability and epilepsy	**Monaghan, R:** Overall study concept and design. Conducted literature review. Requested all required variables from data manager. Data extraction and production of variables. Calculated prescribed daily dose of AEDs (PDD) and retrieved DDDs. Calculated AED load PDD/DDD. Categorisation of mental health disorders. Categorisation of challenging behaviour. Conducted statistical tests. Interpreted results. Wrote first draft of manuscript. Assembled co-authors revisions of manuscript. Submission of manuscript to Epilepsy & Behavior. Management of revisions from peer reviewers **O'Dwyer, M:** Contributed to overall study concept and design. Categorisation of mental health disorders. Development of AED load measure. Proposed statistical methods. Revision of all drafts of manuscript. Aided in Journal selection. **Luus, R:** Reviewed statistical analysis undertaken by R.M. Revision of all drafts of manuscript. **Mulryan, N:** Contributed to overall study concept and design. Revision of all drafts of manuscript. **McCallion, P:** Contributed to overall study concept and design. Revision of all drafts of manuscript. Aided in Journal selection. **McCarron, M:** Contributed to overall study concept and design. Revision of all drafts of manuscript. Aided in Journal selection. **Henman, M.C:** Contributed to overall study concept and design. Categorisation of mental health disorders. Development of AED load measure. Proposed statistical methods. Revision of all drafts of manuscript. Aided in Journal selection.

Table 2.14-1 List of individual contributions to the thesis *(Continued)*

Chapter/Study	Contributors
Chapter 7 Monaghan, R., O'Dwyer, M., AlMutairi, H., Henman, M.C. Psychotropic pharmacotherapy in older adults with intellectual disability reporting mental health disorders - an observational cross-sectional study.	**Monaghan, R:** Overall study concept and design. Conducted literature review. Requested all required variables from data manager. Data extraction and production of variables. Categorisation of mental health disorders. Categorisation of challenging behaviour. Categorisation of psychotropic medication and polypharmacy. Conducted statistical tests. Interpreted results. Wrote first draft of Chapter. Assembled co-authors revisions of Chapter. **O'Dwyer, M:** Contributed to overall study concept and design. Categorisation of mental health conditions. Categorisation of psychotropic medication and polypharmacy. Proposed statistical methods. Revision of all drafts of Chapter. **AlMutairi, H:** Created Venn Diagram. **Henman, M.C:** Contributed to overall study concept and design. Categorisation of mental health disorders. Categorisation of psychotropic medication and polypharmacy. Proposed statistical methods. Revision of all drafts of manuscript.

2.15 Conclusion

This Chapter introduces the study design, representativeness, recruitment of participants, inclusion policies, study ethos, participant welfare policies, ethical approval, regulatory requirements including consent and GDPR, and data collection and extraction techniques. It also introduces various methodologies that are utilised in this thesis. All descriptive and inferential analytical methods employed in the thesis are also described. All individual contributions to studies in this thesis are explained.

Chapter 3

Epilepsy prevalence and use of antiepileptic drugs

3.1 Introduction

A higher prevalence of epilepsy can be found in people with intellectual disability compared to the general population [29, 38]. Wide variations in epilepsy prevalence have been reported among the intellectually disabled population, with an increased prevalence associated with greater severity of intellectual disability [39, 114]. It is believed that half of the people with an IQ <50-55 have epilepsy [143]. Methodological difficulties including case ascertainment and selection bias have been highlighted in a review of incidence and prevalence studies in epilepsy [413]. A systematic review examining 38 studies of people with intellectual disability found a pooled prevalence estimate of epilepsy of 22.2% (95%CI 19.6-25.1) [114]. For people with Down Syndrome, a lower pooled prevalence estimate of epilepsy of 10.3% (95%CI 8.4-12.6) was found from examination of 11 studies [114]. In individuals with cerebral palsy or postnatal brain injury, epilepsy prevalence rates of up to 75% have been reported [50, 219, 414]. This contrasts with prevalence estimates of 0.6% to 1% in people without an intellectual disability [36-38].

A higher prevalence of epilepsy syndromes are also found in this population group, most notably Lennox-Gastaut Syndrome which has an estimated prevalence of 15 per 100,000 [39, 143, 415]. Lennox-Gastaut Syndrome is characterised by multiple generalised seizure types, abnormal EEGs, drop attacks, treatment resistant epilepsy and severe intellectual disability [143, 416]. Moreover, epilepsy is associated with increased hospitalisation and mortality in people with intellectual disability [65, 143, 219]. Two main causes of preventable death in people with both epilepsy and intellectual disability are aspiration pneumonia and convulsions [143]. While no evidence exists of greater morbidity or mortality associated with seizures in people with intellectual disability, Devinsky (2002) highlights that the ‘cerebral reserve’ may be diminished in people with intellectual

disability compared to the general population, resulting in greater predisposition to seizure provoked neurotoxicity [417]. Nonetheless, it is widely accepted that epilepsy is a chronic disabling illness with significant comorbidity leading to a significant burden on the individual, health services and society [418].

Epilepsy is associated with considerable physical and psychiatric comorbidity, both in people with intellectual disability and in the general population [28, 114, 264]. Behavioural problems, autistic spectrum disorders, psychotic, affective and anxiety disorders account for much of the psychiatric comorbidity in people with epilepsy and intellectual disability [87]. Various factors increase the risk of psychiatric illness, including the severity of the intellectual disability, autistic tendencies, individual genotypes and antiepileptic drugs (AEDs) [264]. A cross-sectional study by McCarron et al. (2014) of 753 adults in Wave 1 of IDS-TILDA examining the epidemiology of epilepsy, found that epilepsy was associated with joint disease, gastrointestinal disease and stroke [28]. Additionally, a systematic review of epilepsy prevalence found that people with epilepsy and intellectual disability were more likely to suffer blindness, speech, and motor difficulties compared to those without an epilepsy diagnosis [114]. Epilepsy and AEDs are also reported to be detrimental to bone health. A cross-sectional study by Burke et al. (2017) of 753 adults in Wave 1 of IDS-TILDA found a strong association between osteoporosis, a diagnosis of epilepsy and antiepileptic drug therapy [153]. Antiepileptic drugs are believed to affect the absorption of calcium and vitamin D resulting in greater bone loss [152].

Increased comorbidity among older people increases the likelihood of polypharmacy and drug-drug interactions with AEDs [419]. Antiepileptic drug monotherapy is often preferable to polytherapy thus avoiding drug-drug interactions with concomitant AEDs [419]. In addition, AED treatment can aggravate seizures and instigate

new seizure types in some epilepsy syndromes [143, 420]. A study examining the efficacy of lamotrigine in 21 people with Dravet Syndrome aged 2-18 years, found that lamotrigine caused seizure deterioration, with a >50% increase in convulsive seizures in 40% of patients. [159]. Treatment resistant epilepsy or refractory epilepsy is particularly detrimental to the safety of people with epilepsy and intellectual disability, with up to 50% of cases classified as such [143]. Benzodiazepines (for example, clobazam, clonazepam) are often used in people with intellectual disability, both as regular AEDs and as rescue medicine. They can be an effective add-on therapy in refractory epilepsy but tolerance is a problem, particularly in people with psychiatric illness who have an already high burden of 'benzodiazepine load' [143].

The aim of this Chapter is to examine demographic and clinical factors relating to the prevalence of epilepsy and use of antiepileptic and co-prescribed psychotropic drugs in a nationally representative sample of older adults with intellectual disability in Ireland.

3.1.1 Objectives of Chapter:

I. To describe the demographic characteristics of older adults with intellectual disability reporting a diagnosis of epilepsy and the patterns of their medication use with regard to AEDs.

II. To examine the prevalence of physical and psychiatric comorbidity in participants reporting a diagnosis of epilepsy and compare with participants not reporting a diagnosis of epilepsy.

III. To examine the prevalence of co-prescribed psychotropic medication in participants reporting a diagnosis of epilepsy and compare with participants not reporting a diagnosis of epilepsy.

3.2 Methods

3.2.1 Study design and participants

The data for this study were drawn from the third Wave of data collection, Wave 3 (2016/2017), of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA). For this study, the number of people taking part in Wave 3 was 609 with 44.2% male and 55.8% female. The age range for Wave 3 was 48 to 95 years with a mean of 59.1 years (SD: 8.81) [300]. Overall in Wave 3, 24.8% had a mild intellectual disability, 46.2% a moderate intellectual disability and 29.1% a severe/profound intellectual disability [300]. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) standardised reporting guidelines for cross-sectional studies [421]. The IDS-TILDA study received ethics approval from the Faculty of Health Sciences Ethics Committee, Trinity College Dublin and 138 intellectual disability service providers. Further details on the study methodology can be found in *Chapter 2, sections 2 and 3*.

3.2.2 Measures

The PIQ was sent to each participant one week prior to the interview taking place. This gave participants time to prepare and locate any information that may be needed (e.g., medication data) enhancing the reliability of the data. CAPI interviews were completed by trained field workers, experienced in working with people with intellectual disability. There were three styles of interviewing; self-report, proxy assisted (where the person with intellectual disability answered some but not all questions), and proxy only, where the carer/support person answered the questions on the persons' behalf. In terms of questions relating to epilepsy and the focus of this study, 20.8% of interviews were self-respondent

only, 48.5% used a proxy interview style and 30.7% used a combination of self-respondent and proxy style [422]. Further information regarding data collection can be found in *Chapter 2, section 5*.

3.2.3 Reported diagnosis of epilepsy

In Wave 1**,** each participant/proxy was asked in the PIQ if the individual with intellectual disability was ever diagnosed by a doctor/relevant health professional with epilepsy [29]. In subsequent Waves (2 and 3) of the study, each participant/proxy was asked 'since your last interview, has a doctor ever told you that you have epilepsy?'. This allowed for the creation of a variable for prevalence. Diagnosis data was not available for one (0.2%) participant with medication data. Further information on obtaining this data can be found in *Chapter 2, section 8*.

3.2.4 Drug class categorisation

Antiepileptic drugs (AEDs) were defined as those with the ATC code N03A. All AEDs were separated into those taken by a participant with a diagnosis of epilepsy and those without a diagnosis. Psychotropic co-medication were assessed: these were defined as antipsychotics (N05A), antidepressants (N06A), anxiolytics (N05B), hypnotics & sedatives (N05C), drugs for dementia (N06D) and anti-cholinergic drugs (N04A). Lithium was classified as a mood stabiliser and prochlorperazine was not included in the antipsychotic category as all the doses reported in this study fell within the recommended range used for the treatment of Meniere's Syndrome, labyrinthitis and nausea and vomiting (10-40mg daily) and taken PRN in this study. Clobazam was included in the AED category as it is

primarily used for epilepsy. Midazolam was excluded from the N05C class as it is used for acute seizure control only. The following psychotropic classes were analysed (*Table 3.2-1*):

Table 3.2-1 Psychotropic classes analysed in Wave 3

Psychotropic Class	Psychotropic Subclass	Drug Name
Antipsychotics (N05A)	Typical Antipsychotics	Chlorpromazine (N05AA01)
		Fluphenazine (N05AB02)
		Trifluoperazine (N05AB06)
		Haloperidol (N05AD01)
		Zuclopenthixol (N05AF05)
		Flupenthixol (N05AF01)
		Promazine (N05AA03)
		Benperidol (N05AD07)
	Atypical Antipsychotics	Olanzapine (N05AH03)
		Quetiapine (N05AH04)
		Sulpiride (N05AL01)
		Amisulpride (N05AL05)
		Risperidone (N05AX08)
		Aripiprazole (N05AX12)
		Ziprasidone (N05AE04)
Antidepressants (N06A)	SSRI	Citalopram (N06AB04)
		Escitalopram (N06AB10)
		Paroxetine (N06AB05)
		Fluoxetine (N06AB03)
		Sertraline (N06AB06)
	SNRI	Duloxetine (N06AX21)
		Venlafaxine (N06AX16)
	Other	Mirtazapine (N06AX11)
		Trazodone (N06AX05)
		Agomelatine (N06AX22)
	TCA	Clomipramine (N06AA04)
		Lofepramine (N06AA07)
		Trimipramine N06AA06)
		Doxepin (N06AA12)
		Dosulepin (N06AA16)
		Amitriptyline (N06AA09)
Anxiolytics (N05B)	Anxiolytic Benzodiazepines	Diazepam (N05BA01)
		Chlordiazepoxide (N05BA02)
		Bromazepam (N05BA08)
		Prazepam (N05BA11)
		Alprazolam (N05BA12)
		Lorazepam (N05BA06)
	Other	Hydroxyzine (N05BB01)
		Buspirone (N05BE01)
Mood Stabilising Agent		Lithium (N05AN01)

Table 3.2-1 Psychotropic classes analysed in Wave 3 (*Continued*)

Psychotropic Class	Psychotropic Subclass	Drug Name
Antiepileptics (N03A)		Valproic Acid (N03AG01)
		Lamotrigine (N03AX09)
		Carbamazepine (N03AF01)
		Levetiracetam (N03AX14)
		Phenobarbital (N03AA02)
		Primidone (N03AA03)
		Phenytoin (N03AB02)
		Rufinamide (N03AF03)
		Eslicarbazepine (N03AF04)
		Topiramate (N03AX11)
		Gabapentin (N03AX12)
		Zonisamide (N03AX15)
		Pregabalin (N03AX16)
		Lacosamide (N03AX18)
		Perampanel (N03AX22)
		Clobazam (N05BA09)
		Clonazepam (N03AE01)
Hypnotics & Sedatives (N05C)	Z Drug Hypnotics	Zolpidem (N05CF02)
		Zopiclone (N05CF01)
	Prolonged Acting Hypnotics	Nitrazepam (N05CD02)
		Flurazepam (N05CD01)
	Short Acting Hypnotics	Lormetazepam N05CD06)
		Triazolam (N05CD05)
		Temazepam (N05CD07)
	Other	Melatonin (N05CH01)
Drugs for Dementia (N06D)		Memantine (N06DX01)
		Donepezil (N06DA02)
Anti-cholinergic (NO4A)		Biperiden (N04AA02)
		Procyclidine (N04AA04)
		Benzatropine (N04AC01)

3.2.5 Antiepileptic drugs used in participants with epilepsy

All reported prescription of regular AEDs used to treat epilepsy were examined. Participant exposure to these AEDs was then categorised into number of AEDs prescribed and subsequently into monotherapy and polytherapy. Antiepileptic monotherapy was defined as treatment with one regular AED. Antiepileptic polytherapy was defined as concurrent treatment with two or more regular AEDs. Regular in this instance refers to an AED taken on a regular basis and not for the treatment of acute seizures where emergency rescue

medications are used. All fast-acting agents not used on a regular basis were recorded separately from the other AEDs and included midazolam and lorazepam

3.2.6 Antiepileptic drugs and indications

The following groups are used in this study:

1. Those who reported a Doctor's diagnosis of epilepsy (n=196).
2. Those who reported having a prescription for a regular AED, together with a Doctor's diagnosis of epilepsy (n=174).
3. Those who reported a Doctor's diagnosis of epilepsy but who were not prescribed a regular AED (n=22).

3.2.7 Reported diagnosis of comorbid mental health disorder

Participants were asked in the CAPI, *"has a doctor ever diagnosed you with an emotional/psychiatric disorder?".* If yes, participants were then asked *"what type of emotional, nervous or psychiatric problems do/does you/he/she have?"* The following options were given: hallucinations, anxiety, depression, emotional problems, schizophrenia, psychosis, mood swings, manic depression, post-traumatic stress disorder (PTSD), something else, unclear response, don't know, refused to answer. For the purposes of analysis, three categories of mental health disorder (psychotic/mood/anxiety) were created by grouping the above mental health conditions. Further information on mental health disorder variables can be found in *Chapter 2, section 10*.

3.2.8 Covariates

Covariates investigated were gender (male/female), age (<50/50-64/65+ years), level of intellectual disability (mild/moderate/severe/profound/unverified), place of residence (independent/family/community group home/residential/campus setting), psychotropic medication classes and comorbid mental health disorders. Psychotic disorder includes hallucinations, schizophrenia and psychosis. Mood disorder includes depression, manic depression, mood swings and emotional problems, and anxiety disorder includes anxiety and PTSD. However, there were no reports of PTSD in this study. Residential/campus settings were defined as living arrangements where ten or more people share a single living unit or where the living arrangements are campus based. Community group homes are in a community setting with staff support for small groups of people with intellectual disabilities. Living independently/with family means the person lives by themselves or with family in the community. Further information can be found in *Chapter 2*.

3.2.9 Statistical analyses

Statistical significance was set at <0.05. Descriptive statistics were used to describe the characteristics of the sample being studied. The Chi-Square (χ^2) test for independence was utilised to test for a significant association between categorical variables. Fisher's Exact test was used to test for a significant association between variables where the sample size in subgroups was small (n<5). To control for problems associated with multiple comparisons, thereby increasing the likelihood of Type 1 error (rejecting the null hypothesis when it is true and the false discovery rate), a Bonferroni correction was applied to bivariate Chi-Square/Fisher's Exact tests where necessary [406]. All statistical analyses were carried out using the Statistical Package for Social Sciences, version 25.0 (SPSS Inc.,

Chicago, IL, USA). Further information on statistical tests undertaken can be found in *Chapter 2, section 12*.

3.3 Results

3.3.1 Prevalence of epilepsy in participants with intellectual disability

The prevalence of epilepsy in Wave 3 of our representative group of older adults with an intellectual disability, confirmed epilepsy status and available medication data (n=548) was 35.8% (n=196), with 88.8% (n=174) of those with an epilepsy diagnosis reporting taking a regular AED *(Table 3.3-1)*. The prevalence of epilepsy was found to be significantly associated ($p<0.001$) with place of residence with the majority of people reporting an epilepsy diagnosis living in residential/campus settings (59.2%, n=116) and the minority (10.2%, n=20) living in independent/family settings.

Prevalence of epilepsy was also significantly associated ($p<0.001$) with level of intellectual disability in our study. For those with a categorised level of intellectual disability, the prevalence of epilepsy was highest amongst those with a severe/profound intellectual disability (42.2%, n=79) and lowest amongst those with a mild intellectual disability (16.6%, n=31). There was no significant difference ($p=0.665$) in epilepsy prevalence rates between men and women but a higher prevalence was found in females (58.2%, n=114).

Age was also not found to be a significant factor in bivariate analysis for epilepsy prevalence ($p=0.475$). Those aged 50-64 years reported the highest prevalence (66.3%, n=130). The youngest age group (<50 years) reported the lowest prevalence (10.7%, n=21). Epilepsy prevalence was found to decrease after the age of 65 years in our study (23.0%,

n=45). Prevalence of epilepsy was also found to be significantly ($p<0.001$) associated with type of therapy. A greater number of participants reporting an epilepsy diagnosis reported being exposed to AED polytherapy (48.0%, n=94) compared to AED monotherapy (40.8%, n=80) with 11.2% (n=22) of participants reporting no AED therapy.

Of participants reporting a diagnosis of epilepsy, 39.3% (n=77) reported being prescribed antipsychotics, 30.6% (n=60) antidepressants, 17.3% (n=34) anxiolytics, 11.2% (n=22) hypnotics & sedatives and 2.6% (n=5) lithium. In contrast, of participants not reporting a diagnosis of epilepsy, 47.7% (n=168) were prescribed antipsychotics, 35.2% (n=124) antidepressants, 13.6% (n=48) anxiolytics, 8.2% (n=29) hypnotics & sedatives and 3.1% (n=11) lithium.

Table 3.3-1 Bivariate analysis of demographic and clinical characteristics of participants reporting a diagnosis of epilepsy (n=196) and those not reporting a diagnosis of epilepsy (n=352)

Characteristic	All participants with medicine data n=548 n (%)	Diagnosis of epilepsy n=196 n (%)	No diagnosis of epilepsy n=352 n (%)	P value
Gender				0.665
Male	236 (43.1)	82 (41.8)	154 (43.8)	
Female	312 (56.9)	114 (58.2)	198 (56.2)	
Age				0.475
<50 years	64 (11.7)	21 (10.7)	43 (12.2)	
50-64 years	345 (63.0)	130 (66.3)	215 (61.1)	
65+ years	139 (25.3)	45 (23.0)	94 (26.7)	
Level of intellectual disability	n=506	n=187	n=319	**<0.001***
Mild	121 (23.9)	31 (16.6)	90 (28.2)	
Moderate	231 (45.7)	77 (41.2)	154 (48.3)	
Severe/profound	154 (30.4)	79 (42.2)	75 (23.5)	
Place of residence				**<0.001***
Independent/family	78 (14.2)	20 (10.2)	58 (16.5)	
Community group home	222 (40.5)	60 (30.6)	162 (46.0)	
Residential/campus	248 (45.3)	116 (59.2)	132 (37.5)	
Type of therapy				**<0.001***
AED monotherapy	135 (24.6)	80 (40.8)	55 (15.6)	
AED polytherapy (median =2, max=5)	109 (19.9)	94 (48.0)	15 (4.3)	
No AED therapy	304 (55.5)	22 (11.2)	282 (80.1)	
Comorbid mental health condition				
Psychotic disorder	44 (8.0)	14 (7.1)	30 (8.5)	0.569
Mood disorder	180 (32.8)	74 (37.8)	106 (30.1)	0.068
Anxiety disorder	177 (32.3)	67 (34.2)	110 (31.3)	0.481
Psychotropic medications				
Antipsychotics	245 (44.7)	77 (39.3)	168 (47.7)	0.057
Antidepressants	184 (33.6)	60 (30.6)	124 (35.2)	0.273
Anxiolytics	82 (15.0)	34 (17.3)	48 (13.6)	0.243
Hypnotics & sedatives	51 (9.3)	22 (11.2)	29 (8.2)	0.249
Lithium	16 (2.9)	5 (2.6)	11 (3.1)	0.702

n=196: Participants reporting a diagnosis of epilepsy. n=352: Participants not reporting a diagnosis of epilepsy. n= 548: All participants with medication data and confirmed epilepsy status. n=1 individual with medication data excluded from analysis as no confirmed epilepsy status. P value: Chi-Square Test. **Statistically significant results marked in bold and with an asterisk***

3.3.2 Antiepileptic drugs prescribed

The most frequently prescribed AEDs to participants with an epilepsy diagnosis were the mood stabilising AEDs - valproic acid (44.8%, n=78), carbamazepine (39.1%, n=68) and lamotrigine (35.1%, n=61) *(Table 3.3-2).* Levetiracetam (27.0%, n=47) was the most frequently prescribed AED outside of the mood stabilising AEDs.

Table 3.3-2 Frequency of AEDs prescribed (n=174)

Drug	n (%)
Older antiepileptic drugs	
Valproic Acid	78 (44.8)
Phenytoin	10 (5.8)
Carbamazepine	68 (39.1)
Primidone	<5
Phenobarbital	13 (7.5)
Clobazam	23 (13.2)
Clonazepam	12 (6.9)
Newer antiepileptic drugs	
Lamotrigine	61 (35.1)
Gabapentin	<5
Topiramate	6 (3.5)
Levetiracetam	47 (27.0)
Zonisamide	9 (5.2)
Pregabalin	5 (2.9)
Rufinamide	<5
Eslicarbazepine	<5
Lacosamide	5 (2.9)
Perampanel	<5

n=174 participants taking a regular AED.
<5 denotes fewer than 5 participants.

3.3.3 Antiepileptic drug regimens

Table 3.3-3 presents individual AEDs given in monotherapy and polytherapy regimens. The majority of participants who reported taking the mood stabilising AEDs (valproic acid, carbamazepine, lamotrigine), and levetiracetam took them in polytherapy regimens. All remaining antiepileptic agents (zonisamide, topiramate, pregabalin, lacosamide, primidone, eslicarbazepine, rufinamide, gabapentin, perampanel) were only taken in polytherapy regimens.

Table 3.3-3 Bivariate analysis of AEDs by monotherapy and polytherapy (n=174)

	Total n=174 n (%)	**Monotherapy n=80 n (%)**	**Polytherapy n=94 n (%)**	**P value**
Valproic acid	78 (44.8)	29 (37.2)	49 (62.8)	**0.036***
Carbamazepine	68 (39.0)	24 (35.3)	44 (64.7)	**0.024***
Lamotrigine	61 (35.1)	13 (21.3)	48 (78.7)	**<0.001***
Levetiracetam	47 (27.0)	10 (21.3)	37 (78.7)	**<0.001***

Phenobarbital (n=13) and phenytoin (n=10) were removed from the table due to low participant numbers in the 'monotherapy' category. P value: Chi-Square Test. **Statistically significant results marked in bold and with an asterisk***

Table 3.3-4 presents AEDs reported to be prescribed for the treatment of acute status epilepticus in participants reporting no AED therapy, AED monotherapy, and AED polytherapy.

Table 3.3-4 Fast acting agents for the treatment of acute status epilepticus by AED treatment (n=196)

	Total n=196 n (%)	**No AED therapy n=22 n (%)**	**Monotherapy n=80 n (%)**	**Polytherapy n=94 n (%)**	**P value**
Buccal Midazolam	103 (52.6)	3 (13.6)	39 (48.8)	61 (64.9)	**0.001***
Clobazam	<5	0 (0)	0 (0)	<5	-
Lorazepam	<5	0 (0)	<5	0 (0)	-

P value: Chi-Square Test. - Unable to calculate due to small numbers in subgroups. <5 denotes fewer than 5 participants.
Statistically significant results marked in bold and with an asterisk*

Table 3.3-5 presents the ten most frequently reported AED regimens, with valproic acid as monotherapy most commonly prescribed by 16.7% (n=29) of those taking AEDs.

Table 3.3-5 Analysis of most frequently reported AED regimens (n=174)

	n (%)	Antiepileptic drug	Type of therapy
1	29 (16.7)	Valproic acid	Monotherapy
2	24 (13.8)	Carbamazepine	Monotherapy
3	13 (7.5)	Lamotrigine	Monotherapy
4	10 (5.7)	Levetiracetam	Monotherapy
5	6 (3.4)	Valproic Acid & Lamotrigine	Polytherapy
6	6 (3.4)	Valproic Acid & Carbamazepine	Polytherapy
7	5 (2.9)	Lamotrigine & Carbamazepine	Polytherapy
8	3 (1.7)	Lamotrigine, Levetiracetam & Clobazam	Polytherapy
9	3 (1.7)	Valproic Acid, Lamotrigine & Levetiracetam	Polytherapy
10	2 (1.1)	Carbamazepine & Phenobarbital	Polytherapy
Total	101 (57.9)		

3.3.4 Prevalence of comorbidity with regards to epilepsy diagnosis

Examining comorbidity and prevalence of epilepsy *(Table 3.3-6),* a significantly greater prevalence of dementia (14.8%, n=29, p<0.001), and Alzheimer's disease and/or dementia (15.3%, n=30, p<0.001) were found in participants reporting an epilepsy diagnosis compared to those not reporting an epilepsy diagnosis (5.1%, n=18 and 5.7%, n=20, respectively). Prevalence of constipation (p=0.001) was also found to be significantly higher in those reporting an epilepsy diagnosis (54.1%, n=106) compared to those not reporting an epilepsy diagnosis (39.5%, n=139). A greater prevalence of TIA (7.1%, n=14, p=0.010) and stroke (4.6%, n=9, p=0.047) were found in participants reporting an epilepsy diagnosis compared to those not reporting an epilepsy diagnosis (2.3%, n=8 and 1.7%, n=6, respectively), but these were not significant following Bonferroni correction. In addition, a greater prevalence of osteoporosis (27.6%, n=54, p=0.017) was found in those reporting an epilepsy diagnosis compared to those not reporting an epilepsy diagnosis (18.8%, n=66), again not significant following Bonferroni correction.

Table 3.3-6 Bivariate analysis of prevalence of comorbidity in participants reporting a diagnosis of epilepsy (n=196) and those not reporting a diagnosis of epilepsy (n=352)

Comorbidity	Total n=548 n (%)	Diagnosis of epilepsy n=196 n (%)	No diagnosis of epilepsy n=352 n (%)	P value
Dementia only	47 (8.6)	29 (14.8)	18 (5.1)	**<0.001***
Alzheimer's disease only	17 (3.1)	10 (5.1)	7 (2.0)	0.044
Alzheimer's disease and/or dementia	50 (9.1)	30 (15.3)	20 (5.7)	**<0.001***
Parkinson's disease	7 (1.3)	4 (2.0)	3 (0.9)	0.255 [a]
TIA (Transient Ischaemic Attack)	23 (4.2)	14 (7.1)	8 (2.3)	0.010
Stroke	15 (2.7)	9 (4.6)	6 (1.7)	0.047
Heart attack	9 (1.6)	4 (2.0)	5 (1.4)	0.728 [a]
Abnormal heart rhythm	11 (2.0)	4 (2.0)	7 (2.0)	1.000 [a]
High blood pressure	117 (21.4)	40 (20.4)	77 (21.9)	0.688
High cholesterol	230 (42.0)	87 (44.4)	143 (40.6)	0.392
Congestive heart failure	9 (1.6)	3 (1.5)	6 (1.7)	1.000 [a]
Heart murmur	34 (6.2)	11 (5.6)	23 (6.5)	0.668
Angina	<5	<5	<5	-
Diabetes	52 (9.5)	13 (6.6)	39 (11.1)	0.089
Varicose ulcers	11 (2.0)	6 (3.1)	5 (1.4)	0.213 [a]
Arthritis	106 (19.3)	35 (17.9)	71 (20.2)	0.511
Osteoporosis	120 (21.9)	54 (27.6)	66 (18.8)	0.017
Thyroid disease	128 (23.4)	52 (26.5)	76 (21.6)	0.190
Asthma	37 (6.8)	12 (6.1)	25 (7.1)	0.661
Chronic lung disease	21 (3.8)	6 (3.1)	15 (4.3)	0.483
Constipation	245 (44.7)	106 (54.1)	139 (39.5)	**0.001***
Gastro reflux	91 (16.6)	37 (18.9)	54 (15.3)	0.286
Stomach ulcer	31 (5.7)	15 (7.7)	16 (4.5)	0.131
Coeliac	11 (2.0)	4 (2.0)	7 (2.0)	1.000 [a]
Irritable bowel syndrome	17 (3.1)	7 (3.6)	10 (2.8)	0.636
Chronic liver damage	<5	<5	<5	-
Multiple sclerosis	<5	<5	0 (0)	-
Cerebral palsy	43 (7.8)	23 (11.7)	20 (5.7)	0.012
Scoliosis	47 (8.6)	21 (10.7)	26 (7.4)	0.182
Muscular dystrophy	<5	<5	0 (0)	-
Spina bifida	8 (1.5)	5 (2.6)	3 (0.9)	0.142 [a]
Cancer	11 (2.0)	4 (2.0)	7 (2.0)	1.000 [a]
Psychiatric/emotional disorder	291 (53.1)	113 (57.7)	178 (50.6)	0.111

n=196: Participants reporting a diagnosis of epilepsy. n=352: Participants not reporting a diagnosis of epilepsy. n= 548: All participants with medication data and confirmed epilepsy status. n=1 individual with medication data excluded from analysis as no confirmed epilepsy status. P=Chi-Square. [a] Fisher's Exact test. P value: for Chi-Square test after applying Bonferroni correction α=0.05/33= 0.0015 thus p<0.0015 for significance. <5 denotes fewer than 5 participants. – Unable to calculate p value due to small numbers in subgroups. **Statistically significant results marked in bold and with an asterisk***

3.3.5 Use of psychotropic co-medication and prevalence of epilepsy

The prevalence of psychotropic co-medication in participants reporting an epilepsy diagnosis compared to those not reporting an epilepsy diagnosis can be found in *Tables 3.3-7 – 3.3-10.* Regarding antipsychotics (*Table 3.3-7*), a significantly higher prevalence of haloperidol (p=0.006) was found in those not reporting an epilepsy diagnosis (6.8%, n=24) compared to those reporting an epilepsy diagnosis (1.5%, n=3). Of participants reporting an epilepsy diagnosis, 33.7% (n=66) reported prescription of atypical antipsychotics while only 7.1% (n=14) reported a psychotic disorder.

Table 3.3-7 Bivariate analysis of prevalence of antipsychotic medication in those reporting an epilepsy diagnosis (n=196) and those not reporting an epilepsy diagnosis (n=352)

	Total **n=548** **n (%)**	**Diagnosis of epilepsy** **n=196** **n (%)**	**No diagnosis of epilepsy** **n=352** **n (%)**	**P value**
Psychotic disorder	44 (8.0)	14 (7.1)	30 (8.5)	0.569
Antipsychotic medication				
Typical antipsychotic	78 (14.2)	20 (10.2)	58 (16.5)	**0.044***
Chlorpromazine	35 (6.4)	12 (6.1)	23 (6.5)	0.850
Haloperidol	27 (4.9)	3 (1.5)	24 (6.8)	**0.006*** [a]
Zuclopenthixol	14 (2.6)	3 (1.5)	11 (3.1)	0.257 [a]
Atypical antipsychotic	191 (34.9)	66 (33.7)	125 (35.5)	0.665
Olanzapine	83 (15.2)	29 (14.8)	54 (15.3)	0.865
Quetiapine	28 (5.1)	9 (4.6)	19 (5.4)	0.681
Risperidone	77 (14.1)	25 (12.8)	52 (14.8)	0.515
Aripiprazole	15 (2.7)	5 (2.6)	10 (2.8)	0.842

n=196: Participants reporting a diagnosis of epilepsy. n=352: Participants not reporting a diagnosis of epilepsy. n= 548: All participants with medication data and confirmed epilepsy status. n=1 individual with medication data excluded from analysis as no confirmed epilepsy status. P value: Chi-Square Test, [a] Fisher's Exact Test. P<0.05 for significance. Due to low numbers of participants reporting prescription of some antipsychotics (<5), fluphenazine, promazine, trifluoperazine, sulpride, amisulpride, aripiprazole, benperidol, ziprasidone and flupenthixol were removed from table. **Statistically significant results marked in bold and with an asterisk***

Regarding antidepressants (*Table 3.3-8*), a significantly higher prevalence of escitalopram (9.7%, n=19, p=0.028), mirtazapine (5.6%, n=11, p=0.023) and trazodone (3.6%, n=7, p=0.012) were found in participants reporting a diagnosis of epilepsy compared

to those not reporting a diagnosis of epilepsy (4.8% n=17, 2.0% n=7, and 0.6% n=2, respectively). A significantly higher prevalence of sertraline (p=0.014) was found in participants not reporting an epilepsy diagnosis (7.7%, n=27) compared to participants reporting an epilepsy diagnosis (2.6%, n=5).

Table 3.3-8 Bivariate analysis of prevalence of antidepressant medication in those reporting an epilepsy diagnosis (n=196) and those not reporting an epilepsy diagnosis (n=352)

	Total **n=548** **n (%)**	**Diagnosis of epilepsy** **n=196** **n (%)**	**No diagnosis of epilepsy** **n=352** **n (%)**	**P value**
Mood disorder	180 (32.8)	74 (37.8)	106 (30.1)	0.068
Antidepressant medication				
SSRI	128 (23.4)	37 (18.9)	91 (25.9)	0.064
SNRI	21 (3.8)	9 (4.6)	12 (3.4)	0.489
Other (hydroxyzine/ buspirone)	28 (5.1)	18 (9.2)	10 (2.8)	**0.001***
Citalopram	17 (3.1)	4 (2.0)	13 (3.7)	0.285 [a]
Escitalopram	36 (6.6)	19 (9.7)	17 (4.8)	**0.028***
Paroxetine	18 (3.3)	3 (1.5)	15 (4.3)	0.086 [a]
Fluoxetine	25 (4.6)	6 (3.1)	19 (5.4)	0.209
Sertraline	32 (5.8)	5 (2.6)	27 (7.7)	**0.014***
Mirtazapine	18 (3.3)	11 (5.6)	7 (2.0)	**0.023***
Venlafaxine	17 (3.1)	8 (4.1)	9 (2.6)	0.324
Trazodone	9 (1.6)	7 (3.6)	2 (0.6)	**0.012*** [a]

n=196: Participants reporting a diagnosis of epilepsy. n=352: Participants not reporting a diagnosis of epilepsy. n= 548: All participants with medication data and confirmed epilepsy status. n=1 individual with medication data excluded from analysis as no confirmed epilepsy status P value: Chi-Square Test, [a] Fisher's Exact Test. P<0.05 for significance. Due to low numbers of participants being prescribed some antidepressants (<5), duloxetine, clomipramine, lofepramine, agomelatine, doxepin, amitriptyline and trimipramine were removed from table. TCA (n=15) and trimipramine (n=6) were also removed due to low participant numbers in the no diagnosis of epilepsy category. **Statistically significant results marked in bold and with an asterisk***

With regards to AEDs *(Table 3.3-9),* a significantly higher prevalence of valproic acid (44.8%, n=78, P<0.001), lamotrigine (35.1%, n=61, p<0.001) and carbamazepine (39.1%, n=68, p<0.001) were found in those reporting a diagnosis of epilepsy compared to those not reporting a diagnosis of epilepsy (8.2% n=29, 2.8% n=10 and 7.1% n=25, respectively).

Table 3.3-9 Bivariate analysis of prevalence of antiepileptic medication in those reporting an epilepsy diagnosis (n=196) and those not reporting an epilepsy diagnosis (n=352)

	Total **n=548** **n (%)**	**Diagnosis of epilepsy** **n=196** **n (%)**	**No diagnosis of epilepsy** **n=352** **n (%)**	**P value**
Any emotional/ psychiatric condition	291 (53.1)	113 (57.7)	178 (50.6)	0.111
Mood stabilising AED	211 (38.5)	155 (79.1)	56 (15.9)	**<0.001***
Valproic acid	107 (19.5)	78 (44.8)	29 (8.2)	**<0.001***
Lamotrigine	71 (13.0)	61 (35.1)	10 (2.8)	**<0.001***
Carbamazepine	93 (17.0)	68 (39.1)	25 (7.1)	**<0.001***
Topiramate	6 (1.1)	6 (3.4)	0 (0)	**0.002*** [a]
Zonisamide	9 (1.6)	9 (5.2)	0 (0)	**<0.001*** [a]
Pregabalin	16 (2.9)	5 (2.9)	11 (3.1)	0.702

n=196: Participants reporting a diagnosis of epilepsy. n=352: Participants not reporting a diagnosis of epilepsy. n= 548: All participants with medication data and confirmed epilepsy status. n=1 individual with medication data excluded from analysis as no confirmed epilepsy status P value: Chi-Square Test, [a] Fisher's Exact Test. P<0.05 for significance. Due to low numbers of participants prescribed some antiepileptics (<5), primidone, rufinamide, eslicarbazepine, gabapentin and perampanel were removed from table. Levetiracetam (n=48), phenobarbital (n=14), phenytoin (n=11) and lacosamide (n=6) were also removed from table due to low numbers in the no diagnosis of epilepsy category.
Statistically significant results marked in bold and with an asterisk*

Regarding other psychotropic medication (mood stabilising agents - lithium, anxiolytics, hypnotics & sedatives, drugs for dementia and anti-cholinergic drugs) (*Table 3.3-10*), a higher prevalence of diazepam (p=0.015) was found in those reporting an epilepsy diagnosis (10.7%, n=21) compared to those not reporting an epilepsy diagnosis (5.1%, n=18), although this was not significant following Bonferroni correction. A statistically significant (p=0.002) higher prevalence of drugs prescribed for dementia were found in participants reporting an epilepsy diagnosis (5.6%, n=11) compared to participants not reporting an epilepsy diagnosis (1.1%, n=4).

Table 3.3-10 Bivariate analysis of prevalence of other psychotropic medication in those reporting an epilepsy diagnosis (n=196) and those not reporting an epilepsy diagnosis (n=352)

	Total n=548 n (%)	Diagnosis of epilepsy n=196 n (%)	No diagnosis of epilepsy n=352 n (%)	P value
Anxiety disorder	177 (32.3)	67 (34.2)	110 (31.3)	0.481
Mood stabilising agents				
Lithium	16 (2.9)	5 (2.6)	11 (3.1)	0.702
Anxiolytics				
Anxiolytic benzodiazepines	79 (14.4)	33 (16.8)	46 (13.1)	0.229
Diazepam	39 (7.1)	21 (10.7)	18 (5.1)	0.015
Lorazepam	21 (3.8)	8 (4.1)	13 (3.7)	0.820
Alprazolam	17 (3.1)	4 (2.0)	13 (3.7)	0.285 [a]
Hypnotics & sedatives				
Z drugs	30 (5.5)	13 (6.6)	17 (4.8)	0.374
Prolonged acting hypnotic	10 (1.8)	5 (2.6)	5 (1.4)	0.341 [a]
Short acting hypnotic	5 (0.9)	2 (1.0)	3 (0.9)	1.000 [a]
Zolpidem	12 (2.2)	7 (3.6)	5 (1.4)	0.128
Flurazepam	9 (1.6)	5 (2.6)	4 (1.1)	0.293 [a]
Zopiclone	18 (3.3)	6 (3.1)	12 (3.4)	0.827
Melatonin	9 (1.6)	3 (1.5)	6 (1.7)	1.000 [a]
Drugs for dementia				
Drugs for dementia	15 (2.7)	11 (5.6)	4 (1.1)	**0.002***
Memantine	9 (1.6)	6 (3.1)	3 (0.9)	0.076 [a]
Anti-cholinergic drugs				
Anticholinergic drugs	71 (13.0)	27 (13.8)	44 (12.5)	0.670
Biperiden	53 (9.7)	21 (10.7)	32 (9.1)	0.538
Procyclidine	18 (3.3)	5 (2.6)	13 (3.7)	0.472

n=196: Participants reporting a diagnosis of epilepsy. n=352: Participants not reporting a diagnosis of epilepsy. n= 548: All participants with medication data and confirmed epilepsy status. n=1 individual with medication data excluded from analysis as no confirmed epilepsy status. P value: Chi-Square Test, [a] Fisher's Exact Test. P value: for Chi-Square Test after applying Bonferroni correction α=0.05/18= 0.0028 thus p<0.0028 for significance. Due to low numbers of participants reporting being prescribed some anxiolytics, hypnotics & sedatives and anti-cholinergic medications (<5), chlordiazepoxide, bromazepam, prazepam, hydroxyzine, buspirone, nitrazepam, temazepam, lormetazepam, triazolam and benzatropine were removed from table. Donepezil (n=7) was removed from table due to low numbers in the no diagnosis of epilepsy category. **Statistically significant results marked in bold and with an asterisk***

3.4 Discussion

3.4.1 Main findings

The prevalence of epilepsy reported in this representative group of older adults with intellectual disability and medication data was 35.8%, with 88.8% of those with an epilepsy diagnosis reporting prescription of a regular AED. Over half (52.6%) of participants reporting a diagnosis of epilepsy reported prescription of buccal midazolam for rescue treatment of acute seizures. The prevalence of epilepsy was found to be significantly associated with place of residence at bivariate level, with the majority of participants (59.2%) reporting a diagnosis of epilepsy living in residential/campus settings. Epilepsy prevalence was also significantly associated with level of intellectual disability at bivariate level, with 42.2% of participants reporting an epilepsy diagnosis having a severe/profound intellectual disability compared to 23.5% of participants not reporting an epilepsy diagnosis having a severe/profound intellectual disability. Antiepileptic drug polytherapy (48.0%) was the most common type of therapy reported, with 40.8% reporting AED monotherapy. In total, 11.2% of participants reported no AED therapy. Mood stabilising AEDs (valproic acid, carbamazepine, and lamotrigine) were the most commonly prescribed AEDs in this study.

A diagnosis of dementia and Alzheimer's disease and/or dementia was significantly more prevalent in participants reporting a diagnosis of epilepsy. Constipation was also found to have a significantly greater prevalence in participants reporting a diagnosis of epilepsy. Over half (57.7%) of participants reporting an epilepsy diagnosis reported a doctor's diagnosis of a psychiatric/emotional disorder. A lower prevalence of psychotic disorder was found in participants reporting a diagnosis of epilepsy (7.1%) compared to those not reporting a diagnosis of epilepsy (8.5%). In contrast, a higher prevalence of both

mood (37.8%) and anxiety disorders (34.2%) were found in participants reporting an epilepsy diagnosis compared to those not reporting an epilepsy diagnosis (30.1% and 31.3%, respectively). A significantly greater prevalence of prescription of the antidepressants escitalopram, mirtazapine and trazodone were found in participants reporting a diagnosis of epilepsy with a significantly greater prevalence of the antipsychotic haloperidol in participants not reporting a diagnosis of epilepsy.

3.4.2 Comparisons with other studies

The prevalence of reported epilepsy (35.8%) in participants with intellectual disability in this study is higher than that found in other population based studies of adults with intellectual disability [38, 114]. McGrother et al. (2006) in a UK population based prevalence study of 620 people using the Leicestershire Learning Disability Register found a prevalence of epilepsy of 26%, with a similar prevalence found in both men (25.6%) and women (26.3%) [38]. Furthermore, a systematic review examining the prevalence of epilepsy in people with intellectual disability by Robertson et al. (2015) found a pooled prevalence estimate of 22.2%, with a lower prevalence found in people with Down Syndrome (10.3%) [114]. Unquestionably, the prevalence of epilepsy in people with intellectual disability greatly exceeds the prevalence rates reported in the general population. An Irish study by Linehan et al (2010) using a multiple case ascertainment methodology examined the prevalence of epilepsy in the general population in Ireland and found a prevalence of 10 per 1000 (1%) in people aged 18 years and older [423]. Data sources examined in this study were Irish self-report data, Irish antiepileptic prescription data 2002-2005, Irish primary care data, Irish specialist data and Irish hospital in-patient data (2000-2005) [423].

The prevalence of epilepsy in Wave 3 of this study (35.8%) is similar to the IDS-TILDA Wave 2 prevalence (36%) [424], an increase from Wave 1 where a prevalence of 30.7% was reported [29]. This is perhaps due to the increasing incidence of epilepsy and related Alzheimer's dementia in people as they age, especially in those with Down Syndrome [28].The prevalence of epilepsy in this study was found to be significantly associated ($p<0.001$) with place of residence, with a greater prevalence of epilepsy reported in those living in residential/campus settings. In contrast, Mc Grother et al. (2006) in their UK population based prevalence study (n=620) did not find a significantly higher prevalence of epilepsy in those living in residential care which they attribute in part to a transformation in the delivery of care in the community [38]. Prevalence of epilepsy was also significantly associated ($p<0.001$) with level of intellectual disability in our study. A systematic review examining epilepsy prevalence in people with intellectual disability by Robertson et al. (2015) also found the prevalence of epilepsy to be related to level of intellectual disability [114].

We found a higher prevalence of epilepsy in females (58.2%) as opposed to males (41.8%) This contrasts with studies in the general population where higher rates of epilepsy in men are reported [38]. A community based study by Forsgren et al. (1990) in a northern Swedish county of 299 people with epilepsy and intellectual disability also found a higher prevalence in men as opposed to women in the age group 20-39 and no difference above the age of 40 [425]. Similar to what Robertson et al. (2015) found in their systematic review [114], age was not found to be a significant factor for epilepsy prevalence in our study with 66.3% of participants reporting a diagnosis of epilepsy aged 50-64 years, and 23% over the age of 65 years. Branford et al. (1998) also reported a decline over the age of 50 years,

perhaps due to mortality associated with a diagnosis of both epilepsy and intellectual disability [38, 426].

A greater proportion of participants were exposed to AED polytherapy (48.0%) compared to AED monotherapy (40.8%) in our study. This is in contrast to Wave 1 of IDS-TILDA where monotherapy (49.8%) and polytherapy (50.2%) were almost equally reported by those taking AEDs, in a cross-sectional study by O'Dwyer et al. (2018) of 205 people with epilepsy and intellectual disability [29]. However, a Dutch retrospective cohort study by Leunissen et al. (2011) of 246 people with intellectual disability and epilepsy in a long stay department of an epilepsy centre report much greater variance, with 7.3% of people taking AED monotherapy and 91.1% taking AED polytherapy [40]. The authors of this study attribute this outcome to patients living in an institutional setting with epilepsy that is difficult to treat [40]. Mood stabilising AEDs were the most frequently prescribed AEDs to participants with epilepsy in our study. O'Dwyer et al. (2018) also found mood stabilising AEDs to be the most common in Wave 1 of IDS-TILDA [29].

High levels of psychiatric and behavioural comorbidity in people with intellectual disability [143] has resulted in psychotropic medication being widely prescribed in this population group [176]. Reports of some psychotropic medications having a negative influence on the seizure threshold and instigating seizures has generated caution among prescribers, particularly for people with epilepsy [338]. Indeed, the highest prevalence of antipsychotics were found in participants not reporting epilepsy in this study, although the atypical antipsychotic associated with the greatest risk, clozapine, was not prescribed [427]. In this study, SSRI antidepressants were commonly prescribed to participants reporting an epilepsy diagnosis and are reported to be safe [337], while few participants

reported prescription of tricyclic antidepressants (TCAs) which are believed to have a negative impact on seizure control [33, 337].

For people with epilepsy, comorbidity can have a greater impact on quality of life than the seizures themselves [428]. In this study, a high prevalence of psychiatric/emotional disorders were found in participants reporting a diagnosis of epilepsy (57.7%), corresponding to findings in other studies of people with epilepsy and intellectual disability [87, 88]. A Scottish cross-sectional study by Espie et al. (2003) of a random sample of 186 people (from a database of 685 people) with epilepsy and intellectual disability found that one third of participants with epilepsy met criteria for possible psychiatric disorder [88]. In addition, a systematic review of neuropsychiatric comorbidities in people with epilepsy and intellectual disability by van Ool et al. (2016) found that having epilepsy was associated with higher rates of negative mood symptoms in adults and the elderly with intellectual disability, particularly depressive symptoms, negative mood, and mood swings [87].

We also found a greater prevalence of Alzheimer's disease and/or dementia (15.3%) in participants reporting epilepsy in this study compared to participants not reporting epilepsy (5.7%). An Irish cross-sectional study by McCarron et al. (2014) from Wave 1 of IDS-TILDA of 753 people with intellectual disability, found that epilepsy was significantly associated with dementia in those with Down Syndrome [28]. They also found that participants diagnosed with dementia were 12.98 times more likely to have a diagnosis of epilepsy [28]. Osteoporosis is also a common comorbidity in people with epilepsy and often linked to use of AEDs [152]. In this study, we found a higher prevalence of osteoporosis in participants reporting an epilepsy diagnosis (27.6%) compared to those not reporting an epilepsy diagnosis (18.8%). An Irish cross-sectional study examining bone

health in the first wave of IDS-TILDA by Burke et al. (2017) found strong statistical associations between a doctor's diagnosis of osteoporosis and a diagnosis of epilepsy and use of AEDs ($p<0.0001$) [153].

Constipation is another common comorbidity in people with intellectual disability [429]. Anti-cholinergic side effects, including constipation, associated with antiepileptics and antipsychotics make people with epilepsy particularly vulnerable [430]. A Dutch cross-sectional study of 215 randomly selected people (including 48 children <20 years), living in four institutionalised settings found a significant relationship between constipation and use of anticonvulsants [429]. In addition, an Irish cross-sectional study examining laxative use in 677 people with intellectual disability aged 44+ years using IDS-TILDA Wave 2 data by AlMutairi et al. (2020) found that 53.8% of participants taking antiepileptic medication reported laxative use [430]. Our study using IDS-TILDA Wave 3 data found a significantly higher prevalence of constipation in people with epilepsy, with over half of people with epilepsy reporting constipation. In contrast, an Israeli cross-sectional study of 2400 people with intellectual disability, aged 40 years and older, and living in 60 residential centres did not find a higher prevalence of constipation in people with epilepsy [431].

3.4.3 Implications for practice

Epilepsy has been found to be more common in institutional settings compared to community based settings [432]. The advent of de-institutionalisation policies in Ireland has seen greater numbers of people with epilepsy and intellectual disability living in community based settings. This has created its own challenges as clinicians in primary care may not have the specialist knowledge and expertise in dealing with these complex cases, cases previously managed by specialists in intellectual disability [147]. Additional training

and learning opportunities will be required to enable a smooth transition of care from residential to community based settings. Multidisciplinary medication reviews and collaboration between specialities will be necessary to manage the significant physical and psychiatric comorbidity, and polypharmacy in people with a dual diagnosis of epilepsy and intellectual disability.

3.4.4 Strengths

Our study used a large, nationally representative sample of older adults with intellectual disability, representative of the older population of people with intellectual disability in Ireland. We obtained thorough medication data for 90.1% of Wave 3 participants which was confirmed by interviewers at the time of interview. The design of the medication record allowed for high quality acquisition of medication data. All participants and/or their proxies received the PIQ which contained the medication record one week prior to the face-to-face interview giving them an opportunity to consult the participants' medication/health records.

3.4.5 Limitations

Due to missing medication data, 19 participants with epilepsy were excluded from this study. Data collected regarding medication use, diagnosis of epilepsy, and concomitant mental health conditions were based on participants' self-report or proxy report which may result in bias. Due to the observational cross-sectional study design, we can only describe associations between epilepsy prevalence and demographic and clinical factors.

3.5 Conclusion

This Chapter highlights the high prevalence of epilepsy in older adults with intellectual disability, particularly in those living in residential/campus settings. A high medication burden of both antiepileptic and other co-prescribed psychotropic medications was found, underscoring the significant psychiatric comorbidity associated with a dual diagnosis of epilepsy and intellectual disability. In participants reporting an epilepsy diagnosis, dementia and constipation were also found to be significantly more prevalent. Thus, it is necessary for the health service to ensure that adequate monitoring and regular health and medication reviews of older people with intellectual disability and epilepsy are provided in all settings, especially residential settings.

Chapter 4

Evaluation of antiepileptic drug utilisation methods

4.1 Introduction

The disability-adjusted life year measure of the global burden of epilepsy increased by 30% in the 20 years between 1990 and 2010 [419, 433]. Convulsions are the main reason for avoidable hospitalisation in people with intellectual disability and are said to account for 40% of all emergency hospital admissions [143]. Antiepileptic drugs (AEDs) are the mainstay of epilepsy treatment [45, 434]. The age old question of whether monotherapy or polytherapy is of greatest benefit in the treatment of epilepsy is increasingly relevant with the ever greater availability of new AEDs [435].

Epilepsy incidence increases exponentially in old age with older people more susceptible to adverse effects of AEDs [45, 436]. Monotherapy is often heralded as the ideal treatment due to decreased side effects, lack of drug-drug interactions, reduced expenditure, improved patient compliance, and importantly in many cases, greater seizure control [437]. Nevertheless, many people with intellectual disability have difficult to treat epilepsy [432], which may require polytherapy treatment. However, overtreatment of drug resistant epilepsy has been identified as a problem in people with intellectual disability [438]. Overtreatment has been defined as *"an excessive drug load (that is, excessive drug dosages or unnecessary polypharmacy) leading to a suboptimal risk to benefit ratio"* [439].

Early studies showed a simplification of AED treatment could result in improvement in seizure control [437]. Schmidt (1983) examined prospectively the effects of reducing AED polytherapy treatment to AED monotherapy in 36 patients with intractable complex partial seizures [440]. The study found that 83% of patients were successfully changed without a corresponding increase in seizure frequency [440]. An improvement in seizure control in 13 patients (36%) was also found, with the number of side effects lower for

monotherapy regimens [440]. Additionally, a retrospective study by Shorvon & Reynolds (1977) examined 50 adult outpatients with epilepsy who were taking two AEDs and found seizure frequency improved in only 36% in the six months after the introduction of the second drug [437, 441].

Modern AEDs have not been the panacea for people with drug resistant epilepsy, with new add-on treatments reported to be only moderately more successful than placebo [419]. The aetiology of drug resistant epilepsy is poorly understood. The ILAE classify drug resistant epilepsy as *"failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve seizure freedom"* [442]. Various theories have been put forward including the transporter hypothesis, the target hypothesis, the network hypothesis, the gene variant hypothesis and the intrinsic severity hypothesis but little scientific progress has been made [419]. Antiepileptic drugs while treating the seizure, typically have little effect on epileptogenesis and do not reverse underlying pathology or comorbidities associated with epilepsy [419, 438]. High seizure frequency and history of depression have also been associated with drug resistant epilepsy, indicating the presence of neurobiological factors common to drug resistant epilepsy, disease severity and psychiatric comorbidity [419].

A number of methods can be found in the literature to evaluate the use of AEDs. A cross-sectional study by O'Dwyer et al. (2018) in Wave 1 of IDS-TILDA examined AED monotherapy and AED polytherapy classification in a population of 205 older adults with intellectual disability and epilepsy [29]. Various studies have also measured AED load using the PDD/DDD ratio in both the general and intellectual disability populations [89, 267, 270-272]. Total AED load can be quantified as the sum of the prescribed daily dose (PDD) divided by the defined daily dose (DDD) (average maintenance dose) ratios (PDD/DDD) for

each AED prescribed [443]. Lammers et al. (1995) in a Dutch cohort study of 289 outpatients of tertiary epilepsy centres calculated the total AED load using the PDD/DDD ratio and categorised it into ≤ 2 and >2. A higher prevalence (71-100%) of neurological adverse effects in participants with an AED load >2 was found, and all (100%) participants with a PDD/DDD ratio >4 had neurological adverse effects [409].

The aim of this Chapter is to examine antiepileptic drug therapy in people with epilepsy and intellectual disability in Wave 3 of IDS-TILDA using drug utilisation research methods.

4.1.1 Objectives of Chapter:

I. To examine AED monotherapy and AED polytherapy with regards to demographic and clinical characteristics in older adults with epilepsy and intellectual disability.

II. To examine the relationship between categorised AED load using the PDD/DDD ratio (<2 and ≥ 2) and demographic and clinical characteristics in older adults with epilepsy and intellectual disability.

III. To examine the relationship between numerical AED load (PDD/DDD) and demographic and clinical characteristics in older adults with epilepsy and intellectual disability.

4.2 Methods

4.2.1 Study design and participants

The data for this study were drawn from the third Wave of data collection, Wave 3 (2016/2017), of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA). For this study, the number of people taking part in Wave 3 was 609 with 44.2% male and 55.8% female. The age range for Wave 3 was 48 to 95 years with a mean of 59.1 years (SD: 8.81) [300]. Overall in Wave 3, 24.8% had a mild intellectual disability, 46.2% a moderate intellectual disability and 29.1% a severe/profound intellectual disability [300]. Further details of this study design can be found in *Chapter 2, sections 2 and 3*.

4.2.2 Measures

A PIQ was sent to each participant one week prior to the interview taking place. This gave participants time to prepare and locate any information that may be needed (e.g. medication data) enhancing the reliability of the data. CAPI interviews were completed by trained field workers, experienced in working with people with intellectual disability. Different interviewing styles were undertaken by participants depending on their level of intellectual disability and capacity to communicate. Further information on measures used can be found in *Chapter 2, section 5*.

4.2.3 Reported diagnosis of epilepsy

In Wave 1**,** each participant/proxy was asked in the PIQ if the individual with intellectual disability was ever diagnosed by a doctor/relevant health professional with epilepsy [29]. In subsequent Waves (2 and 3) of the study, each participant/proxy was asked *"since your*

last interview, has a doctor ever told you that you have epilepsy?". This allowed for the creation of a variable for prevalence. Further information on obtaining this data can be found in *Chapter 2, section 8*.

4.2.4 Drug class categorisation

Antiepileptic drugs were defined as those with the ATC code N03A. Clobazam was included in the AED category as it is primarily used for epilepsy. Psychotropic co-medication were assessed: these were defined as antipsychotics (N05A), antidepressants (N06A), anxiolytics (N05B), hypnotics and sedatives (N05C), drugs for dementia (N06D), and anti-cholinergic drugs (N04A). Lithium was classified as a mood stabiliser and prochlorperazine was not included in the antipsychotic category as all the doses reported in this study fell within the recommended range used for the treatment of Meniere's syndrome, labyrinthitis and nausea and vomiting (10mg-40mg daily). Further information on the medication prescribed in this study can be found in *Chapter 3.*

4.2.5 Antiepileptic drugs used in participants with epilepsy

All reported prescription of regular AEDs used to treat epilepsy were examined. Participant exposure to these AEDs was then categorised into number of AED's prescribed and subsequently into 'monotherapy' and 'polytherapy'. Antiepileptic monotherapy was defined as treatment with one regular AED. Antiepileptic polytherapy was defined as concurrent treatment with two or more regular AEDs. Regular in this instance refers to an AED medicine taken on a regular basis and not for the treatment of acute seizures, where emergency rescue medications are used. Further information on AEDs prescribed in this study can be found in *Chapter 3.*

4.2.6 Fast-acting agents for the control of prolonged, acute, convulsive seizures

All fast-acting agents prescribed for prolonged, acute, convulsive seizures and not used on a regular basis were recorded separately from the other AEDs. Participants were asked in the CAPI *"Are any of the following medications prescribed for [you/him/her] to use in an emergency (rescue medication)?"* Options given included Epistatus (buccal midazolam), Frisium (clobazam), Stesolid (rectal diazepam), Rivotril (clonazepam), Ativan (lorazepam), other, none of the above, unclear response, don't know, refused to answer.

4.2.7 Antiepileptic drug load

The PDD/DDD ratio [266, 267] for AEDs was calculated for all participants with medication data reporting prescription of a regular AED. Due to incomplete dosage data for six participants (excluded from this analysis), we were able to calculate this ratio for 96.9% (n=190) of those with a reported diagnosis of epilepsy. The PDD/DDD ratio is the ratio of prescribed daily dose (PDD) to defined daily dose (DDD) [40]. The DDD is the assumed average maintenance daily dose, for a drug taken for its main indication in adults (*Appendix 26*) [40]. The PDD is the actual prescribed daily dose. A PDD/DDD ratio can be used as a measure of drug load [40]. This analysis was completed using Excel and a cumulative ratio of all AEDs being taken, calculated.

$$total\ drug\ load = \sum_i \frac{PDD_i}{DDD_i}$$

Numerical descriptive measures, namely median and interquartile range (IQR), of the total AED load variable were obtained and analysed. The total AED load variable was also categorised into a <2 and ≥2 variable (adapted from Lammers et al. (1995)). If a participant

was not taking any AED, they were assigned a value of 0. More detail on AED load can be found in *Chapter 1, section 9*.

4.2.8 Epilepsy limiting activities

Participants and/or their proxies were asked whether they believe epilepsy limits their ability to undertake certain activities. Specifically, participants and/or their proxies were asked *"Does epilepsy limit [you/name] doing the following?"* Options given were household chores; work; social activities; sports activities; driving; going out alone; other; none of the above; unclear response; don't know; refused to answer.

4.2.9 Reported diagnosis of comorbid mental health disorder

Participants were asked in the CAPI, *"has a doctor ever diagnosed you with an emotional/psychiatric disorder?".* If yes, participants were then asked *"what type of emotional, nervous or psychiatric problems do/does you/he/she have?"* The following options were given: hallucinations, anxiety, depression, emotional problems, schizophrenia, psychosis, mood swings, manic depression, post-traumatic stress disorder (PTSD), something else, unclear response, don't know, refused to answer. For the purposes of analysis, three categories of mental health disorder (psychotic/mood/anxiety) were created by grouping the above mental health conditions. Further information on mental health disorder variables can be found in *Chapter 2, section 10*.

4.2.10 Challenging behaviours

The Behaviour Problems Inventory-Short Form (BPI-S), an informant based questionnaire, was used to assess challenging behaviours [95]. The instrument examines three subtypes

of challenging behaviours; self-injurious behaviour (SIB) (8 items), aggressive/destructive behaviour (10 items), and stereotyped behaviour (12 items) [405]. This section was completed by the carer/key worker/support person who knew the person with intellectual disability very well (minimum of 6 months). A variable (YES/NO) was created for individual types of behaviours which were grouped into SIB, aggressive/destructive, and stereotyped behaviour per the BPI-S scale [95], and then grouped into overall presence of challenging behaviours. Further information on the creation of variables relating to challenging behaviour can be found in *Chapter 2, section 11.*

4.2.11 Concurrent medications that may decrease the seizure threshold

The prescribing of co-medications that are listed as having the potential to lower the seizure threshold or contraindicated for use in people with epilepsy were examined using the Maudsley Prescribing Guidelines in Psychiatry (2018) [330], and categorised as low, probably low, moderate, and high risk. For the purposes of analysis, medications classified as low and probably low risk are combined as low risk. Further information can be found in *Chapter 2, section 9*.

4.2.12 Covariates

Covariates investigated were gender (male/female), age (<50/50-64/65+ years), level of intellectual disability (mild/moderate/severe/profound/unverified), place of residence (independent/family/community group home/residential/campus setting), psychotropic medication classes, comorbid mental health conditions, any challenging behaviours, categorised challenging behaviours (SIB/aggressive/destructive/stereotyped behaviour),

and concurrent psychotropic medications that could potentially lower the seizure threshold.

The mental health questions asked in this study can be found in *Chapter 2, section 10*. Psychotic disorder includes hallucinations, schizophrenia, and psychosis. Mood disorder includes depression, manic depression, mood swings, and emotional problems, and anxiety disorder includes anxiety and PTSD. However, there were no reports of PTSD in this study. Seizure frequency was categorised as none in the last year and at least one in the last year. The latter category includes daily, weekly (not daily), more than once/month (not weekly), and less than once/month.

The categorised seizure type is based on the 2017 ILAE classification of seizures [56]. Generalised seizures include tonic-clonic, tonic, clonic, atonic, myoclonic, and absence. Focal seizures include simple partial seizures and complex partial seizures. Residential/campus settings were defined as living arrangements where 10 or more people share a single living unit or where the living arrangements are campus based. Community group homes are in a community setting with staff support for small groups of people with intellectual disabilities. Living independently/with family means living independently or with family in the community.

4.2.13 Statistical analyses

Statistical significance was set at <0.05. Descriptive statistics were used to describe the characteristics of the sample being studied. The Chi-Square (χ^2) test for independence was utilised to test for a significant association between categorical variables. Fisher's Exact test was used to test for a significant association between variables where the sample size in subgroups was small (n<5). To control for problems associated with multiple

comparisons, thereby increasing the likelihood of Type 1 error (rejecting the null hypothesis when it is true and the false discovery rate), a Bonferroni correction was applied to bivariate Chi Square/Fisher's Exact tests where necessary [406].

The Kolmogorov-Smirnov test and Shapiro-Wilk test were used to assess if the numerical variable for AED load (PDD/DDD) was normally distributed. As the AED load data significantly deviated from a normal distribution, the non-parametric tests, Mann Whitney U and Kruskal Wallis H were used to analyse the numerical data for AED load. Descriptive statistics, including medians (with 95% CI) and interquartile range (IQR) were used to describe the groups. Levene's test for homogeneity of variance was used to assess this assumption for non-parametric tests. Boxplots were used to visualise AED load with regards to demographic characteristics (gender, age, type of residence, level of intellectual disability, and cause of intellectual disability) and were completed using data visualisation software *Tableau*. All statistical analyses were carried out using the Statistical Package for Social Sciences, version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

4.3 Antiepileptic drug monotherapy and polytherapy classification

4.3.1 Demographic and clinical characteristics of participants reporting no antiepileptic drug therapy

An equal number of males (n=11) and females (n=11) reporting an epilepsy diagnosis reported no AED therapy *(Table 4.3-1).* Of these, 54.5% (n=12) were found to be in the 50-64 year age group with the lowest prevalence in those aged <50 years (13.6%, n=3). In addition, 59.1% (n=13) of those reporting no AED therapy had a moderate intellectual

disability, and 60.0% (n=12) had an unknown cause of intellectual disability. Over half (54.5%, n=12) of participants reporting no AED therapy lived in residential/campus settings, with an equal number living in family/independent (22.7%, n=5) and community group home settings (22.7%, n=5).

Table 4.3-1 Demographic characteristics of participants reporting no AED therapy (n=22)

Characteristic	Total n=196 n (%)	No AED therapy n=22 n (%)
Gender		
Male	82 (41.8)	11 (50.0)
Female	114 (58.2)	11 (50.0)
Age		
<50 years	21 (10.7)	3 (13.6)
50-64 years	130 (66.3)	12 (54.5)
65+ years	45 (23.0)	7 (31.8)
Level of intellectual disability	n=187	n=22
Mild	31 (16.6)	4 (18.2)
Moderate	77 (41.2)	13 (59.1)
Severe/Profound	79 (42.2)	5 (22.7)
Cause of intellectual disability	n=192	n=20
Down Syndrome	29 (15.1)	3 (15.0)
Other aetiology	49 (25.5)	5 (25.0)
Unknown cause	114 (59.4)	12 (60.0)
Type of residence		
Family/independent	20 (10.2)	5 (22.7)
Community group home	60 (30.6)	5 (22.7)
Residential/campus setting	116 (59.2)	12 (54.5)

n=196 participants with reported epilepsy diagnosis. n=22 participants taking no regular AED.

With regards to seizure frequency (n=190) *(Table 4.3-2)*, 81.0% (n=17) of participants reporting no AED therapy and who had available seizure data (n=21) reported no seizures in the last year. However, 19.0% (n=4) of participants still reported at least one seizure in the last year despite no regular AED therapy being prescribed. Buccal midazolam was prescribed to 13.6% (n=3) of participants reporting no AED therapy. No prescription

for emergency clobazam or lorazepam was reported by people reporting no AED therapy. Interestingly, 9.5% (n=2) of participants reporting no AED therapy reported that their epilepsy was reviewed by a neurologist, with 33.3% (n=7) reporting a review by a psychiatrist.

None of the participants reporting no AED therapy reported visiting A&E in the last year with epilepsy, and 80.0% (n=16) reported receiving no education on how to manage their epilepsy. Almost a third (31.8%, n=7) of participants reporting no AED therapy reported experiencing generalised seizures and 68.2% (n=15) reported experiencing 'other' seizures which encompasses focal and unknown seizures.

Antipsychotics were taken by 31.8% (n=7) of participants reporting no AED therapy, while 27.3% (n=6) reported prescription of antidepressants. Of participants reporting no AED therapy, 45.5% (n=10) reported suffering from an anxiety disorder and 36.4% (n=8) from a mood disorder. Nearly three-quarters (73.7%, n=14) of participants reporting no AED therapy were found to exhibit challenging behaviours with 36.8% (n=7) exhibiting SIB, 52.6% (n=10) exhibiting aggressive/destructive behaviour, and 57.9% (n=11) exhibiting stereotyped behaviour.

Table 4.3-2 Clinical characteristics of participants reporting no AED therapy (n=22)

Characteristic	Total n=196 n (%)	No AED therapy n=22 n (%)
Seizure frequency	n=190	n=21
None in the last year	113 (59.5)	17 (81.0)
At least one in the last year	77 (40.5)	4 (19.0)
Keep seizure record	n=193	n=20
Yes	163 (84.5)	9 (45.0)
No	30 (15.5)	11 (55.0)
Type of seizures		
Generalised seizures	107 (54.6)	7 (31.8)
Other seizures	89 (45.4)	15 (68.2)
Categorised number of seizure types		
1	77 (39.3)	7 (31.8)
2+	33 (16.8)	0 (0)
Unknown number of seizure types	86 (43.9)	15 (68.2)
Attend epilepsy clinic or specialist	n=192	n=20
Yes	104 (54.2)	4 (20.0)
No	88 (45.8)	16 (80.0)
Who reviewed epilepsy	n=192	n=21
GP	70 (36.5)	5 (23.8)
Neurologist	65 (33.9)	2 (9.5)
Psychiatrist	55 (28.6)	7 (33.3)
Other	5 (2.6)	<5
Don't know	16 (8.3)	6 (28.6)
Visited A&E in the last year with epilepsy	n=176	n=20
Yes	17 (9.7)	0 (0)
No	159 (90.3)	20 (100.0)
Education to manage epilepsy	n=179	n=20
Yes	44 (24.6)	4 (20.0)
No	135 (75.4)	16 (80.0)
Medication for acute seizures		
Buccal midazolam	103 (52.6)	3 (13.6)
Comorbid mental health disorder		
Psychotic disorder	13 (6.6)	<5
Mood disorder	74 (37.8)	8 (36.4)
Anxiety disorder	67 (34.2)	10 (45.5)
Challenging behaviour	n=161	n=19
Yes	103 (64.0)	14 (73.7)
No	58 (36.0)	5 (26.3)

Table 4.3-2 Clinical characteristics of participants reporting no AED therapy (n=22) (*Continued*)

Characteristic	Total n=196 n (%)	No AED therapy n=22 n (%)
Type of challenging behaviour	n=161	n=19
SIB	59 (36.6)	7 (36.8)
Aggressive/destructive behaviour	64 (39.8)	10 (52.6)
Stereotyped behaviour	82 (50.9)	11 (57.9)
Other psychotropic medication		
Antipsychotics	77 (39.3)	7 (31.8)
Antidepressants	60 (30.6)	6 (27.3)
Anxiolytics	34 (17.3)	3 (13.6)
Hypnotics & sedatives	22 (11.2)	<5
Anti-cholinergic	20 (10.2)	<5
Drugs for dementia	6 (3.1)	<5
Lithium	5 (2.6)	0 (0)

n=196 participants with reported epilepsy diagnosis. n=22 participants taking no regular AED. <5 denotes fewer than 5 participants. Due to low numbers of participants (<5), review by clinical nurse specialist was removed from table. Medications for acute seizures - clobazam and lorazepam (<5) were also removed. No participant who reported taking no AED therapy was reviewed by a clinical nurse specialist or was taking clobazam or lorazepam.

Due to low numbers in subgroups in the 'No AED therapy' category causing lack of power in Chi Square tests, this group was excluded from analysis with the AED monotherapy and AED polytherapy groups and a bivariate analysis of demographic *(Table 4.3-3)* and clinical characteristics *(Table 4.3-4)* of those reporting AED monotherapy and AED polytherapy was undertaken. Suitable statistical conditions were not present to undertake a Fisher Exact Test, as not of the required 2x2 matrix structure.

4.3.2 Demographic and clinical characteristics of participants reporting antiepileptic drug monotherapy and polytherapy

Of participants reporting a diagnosis of epilepsy, 40.8% (n=80) were exposed to AED monotherapy and 48.0% (n=94) exposed to AED polytherapy (*Table 4.3-3*). In total, 63.8% (n=51) of participants reporting AED monotherapy and 55.3% (n=52) of participants reporting AED polytherapy were female. Regarding age, 66.2% (n=53) of those reporting

AED monotherapy and 69.1% (n=65) of those reporting AED polytherapy were aged 50-64 years. No significant difference between AED monotherapy and AED polytherapy was found for level of intellectual disability (p=0.729), with 47.4% (n=36) of participants reporting AED monotherapy and 42.7% (n=38) of participants reporting AED polytherapy having a severe/profound intellectual disability. Regarding type of residence, 11.3% (n=9) of participants reporting AED monotherapy and 6.4% (n=6) of participants reporting AED polytherapy lived in family/independent settings with the majority of participants reporting both therapy types living in residential/campus settings (62.5%, n=50 and 57.4%, n=54, respectively).

Table 4.3-3 Bivariate analysis of demographic characteristics (n=174) of those reporting AED monotherapy (n=80) and AED polytherapy (n=94)

Characteristic	Total n=174 n (%)	AED monotherapy n=80 n (%)	AED polytherapy n=94 n (%)	P value
Gender				0.259
Male	71 (40.8)	29 (36.2)	42 (44.7)	
Female	103 (59.2)	51 (63.8)	52 (55.3)	
Age				0.578
<50 years	18 (10.3)	7 (8.8)	11 (11.7)	
50-64 years	118 (67.8)	53 (66.2)	65 (69.1)	
65+ years	38 (21.8)	20 (25.0)	18 (19.2)	
Level of intellectual disability	n=165	n=76	n=89	0.729
Mild	27 (16.4)	13 (17.1)	14 (15.7)	
Moderate	64 (38.8)	27 (35.5)	37 (41.6)	
Severe/Profound	74 (44.8)	36 (47.4)	38 (42.7)	
Cause of intellectual disability	n=172	n=80	n=92	0.075
Down Syndrome	26 (15.1)	16 (20.0)	10 (10.9)	
Other aetiology	44 (25.6)	15 (18.8)	29 (31.5)	
Unknown cause	102 (59.3)	49 (61.2)	53 (57.6)	
Type of residence				0.257
Family/independent	15 (8.6)	9 (11.3)	6 (6.4)	
Community group home	55 (31.6)	21 (26.3)	34 (36.2)	
Residential/campus	104 (59.8)	50 (62.5)	54 (57.4)	

P value: Chi Square. **Statistically significant results marked in bold and with an asterisk***

A statistically significant difference was found for seizure frequency with regards to reporting AED monotherapy and AED polytherapy (p<0.001). Of those with available data, 74.0% (n=57) of participants exposed to AED monotherapy reported no seizure in the last year, while only 42.4% (n=39) of participants exposed to AED polytherapy reported same *(Table 4.3-4)*. The majority of participants reporting both AED monotherapy (83.8%, n=67) and AED polytherapy (93.5%, n=87) reported keeping a seizure record. Regarding medication for acute seizures, 64.9% (n=61) of participants exposed to AED polytherapy reported prescription of buccal midazolam compared to 48.8% (n=39) of participants exposed to AED monotherapy (p=0.032). A greater number of participants reporting AED polytherapy (45.2%, n=42) reported getting their epilepsy reviewed by a neurologist compared to 26.9% (n=21) of participants reporting AED monotherapy (p=0.014). Regarding education to manage epilepsy, 82.6% (n=62) of participants reporting AED monotherapy reported not receiving education to manage their epilepsy compared with 67.9% (n=57) of participants reporting AED polytherapy. With regards to type of seizure, 70.2% (n=66) of participants exposed to AED polytherapy reported experiencing generalised seizures with 42.5% (n=34) of participants exposed to AED monotherapy reporting same (p<0.001).

Reporting a mood disorder was found to be significantly (p=0.001) more common in participants exposed to AED monotherapy (42.5%, n=34) compared to participants exposed to AED polytherapy (34.0%, n=32), while reporting an anxiety disorder was found to be more common (p=0.400) in participants exposed to AED polytherapy (38.3%, n=36) compared to participants exposed to AED monotherapy (26.3%, n=21). A greater proportion of participants exposed to AED polytherapy reported a psychotic disorder (8.5%, n=8) compared to participants exposed to AED monotherapy (5.0%, n=4) (p=0.757).

Two thirds (66.7%, n=42) of participants reporting AED monotherapy and 59.5% (n=47) of participants reporting AED polytherapy were found to exhibit challenging behaviours. A greater proportion of participants reporting AED monotherapy were found to exhibit SIB (41.3%, n=26, p=0.217) and stereotyped behaviour (55.6%, n=35, p=0.267), compared to participants reporting AED polytherapy (32.9%, n=26 and 45.6%, n=36, respectively). A greater proportion of participants reporting AED polytherapy were found to exhibit aggressive/destructive behaviour (39.2%, n=31, p=0.819) compared to participants reporting AED monotherapy (36.5%, n=23).

Over half (51.9%, n=40) of participants exposed to AED polytherapy reported a prescription for antipsychotics compared to 39.0% (n=30) of participants exposed to AED monotherapy. Similarly, a higher proportion of participants exposed to AED polytherapy reported prescription of anxiolytics (55.9%, n=19) and hypnotics and sedatives (72.7%, n=16) compared to those exposed to AED monotherapy (35.3%, n=12 and 22.7%, n=5).

Table 4.3-4 Bivariate analysis of clinical characteristics (n=174) of those reporting AED monotherapy (n=80) and AED polytherapy (n=94)

Characteristic	Total n=174 n (%)	AED monotherapy n=80 n (%)	AED polytherapy n=94 n (%)	P value
Seizure frequency	n=169	n=77	n=92	**<0.001***
None in the last year	96	57 (74.0)	39 (42.4)	
At least one in the last year	73	20 (26.0)	53 (57.6)	
Keep seizure record	n=173	n=80	n=93	0.040
Yes	154 (89.0)	67 (83.8)	87 (93.5)	
No	19 (11.0)	13 (16.3)	6 (6.5)	
Type of seizures				**<0.001***
Generalised seizures	100 (57.5)	34 (42.5)	66 (70.2)	
Other seizures	74 (42.5)	46 (57.5)	28 (29.8)	
Categorised number of seizure types				**<0.001***
1	70 (40.2)	30 (37.5)	40 (42.6)	
2+	33 (19.0)	6 (7.5)	27 (28.7)	
Unknown	71 (40.8)	44 (55.0)	27 (28.7)	

Table 4.3-4 Bivariate analysis of clinical characteristics (n=174) of those reporting AED monotherapy (n=80) and AED polytherapy (n=94) (*Continued*)

Characteristic	Total n=174 n (%)	AED monotherapy n=80 n (%)	AED polytherapy n=94 n (%)	P value
Attend epilepsy clinic or specialist	n=172	n=79	n=93	0.126
Yes	100 (58.1)	41 (51.9)	59 (63.4)	
No	72 (41.9)	38 (48.1)	34 (36.6)	
Who reviewed epilepsy	n=171	n=78	n=93	
GP	65 (38.0)	35 (44.9)	30 (32.3)	0.091
Neurologist	63 (36.8)	21 (26.9)	42 (45.2)	0.014
Psychiatrist	48 (28.1)	22 (28.2)	26 (28.0)	0.971
Don't know	10 (5.8)	6 (7.7)	4 (4.3)	0.515 [a]
Visited A&E with epilepsy last year	n=156	n=70	n=86	0.746
Yes	17 (10.9)	7 (10.0)	10 (11.6)	
No	139 (89.1)	63 (90.0)	76 (88.4)	
Education to manage epilepsy	n=159	n=75	n=84	0.032
Yes	40 (25.2)	13 (17.3)	27 (32.1)	
No	119 (74.8)	62 (82.6)	57 (67.9)	
Medication for acute seizures				
Buccal midazolam	100 (57.5)	39 (48.8)	61 (64.9)	0.032
Comorbid mental health disorder				
Psychotic disorder	12 (6.9)	4 (5.0)	8 (8.5)	0.757 [a]
Mood disorder	66 (37.9)	34 (42.5)	32 (34.0)	**0.001***
Anxiety disorder	57 (32.8)	21 (26.3)	36 (38.3)	0.400
Challenging behaviour	n=142	n=63	n=79	0.380
Yes	89 (62.7)	42 (66.7)	47 (59.5)	
No	53 (37.3)	21 (33.3)	32 (40.5)	
Type of challenging behaviour	n=142	n=63	n=79	
SIB	52 (36.6)	26 (41.3)	26 (32.9)	0.217
Aggressive/destructive behaviour	54 (38.0)	23 (36.5)	31 (39.2)	0.819
Stereotyped behaviour	71 (50.0)	35 (55.6)	36 (45.6)	0.267
Other psychotropic medicines				
Antipsychotics	70 (40.2)	30 (39.0)	40 (51.9)	0.498
Antidepressants	54 (31.0)	21 (35.0)	33 (35.1)	0.208
Anxiolytics	31 (17.8)	12 (35.3)	19 (55.9)	0.370
Hypnotics & sedatives	21 (12.1)	5 (22.7)	16 (72.7)	0.030 [a]
Anti-cholinergic	19 (10.9)	8 (40.0)	11 (55.0)	0.720
Drugs for dementia	5 (2.9)	2 (33.3)	3 (50.0)	1.000
Lithium	5 (2.9)	0 (0)	5 (5.3)	0.063 [a]

P value: Chi Square Test. [a] Fisher's Exact Test. P value: for Chi Square Test after applying Bonferroni correction α=0.05/26= 0.002 thus p<0.002 for significance. Polytherapy: median= 2 AEDs, max= 5 AEDs. <5 denotes fewer than 5 participants**.** Due to low numbers of participants (<5), review by clinical nurse specialist and 'other' category were removed from table. Medications for acute seizures, clobazam and lorazepam (<5) were also removed. **Statistically significant results marked in bold and with an asterisk***

4.3.3 Type of seizures and antiepileptic drug therapy

Of the 196 people who reported a doctor's diagnosis of epilepsy, 42.3% (n=83) reported being diagnosed with tonic-clonic seizures, 14.8% (n=29) absence seizures, 8.7% (n=17) tonic seizures, 7.1% (n=14) myoclonic seizures, 2.6% (n=5) atonic seizures, with fewer than five participants reporting clonic seizures, simple partial, and complex partial seizures. *Table 4.3-5* illustrates the type of seizures experienced by participants reporting no AED therapy. Of participants reporting no AED therapy, 22.7% (n=5) reported experiencing tonic-clonic seizures and fewer than five participants reported experiencing tonic, absence and other seizure types. Bivariate analysis of participants reporting no AED therapy with participants taking AED monotherapy and AED polytherapy was not undertaken due to low numbers in subgroups.

Table 4.3-5 Type of seizures in participants reporting no AED therapy (n=196)

Type of Seizure	Total n=196 n (%)	No AED therapy n=22 n (%)
Tonic-clonic	83 (42.3)	5 (22.7)
Tonic	17 (8.7)	<5
Atonic	5 (2.6)	0 (0)
Myoclonic	14 (7.1)	0 (0)
Absence	29 (14.8)	<5
Other	20 (10.2)	2 (9.1)
Don't know	64 (32.7)	13 (59.1)

n=196: participants with reported epilepsy diagnosis. n=22: participants reporting no regular AED. <5 denotes fewer than 5 participants. Due to low numbers of participants reporting some seizure types (<5), clonic, simple partial, complex partial, and unclear seizure categories were removed from the table.

Regarding type of AED therapy (monotherapy and polytherapy) and those reporting individual seizure types (*Table 4.3-6*), 54.3% (n=51) of participants exposed to AED polytherapy reported experiencing tonic-clonic seizures compared to 33.8% (n=27) of participants exposed to AED monotherapy (p=0.007). Similarly, 14.9% (n=14) of participants exposed to AED polytherapy reported experiencing tonic seizures compared

to 2.5% (n=2) of participants exposed to AED monotherapy (p=0.005). A similar trend was seen for absence seizures, with 22.3% (n=21) of participants exposed to AED polytherapy and 8.8% (n=7) of participants exposed to AED monotherapy reporting this type of seizure (p=0.015). As previously outlined, fewer than five participants reported experiencing clonic, simple partial, and complex partial seizures.

Table 4.3-6 Bivariate analysis of type of seizure and exposure to AED monotherapy and AED polytherapy (n=174)

Type of Seizure	Total n=174 n (%)	AED monotherapy n=80 n (%)	AED polytherapy n=94 n (%)	P value
Tonic-clonic	78 (44.8)	27 (33.8)	51 (54.3)	**0.007***
Tonic	16 (9.2)	2 (2.5)	14 (14.9)	**0.005***
Myoclonic	14 (8.0)	4 (5.0)	10 (10.6)	0.173
Absence	28 (16.1)	7 (8.8)	21 (22.3)	**0.015***
Other	18 (10.3)	11 (13.8)	7 (7.4)	0.174
Don't know	51 (29.3)	32 (40.0)	19 (20.2)	**0.004***

P value: Chi Square. [a]Fisher's Exact Test**.** <5 denotes fewer than 5 participants. Due to low numbers of participants reporting some seizure types (<5), clonic, simple partial, complex partial, and unclear seizure categories were removed from table. Atonic seizure category (n=5) was also removed from the table due to low numbers in the AED monotherapy category. **Statistically significant results marked in bold and with an asterisk***

4.3.4 Limiting activities and type of antiepileptic drug therapy

Participants were asked if epilepsy limits their ability to do some everyday tasks, and thus impact on their quality of life. *Table 4.3-7* shows the response of participants reporting that epilepsy limits their ability to undertake certain activities with regards to those reporting no AED therapy. Of participants reporting no AED therapy, 90.9% (n=20) reported that epilepsy limits none of the listed activities. Bivariate analysis for participants taking no AED therapy was not undertaken due to small numbers in subgroups.

Table 4.3-7 Limiting activities and participants reporting no AED therapy (n=22)

Activity	Total n=196 n (%)	No AED therapy n=22 n (%)
Household chores	14 (7.1)	0 (0)
Work	14 (7.1)	0 (0)
Social activities	20 (10.2)	<5
Sports activities	12 (6.1)	0 (0)
Driving	11 (5.6)	0 (0)
Going out alone	25 (12.8)	0 (0)
Other	5 (2.6)	0 (0)
None of the above	152 (77.6)	20 (90.9)

n=196: participants with a diagnosis of epilepsy. n=22: participants taking no regular AED. <5 denotes fewer than 5 participants. Due to low numbers of participants (<5), participants who responded don't know were removed from table. No participant who reported no AED therapy responded don't know.

Table 4.3-8 presents the response of participants reporting that epilepsy limits their ability to undertake certain activities in terms of AED monotherapy and AED polytherapy. A statistically significant association was found for type of therapy (AED monotherapy and AED polytherapy) and household chores (p=0.022), work (p=0.022), social activities (p=0.027) and going out alone (p=0.001) with a greater proportion of participants exposed to AED polytherapy reporting that epilepsy limits these activities. For participants who reported that epilepsy limits none of the listed activities, a statistically significant association (p=0.001) in relation to AED monotherapy and AED polytherapy was also found with 87.5% (n=70) of participants exposed to AED monotherapy reporting that epilepsy limits none of these activities and 66.0% (n=62) of participants exposed to AED polytherapy reporting same.

Table 4.3-8 Bivariate analysis of limiting activities and type of therapy (AED monotherapy and AED polytherapy) (n=174)

Activity	Total n=174 n (%)	AED monotherapy n= 80 n (%)	AED polytherapy n=94 n (%)	P value
Household chores	14 (8.0)	2 (2.5)	12 (12.8)	**0.022***
Work	14 (8.0)	2 (2.5)	12 (12.8)	**0.022***
Social activities	19 (10.9)	4 (5.0)	15 (16.0)	**0.027***
Driving	11 (6.3)	2 (2.5)	9 (9.6)	0.066
Going out alone	25 (14.4)	4 (5.0)	21 (22.3)	**0.001***
None of the above	132 (75.9)	70 (87.5)	62 (66.0)	**0.001***

P value: Fisher Exact test (two sided). n=174: participants with a diagnosis of epilepsy taking a regular AED. <5 denotes fewer than 5 participants. Sports activities (n=12) and other activities (n=5) were removed from table due to low numbers in the AED monotherapy category. Due to low numbers of participants (<5), participants who responded 'don't know' were removed from the table. **Statistically significant results marked in bold and with an asterisk***

When this question of epilepsy limiting activities was examined in relation to seizure frequency (*Table 4.3-9*) (no seizure in the last year/at least one seizure in the last year), a statistically significant association ($p<0.001$) was found for going out alone following Bonferroni correction. It is worth noting that 78.6% (n=11) of those who reported it limits work, 83.3% (n=10) of those who reported it limits sports activities and 84.0% (n=21) of those who reported it limits their ability to go out alone, all reported experiencing at least one seizure in the last year. Of those who reported that it limits none of the above activities, 68.7% (n=101) reported that they had no seizures in the last year with only 31.3% reporting at least one seizure in the last year.

Table 4.3-9 Bivariate analysis of seizure frequency and type of seizure, type of AED therapy, emergency medicines, and limiting activities (n=190)

	Total n=190 n (%)	No seizure in the last year n=113 n (%)	At least one seizure in the last year n=77 n (%)	P value
Seizure type				
Tonic-clonic	82 (43.2)	36 (43.9)	46 (56.1)	**<0.001*[a]**
Tonic	16 (8.4)	3 (18.8)	13 (81.2)	**0.001*[a]**
Atonic	5 (2.6)	0 (0)	5 (100.0)	0.010
Absence	29 (15.2)	8 (27.6)	21 (72.4)	**<0.001*[a]**
Other	17 (8.9)	15 (88.2)	2 (11.8)	0.017
Don't know	63 (33.2)	52 (82.5)	11 (17.5)	**<0.001*[a]**
Type of therapy				**<0.001*[a]**
No AED	21 (11.1)	17 (81.0)	4 (19.0)	
AED monotherapy	77 (40.5)	57 (74.0)	20 (26.0)	
AED polytherapy	92 (48.4)	39 (42.4)	53 (57.6)	
Emergency medicines prescribed				
Buccal midazolam	103 (54.2)	45 (43.7)	58 (56.3)	**<0.001*[a]**
Does epilepsy limit the following...?				
Work	14 (7.4)	3 (21.4)	11 (78.6)	0.004
Driving	11 (5.8)	3 (27.3)	8 (72.7)	0.053
Sports activities	12 (6.3)	2 (16.7)	10 (83.3)	0.004
Going out alone	25 (13.2)	4 (16.0)	21 (84.0)	**<0.001*[a]**
Other	5 (2.6)	2 (40.0)	3 (60.0)	0.397
None of the above	147 (77.4)	101 (68.7)	46 (31.3)	**<0.001*[a]**

P value: Fisher's Exact test (two-sided). [a]Chi Square test. P value: for Chi-Square/Fisher's Exact test after applying Bonferroni correction α=0.05/14= 0.0035 thus p<0.0035 for significance. Polytherapy: median= 2 AEDs, max= 5 AEDs. <5 denotes fewer than 5 participants. Due to low numbers of participants reporting some seizure types (<5), clonic, simple partial, complex partial, and unclear seizure categories were removed from the table. Medications for acute seizures, clobazam and lorazepam (<5), and participants who responded that they don't know if epilepsy limits activities (<5) were also removed. Myoclonic seizures (n=13), household chores (n=14), and social activities (n=20) were removed from table due to low numbers in the no seizure in the last year category. **Statistically significant results marked in bold and with an asterisk***

4.3.5 Potential seizure threshold-lowering medication and type of therapy

Tables 4.3-10 - 4.3-12 illustrate the type of AED therapy (monotherapy and polytherapy) taken by participants who also report a co-prescribed psychotropic medication (antipsychotics, lithium and antidepressants) with the potential to lower the seizure threshold. No statistical differences were found in the analyses.

Table 4.3-10 Bivariate analysis of type of therapy and potential seizure threshold-lowering medication - antipsychotics (n=174)

Potential seizure threshold-lowering medication	Total n=174 n (%)	AED monotherapy n=80 n (%)	AED polytherapy n=94 n (%)	P value
Antipsychotics				
Chlorpromazine	11 (6.3)	6 (7.5)	5 (5.3)	0.556
Olanzapine	27 (15.5)	12 (15.0)	15 (16.0)	0.862
Quetiapine	9 (5.2)	3 (3.8)	6 (6.4)	0.510 [a]
Risperidone	22 (12.6)	10 (12.5)	12 (12.8)	0.958

P value: Chi Square test, [a] Fisher's Exact Test. Due to low numbers of participants being prescribed some antipsychotics (<5), promazine, trifluoperazine, haloperidol, zuclopenthixol, aripiprazole, and flupenthixol were removed from the table. **Statistically significant results marked in bold and with an asterisk***

Table 4.3-11 Bivariate analysis of type of therapy and potential seizure threshold-lowering medication - mood stabiliser lithium (n=174)

Potential seizure threshold-lowering medication	Total n=174 n (%)	AED monotherapy n=80 n (%)	AED polytherapy n=94 n (%)	P value
Mood Stabilisers				
Lithium	5 (2.9)	0 (0)	5 (5.3)	0.063 [a]

Fisher Exact Test (two sided). **Statistically significant results marked in bold and with an asterisk***

Table 4.3-12 Bivariate analysis of type of therapy and potential seizure threshold-lowering medication - antidepressants (n=174)

Potential seizure threshold-lowering medication	Total n=174 n (%)	AED monotherapy n=80 n (%)	AED polytherapy n=94 n (%)	P value
Antidepressants				
Escitalopram	17 (9.8)	8 (10.0)	9 (9.6)	0.925
Sertraline	5 (2.9)	3 (3.8)	2 (2.1)	0.662 [a]
Mirtazapine	10 (5.7)	4 (5.0)	6 (6.4)	0.755 [a]
Venlafaxine	7 (4.0)	2 (2.5)	5 (5.3)	0.454 [a]

P value: Chi Square test, [a] Fisher's Exact Test. Due to low numbers of participants being prescribed some antidepressants (<5), citalopram, paroxetine, duloxetine and trimipramine were removed from the table. Fluoxetine (n=5) and trazodone (n=6) were also removed from the table due to low numbers in the AED monotherapy category. **Statistically significant results marked in bold and with an asterisk***

4.4 Categorised antiepileptic drug load (<2, ≥2)

4.4.1 Relationship between antiepileptic drug load and number of antiepileptic drugs

The AED load ratio (PDD/DDD) for all participants with complete medication data was calculated (n=190). A strong relationship was found between number of AEDs reported by each participant and total AED load (R^2=0.797) *(Figure 4.4-1).* Statistical parameters calculated for the total AED load variable gave a median of 1.0 and IQR of 1.79. Spearman's Correlation showed a statistically significant association between total AED load and number of AED's, indicating a correlation as expected.

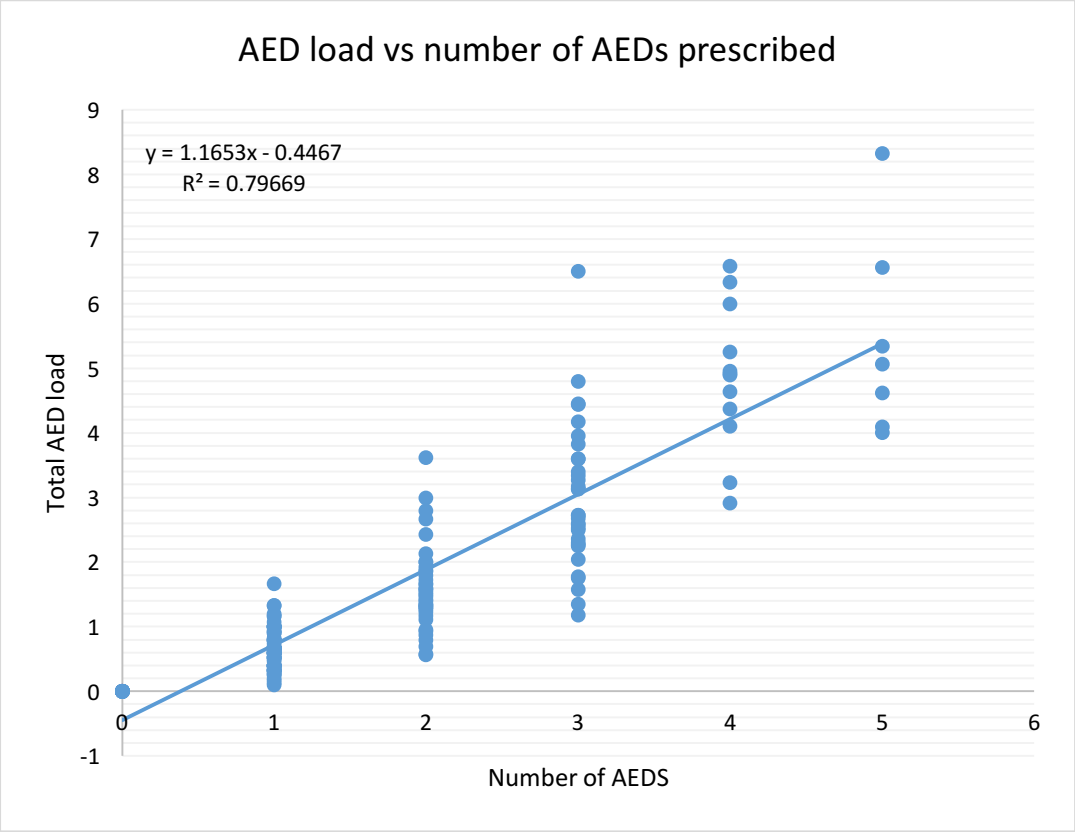


Figure 4.4-1 Antiepileptic drug load and number of AED's prescribed
n=190

0 AED: n=22 participants.
1 AED: n=78 participants.
2 AED: n=39 participants.
3 AED: n=32 participants.
4 AED: n=12 participants.
5 AED: n=7 participants.

4.4.2 Categorised antiepileptic drug load <2, ≥2 and demographic and clinical factors

Antiepileptic drug load was categorised into <2 and ≥2, adapted from Lammers et al. (1995) [409]. Demographic characteristics and categorised AED load are presented in *Table 4.4-1*. Of participants with an AED load <2, 61.0% (n=83) were female. An equal number of males (n=27) and females (n=27) had an AED load ≥2. The majority of participants with an AED load <2 (61.8%, n=84) and with an AED load ≥2 (77.7%, n=42) were aged 50-64 years. Over half (52.9%, n=27) of those with an AED load ≥2 were classified as having a moderate intellectual disability. A statistically significant association (p=0.012) was found for cause of intellectual disability and categorised AED load, with 19.4% (n=26) of those with an AED load <2 having a diagnosis of Down Syndrome compared to 3.9% (n=2) of those with an AED load ≥2 having a diagnosis of Down Syndrome. The majority of participants with an AED load ≥2 lived in residential/campus settings (57.4%, n=31) with only 5.5% (n=3) of those having an AED load ≥2 living in independent/family settings.

Table 4.4-1 Bivariate analysis of demographic characteristics (n=190) of participants with an AED load <2 (n=136) and AED load ≥2 (n=54)

Characteristic	Total n=190 n (%)	AED load <2 n=136 n (%)	AED load ≥2 n=54 n (%)	P value
Gender				0.165
Male	80 (42.1)	53 (39.0)	27 (50.0)	
Female	110 (57.9)	83 (61.0)	27 (50.0)	
Age				0.082
<50 years	20 (10.5)	15 (11.0)	5 (9.3)	
50-64 years	126 (66.3)	84 (61.8)	42 (77.7)	
65+ years	44 (23.2)	37 (27.2)	7 (13.0)	
Level of intellectual disability	n=182	n=131	n=51	0.191
Mild	29 (15.9)	22 (16.8)	7 (13.7)	
Moderate	77 (42.3)	50 (38.2)	27 (52.9)	
Severe/profound	76 (41.8)	59 (45.0)	17 (33.3)	
Cause of intellectual disability	n=186	n=134	n=52	**0.012***
Down Syndrome	28 (15.1)	26 (19.4)	2 (3.9)	
Other aetiology	49 (26.3)	30 (22.4)	19 (36.5)	
Unknown cause	109 (58.6)	78 (58.2)	31 (59.6)	
Type of residence				0.165
Family/independent	20 (10.5)	17 (12.5)	3 (5.5)	
Community group home	55 (28.9)	35 (25.7)	20 (37.0)	
Residential/campus setting	115 (60.5)	84 (61.8)	31 (57.4)	

n=190 due to missing AED load data for 6 participants which were excluded from this analysis.
p value: Chi Square. **Statistically significant results marked in bold and with an asterisk***

Clinical characteristics are presented in *Table 4.4-2.* Of those with an AED load <2, 68.4% (n=78) reported taking AED monotherapy, while for those with an AED load ≥2, 100.0% (n=54) reported taking AED polytherapy. Almost three quarters (72.3%, n=94) of participants with an AED load <2 reported no seizures in the last year. In contrast, 70.4% (n=38) of those with an AED load ≥2 reported at least one seizure in the last year. A significantly greater proportion of participants with an AED load ≥2 reported attending an epilepsy clinic or specialist (83.0%, n=44), compared to those with an AED load <2 (43.6%,

n=58). Over half (55.6%, n=30) of participants with an AED load ≥2 reported having their epilepsy reviewed by a neurologist compared to 25.8% (n=34) of participants with an AED load <2 (p<0.001). Buccal midazolam was prescribed to 74.1% (n=40) of participants with an AED load ≥2 and 42.7% (n=58) of participants with an AED load <2. A higher prevalence of aggressive/destructive behaviour was found in participants with an AED load ≥2 (p=0.417).

Table 4.4-2 Bivariate analysis of clinical characteristics (n=190) of participants with an AED load <2 (n=136) and AED load ≥2 (n=54)

Characteristic	Total n=190 n (%)	AED load <2 n=136 n (%)	AED Load ≥2 n=54 n (%)	P value
Type of AED therapy	n=168	n=114	n=54	**<0.001***
AED monotherapy	78 (46.4)	78 (68.4)	0 (0)	
AED polytherapy	90 (53.6)	36 (31.6)	54 (100.0)	
Seizure frequency	n=184	n=130	n=54	**<0.001***
None in the last year	110 (59.8)	94 (72.3)	16 (29.6)	
At least one in the last year	74 (40.2)	36 (27.7)	38 (70.4)	
Keep seizure record	n=187	n=133	n=54	0.004
Yes	158 (84.5)	106 (79.7)	52 (96.3)	
No	29 (15.5)	27 (20.3)	2 (3.7)	
Types of seizures				**<0.001***
Generalised seizures	102 (53.7)	59 (43.4)	43 (79.6)	
Other seizures	88 (46.3)	77 (56.6)	11 (20.4)	
Categorised number of seizure types				**<0.001***
1	73 (38.4)	50 (36.8)	23 (42.6)	
2+	32 (16.8)	11 (8.1)	21 (38.8)	
Unknown number	85 (44.7)	75 (55.1)	10 (18.5)	
Attend epilepsy clinic or specialist	n=186	n=133	n=53	**<0.001***
Yes	102 (54.8)	58 (43.6)	44 (83.0)	
No	84 (45.2)	75 (56.4)	9 (17.0)	
Who reviewed epilepsy	n=186	n=132	n=54	
GP	68 (36.6)	53 (40.2)	15 (27.8)	0.112
Neurologist	64 (34.4)	34 (25.8)	30 (55.6)	**<0.001***
Psychiatrist	54 (29.0)	43 (32.6)	11 (20.4)	0.096
Other	5 (2.7)	3 (2.3)	2 (3.7)	0.629 [a]

Table 4.4-2 Bivariate analysis of clinical characteristics (n=190) of participants with an AED load <2 (n=136) and AED load ≥2 (n=54) (*Continued*)

Characteristic	Total n=190 n (%)	AED load <2 n=136 n (%)	AED Load ≥2 n=54 n (%)	P value
Visited A&E in the last year with epilepsy	n=171	n=121	n=50	0.099 [a]
Yes	17 (9.9)	9 (7.4)	8 (16.0)	
No	154 (90.1)	112 (92.6)	42 (84.0)	
Education to manage epilepsy	n=173	n=123	n=50	0.022
Yes	42 (24.3)	24 (19.5)	18 (36.0)	
No	131 (75.7)	99 (80.5)	32 (64.0)	
Medication for acute seizures				
Buccal midazolam	98 (51.6)	58 (42.7)	40 (74.1)	**<0.001***
Comorbid mental health disorder				
Psychotic disorder	12 (6.3)	9 (6.6)	3 (5.5)	1.000[a]
Mood disorder	71 (37.4)	55 (40.4)	16 (29.6)	0.165
Anxiety disorder	65 (34.2)	47 (34.6)	18 (33.3)	0.872
Exhibit challenging behaviour	n=156	n=111	n=45	0.496
Yes	100 (64.1)	73(65.8)	27 (60.0)	
No	56 (35.9)	38 (34.2)	18 (40.0)	
Types of behaviour	n=156	n=111	n=45	
Self-Injurious behaviour	58 (37.2)	43 (38.7)	15 (33.3)	0.469
Aggressive/destructive behaviour	61 (39.1)	41 (36.9)	20 (44.4)	0.417
Stereotyped behaviour	79 (50.6)	61 (55.0)	18 (40.0)	0.128
Other psychotropic medicines				
Antipsychotics	73 (38.4)	56 (41.2)	17 (31.5)	0.215
Antidepressants	59 (31.1)	43 (31.6)	16 (29.6)	0.789
Anxiolytics	33 (17.4)	23 (16.9)	10 (18.5)	0.792
Hypnotics & sedatives	22 (11.6)	14 (10.3)	8 (14.8)	0.380
Anti- cholinergic	20 (10.5)	14 (10.3)	6 (11.1)	0.869

n=190 due to missing AED load data for 6 participants which were excluded from this analysis. P value: Chi Square Test, [a] Fisher's Exact Test. P value: for Chi-Square/Fisher's Exact Test after applying Bonferroni Correction α=0.05/25= 0.002 thus p<0.002 for significance. <5 denotes fewer than 5 participants. Due to low numbers of participants (<5), emergency medications for acute seizures clobazam and lorazepam, and drugs for dementia were removed from the table. Review by clinical nurse specialist (<5) was also removed. Lithium (n=5) was removed from the table due to low numbers in the AED load <2 category. Response of 'don't know who reviewed epilepsy' (n=14) was also removed from the table due to low numbers in the AED load ≥2 category. **Statistically significant results marked in bold and with an asterisk***

4.4.3 Categorised antiepileptic drug load and antiepileptic drugs prescribed

From examining individual AEDs and categorised AED load (*Table 4.4-3*), 62.2% (n=46) of participants who reported taking valproic acid (p=0.022), 64.6% (n=42) of participants who reported taking carbamazepine (p=0.125) and 55.9% (n=33) of participants who reported taking lamotrigine (p=0.001) were found to have an AED load <2. In total, 100% of participants who reported taking zonisamide (n=9), topiramate (n=6), and lacosamide (n=5) were found to have an AED drug load ≥2. These AEDs were used in polytherapy regimens in this study.

Table 4.4-3 Bivariate analysis of AEDs prescribed (n=190) to participants with an AED load <2 (n=136) and AED load ≥2 (n=54)

AED	Total n (%) n=190	AED load <2 n (%) n=136	AED load ≥2 n (%) n=54	P value
Valproic acid	74 (39.0)	46 (62.2)	28 (37.8)	**0.022***
Carbamazepine	65 (34.2)	42 (64.6)	23 (35.4)	0.125
Lamotrigine	59 (31.1)	33 (55.9)	26 (44.1)	**0.001***
Levetiracetam	45 (23.7)	15 (33.3)	30 (66.7)	**<0.001***
Phenobarbital	13 (6.8)	4 (30.8)	9 (69.2)	**0.002*** [a]
Zonisamide	9 (4.7)	0 (0)	9 (100.0)	**<0.001*** [a]
Topiramate	6 (3.2)	0 (0)	6 (100.0)	**<0.001*** [a]
Pregabalin	5 (2.6)	2 (40.0)	3 (60.0)	0.140 [a]
Lacosamide	5 (2.6)	0 (0)	5 (100.0)	**0.002*** [a]
Phenytoin	10 (5.3)	2 (20.0)	8 (80.0)	**0.001*** [a]
Clonazepam	11 (5.8)	7 (63.6)	4 (36.4)	0.511 [a]
Clobazam	21 (11.1)	2 (9.5)	19 (90.5)	**<0.001***

P value: Chi Square Test, [a] Fisher's Exact Test. n=6 missing AED load data. Due to low numbers of participants being prescribed some AEDs (<5), namely eslicarbazepine, rufinamide, primidone, perampanel and gabapentin, these AEDs were removed from the table. **Statistically significant results marked in bold and with an asterisk***

4.4.4 Categorised antiepileptic drug load and type of seizure

Categorised AED load and type of seizures are presented in *Table 4.4-4*. Over half (54.4%, n=43) of participants reporting tonic-clonic seizures had an AED load <2 (p<0.001). On the contrary, 64.7% (n=11) of participants reporting tonic seizures (p=0.001), and 51.9% (n=14) reporting absence seizures (p=0.004) had AED loads ≥2.

Table 4.4-4 Bivariate analysis of individual seizure types (n=190) in participants with an AED load <2 (n=136) and AED load ≥2 (n=54)

Type of Seizure	Total n (%) n=190	AED load <2 n (%) n=136	AED load ≥2 n (%) n=54	P Value
Tonic-clonic seizure	79 (41.6)	43 (54.4)	36 (45.6)	**<0.001***
Tonic seizure	17 (9.0)	6 (35.3)	11 (64.7)	**0.001*** [a]
Myoclonic seizures	14 (7.4)	8 (57.1)	6 (42.9)	0.227 [a]
Absence seizures	27 (14.2)	13 (48.1)	14 (51.9)	**0.004***
Other	20 (10.5)	16 (80.0)	4 (20.0)	0.377
Don't know	63 (33.2)	57 (90.5)	6 (9.5)	**<0.001***

P value: Chi Square Test. [a] Fisher's Exact Test. n=6 missing AED load data. <5 denotes fewer than 5 participants. Due to low numbers of participants reporting some seizure types (<5), clonic, simple partial, complex partial, and unclear seizure categories were removed from the table. Atonic seizure (n=5) category was also removed from the table due to low numbers in the AED load <2 category. **Statistically significant results marked in bold and with an asterisk***

4.4.5 Categorised antiepileptic drug load and limiting activities

Regarding activities that may be limited by having a diagnosis of epilepsy (*Table 4.4-5*), household chores (p=0.001), work (p=0.001), social activities (p=0.001), sports activities (p<0.001), driving (p=0.002) and going out alone (p<0.001) were significantly associated with having an AED load ≥2. Reporting that a diagnosis of epilepsy limits 'none of the above' activities was significantly associated (p<0.001) with having an AED load <2.

Table 4.4-5 Bivariate analysis of epilepsy limiting activities (n=190) in participants with an AED load <2 (n=136) and AED load ≥2 (n=54)

Activity	Total n=190 n (%)	AED Load <2 n= 136 n (%)	AED load ≥2 n= 54 n (%)	P value
Household chores	14 (7.4)	4 (28.6)	10 (71.4)	**0.001*** [a]
Work	14 (7.4)	4 (28.6)	10 (71.4)	**0.001*** [a]
Social activities	20 (10.5)	8 (40.0)	12 (60.0)	**0.001***
Sports activities	12 (6.3)	2 (16.6)	10 (83.3)	**<0.001*** [a]
Driving	11 (5.8)	3 (27.3)	8 (72.7)	**0.002*** [a]
Going out alone	25 (13.2)	8 (32.0)	17 (68.0)	**<0.001***
Other	5 (2.6)	2 (40.0)	3 (60.0)	0.140 [a]
None of the above	147 (77.4)	118 (80.3)	29 (19.7)	**<0.001***

P value: Chi Square Test. [a] Fisher's Exact Test. n=6 missing AED load data. Due to low numbers of participants reporting some limiting activities (<5), the categories don't know and unclear response were removed from the table. **Statistically significant results marked in bold and with an asterisk***

4.4.6 Categorised antiepileptic drug load and psychotropic drugs with the potential to lower the seizure threshold

Tables 4.4-6 and *4.4-7* outline categorised AED load (<2, ≥2) with regards to co-prescribed psychotropic medications with the potential to lower the seizure threshold (antipsychotics and antidepressants). No statistical differences were found in the analyses. The majority of participants taking lithium (n=5) were found to have an AED load ≥2 (not shown due to low numbers in AED load <2 category).

Table 4.4-6 Bivariate analysis of potential seizure threshold-lowering antipsychotic medication (n=190) in participants with an AED load <2 (n=136) and AED load ≥2 (n=54)

Antipsychotics	Total n (%) n=190	AED load <2 n (%) n=136	AED load ≥2 n (%) n=54	P value
Chlorpromazine	12 (6.3)	10 (83.3)	2 (16.7)	0.514 [a]
Olanzapine	27 (14.2)	19 (70.4)	8 (29.6)	0.881
Quetiapine	9 (4.7)	7 (77.7)	2 (22.3)	1.000 [a]
Risperidone	23 (12.1)	19 (82.6)	4 (17.4)	0.211
Aripiprazole	5 (2.6)	2 (40.0)	3 (60.0)	0.140 [a]

P value: Chi Square Test, [a] Fisher's Exact Test. n=6 missing AED load data. Due to low numbers of participants being prescribed some antipsychotics (<5), promazine, trifluoperazine, haloperidol, zuclopenthixol and flupenthixol were removed from the table. **Statistically significant results marked in bold and with an asterisk***

Table 4.4-7 Bivariate analysis of potential seizure threshold-lowering antidepressant medication (n=190) in participants with an AED load <2 (n=136) and AED load ≥2 (n=54)

Antidepressants	Total n (%) n=190	AED load <2 n (%) n=136	AED load ≥2 n (%) n=54	P value
Escitalopram	18 (9.5)	14 (77.7)	4 (22.3)	0.540
Fluoxetine	6 (3.2)	4 (66.7)	2 (33.3)	1.000 [a]
Mirtazapine	11 (5.8)	9 (81.8)	2 (18.2)	0.731
Venlafaxine	8 (4.2)	6 (75.0)	2 (25.0)	1.000 [a]
Trazodone	7 (3.7)	5 (71.4)	2 (28.6)	1.000 [a]

P value: Chi Square Test, [a] Fisher's Exact Test. n=6 missing AED load data. Due to low numbers of participants being prescribed some antidepressants (<5), citalopram, paroxetine, duloxetine and trimipramine were removed from the table. Sertraline (n=5) was also removed from the table due to low numbers in the AED load ≥2 category. **Statistically significant results marked in bold and with an asterisk***

4.5 Numerical drug load

4.5.1 Normality tests

Normality tests including Kolmogorov-Smirnov and Shapiro-Wilk tests indicated that the AED load variable was not normally distributed (p<0.001) *(Table 4.5-1)*. Therefore, non-parametric tests were utilised in analysing this data. Descriptive statistics (max, min, IQR, variance, kurtosis, skew), and median tests are presented in *Appendices 11-16* to this thesis. Non-parametric Mann-Whitney U and Kruskal- Wallis H tests are presented in the following tables.

Table 4.5-1 Tests for normality – Total AED load

Test	Statistic	P value
Kolmogorov-Smirnov	0.178	**<0.001***
Shapiro-Wilk	0.832	**<0.001***

Statistically significant results marked in bold and with an asterisk*

The following boxplots (*Figures 4.5-1 – 4.5-5)* illustrate the spread of AED load with regards to the following demographic characteristics - gender, age, type of residence, level of intellectual disability, and cause of intellectual disability:

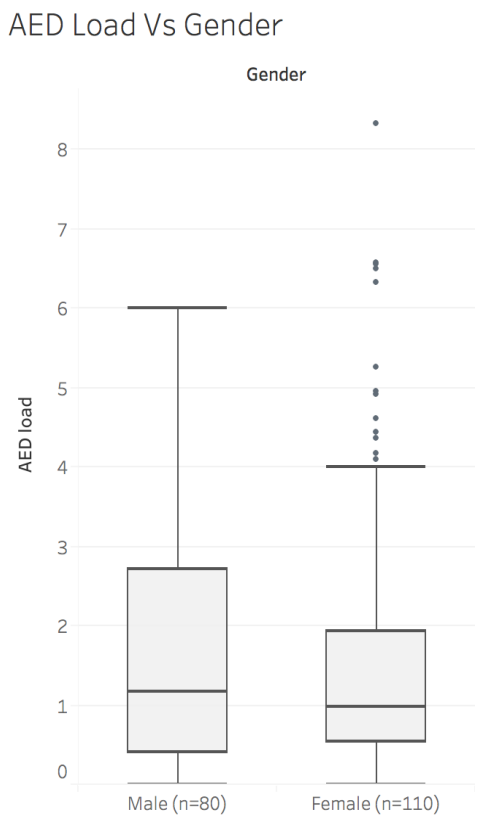


Figure 4.5-1 Gender (n=190)

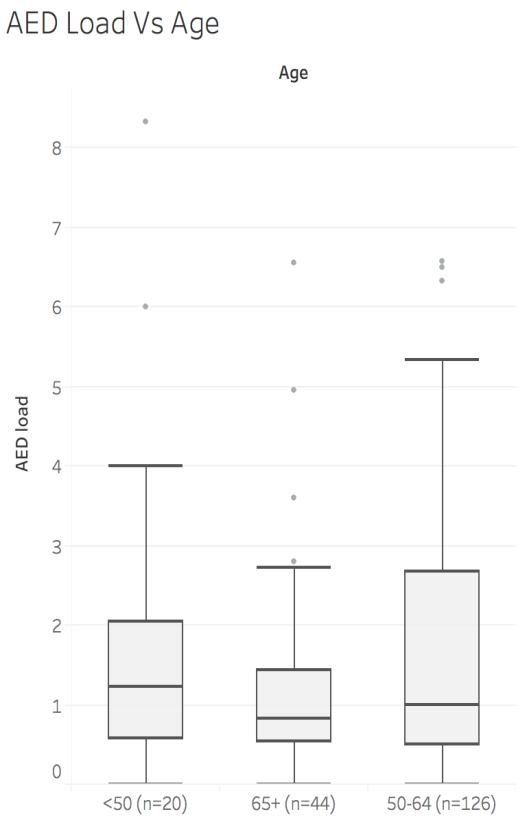


Figure 4.5-2 Age (years) (n=190)

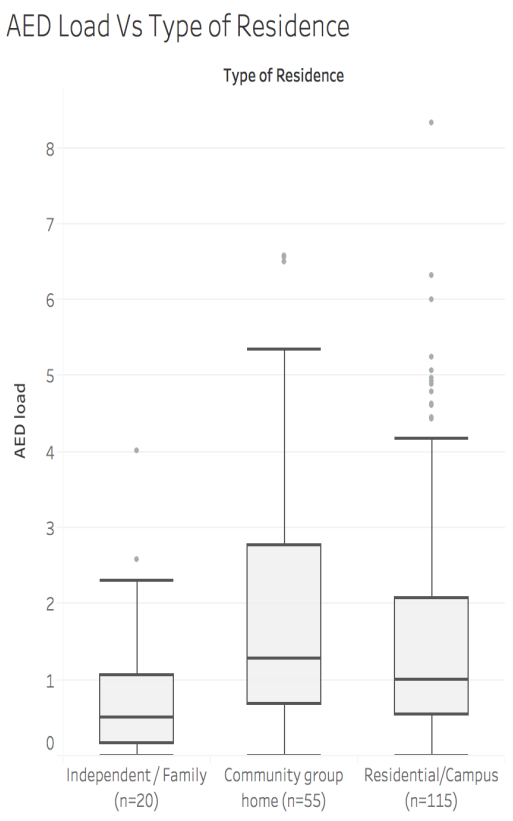


Figure 4.5-3 Type of residence (n=190)

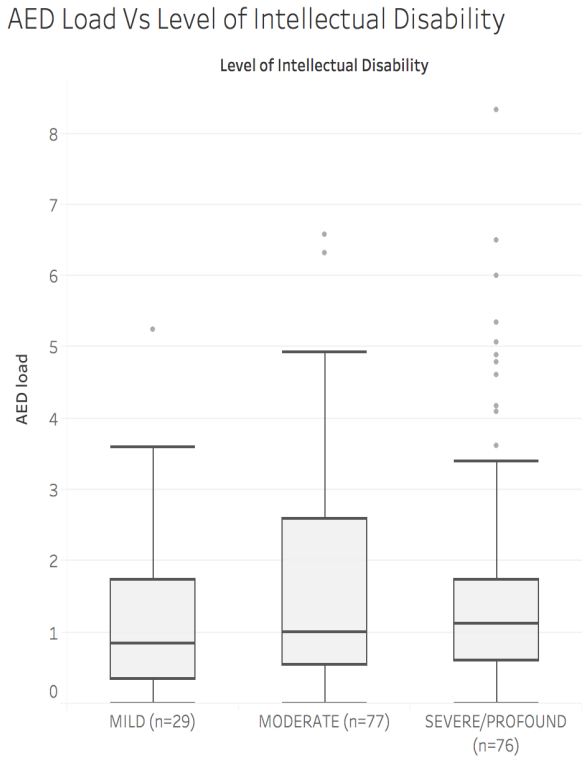


Figure 4.5-4 Level of intellectual disability (n=182)

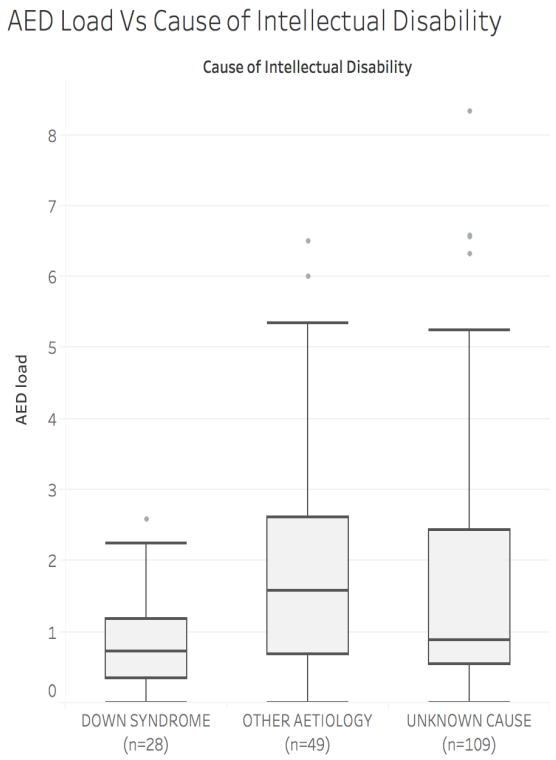


Figure 4.5-5 Cause of intellectual disability (n=186)

4.5.2 Examination of numerical antiepileptic drug load for demographic & clinical characteristics - Mann Whitney U Test (Variables with 2 groups)

A Mann Whitney U test (*Table 4.5-2*) showed that there was no significant difference (U=4269.000, p=0.726) between median AED Loads for males (n=80) compared with females (n=110). The median AED Load for males was 1.17 (95% CI 0.67-1.67, mean rank 97.14) compared with 0.98 (95% CI 0.70-1.27, mean rank 94.31) for females. The difference between the groups was small (Cohen effect size r=0.03). No significant difference in the Mann Whitney U test was also found for median AED load and co-prescribed antipsychotics (U=4090.000, p=0.624), hypnotics and sedatives (U=1462.500, p=0.112), anxiolytics (U=2310.500, p=0.329) or antidepressants (U=3594.500, p=0.441).

A comorbid psychiatric disorder also showed no significant difference in median AED load using the Mann Whitney U test, with psychotic disorder (U=1019.500, p=0.792), mood disorder (U=4416.000, p=0.601), and anxiety disorder (U=3989.500, p=0.839) also giving small Cohen effect sizes. A Mann Whitney U test showed that there was a significantly higher median AED load (U=2171.000, p=0.040) in those receiving education to manage their epilepsy (n=42) compared to those not receiving education to manage their epilepsy (n=131). The median AED load for those receiving education was 1.60 (95% CI 1.00-2.43, mean rank 100.81) compared with 0.90 (95%CI 0.67-1.18, mean rank 82.57) for those not receiving education. A small Cohen effect size was found (r=0.2). Due to failure to satisfy the assumption of equal distributions using the Levine test (*Appendices 17 and 19*), caution is needed when interpreting any significance of the Mann Whitney U test with the following variables; type of therapy, seizure frequency, attending an epilepsy clinic or specialist, categorised number of AEDs, seizure type, GP and neurologist review (denoted ** in *Table 4.5-2*).

Table 4.5-2 Mann Whitney U analysis for demographic & clinical characteristics (n=190)

Variable	n	Median AED load (95% CI)	Mann Whitney U	P value	Mean Rank	Z value	Approximate r value: z/√n	Cohen Effect Size - r Analysis
Gender	190	1.00 (0.80-1.27)	4269.000	0.726		-0.350	0.03	Small effect
Male	80	1.17 (0.67-1.67)			97.14			
Female	110	0.98 (0.70-1.27)			94.31			
Type of therapy	168	1.19 (0.95-1.47)	6786.000	<0.001**		10.425	0.8	Very large effect
Monotherapy	78	0.67 (0.60-0.67)			42.50			
Polytherapy	90	2.47 (1.93-2.92)			120.90			
Seizure frequency	184	1.00 (0.80-1.30)	6111.500	<0.001**		5.769	0.4	Medium effect
None in the last year	110	0.67 (0.60-0.90)			73.94			
At least one in last year	74	2.13 (1.50-2.92)			120.09			
Attend epilepsy clinic or specialist	186	1.00 (0.80-1.30)	2802.000	<0.001**		-4.060	0.3	Medium effect
Yes	102	1.30 (0.90-2.27)			108.03			
No	84	0.75 (0.60-1.07)			75.86			
Visited A&E with epilepsy	171	1.00 (0.80-1.33)	1050.000	0.181		-1.338	0.1	Small effect
Yes	17	1.87 (0.67-2.92)						
No	154	1.00 (0.75-1.30)						
Had education to manage epilepsy?	173	1.00 (0.80-1.30)	2171.000	**0.040***		-2.056	0.2	Small effect
Yes	42	1.60 (1.00-2.43)			100.81			
No	131	0.90 (0.67-1.18)			82.57			

Table 4.5-2 Mann Whitney U analysis for demographic & clinical characteristics (n=190) *(Continued)*

Variable	n	Median AED load (95% CI)	Mann Whitney U	P value	Mean Rank	Z value	Approximate r value: z/√n	Cohen Effect Size - r Analysis
Who reviewed epilepsy - GP	186	1.00 (0.80-1.30)	3699.500	0.376**		-0.885	0.07	Small effect
Yes	68	0.98 (0.67-1.27)			88.90			
No	118	1.00 (0.75-1.50)			96.15			
Who reviewed Epilepsy - Psychiatrist	186	1.00 (0.80-1.30)	3394.500	0.611		-0.509	0.04	Small effect
Yes	54	0.93 (0.67-1.42)			90.36			
No	132	1.00 (0.80-1.30)			94.78			
Who reviewed epilepsy - Neurologist	186	1.00 (0.80-1.30)	5184.000	<0.001**		3.674	0.3	Medium effect
Yes	64	1.67 (1.00-2.58)			113.50			
No	122	0.80 (0.67-1.11)			83.01			
Who reviewed epilepsy - CNS	186	1.00 (0.80-1.30)	406.000	0.155		1.423	0.1	Small effect
Yes	3	2.92 (0.93-4.64)			137.33			
No	183	1.00 (0.80-1.30)			92.78			
Who reviewed epilepsy - other	186	1.00 (0.80-1.30)	484.000	0.791		0.266	0.02	Small effect
Yes	5	0.80 (0.00-6.33)			99.80			
No	181	1.00 (0.80-1.30)			93.33			
Who reviewed epilepsy - don't know	186	1.00 (0.80-1.30)	556.000	**0.001***		-3.349	0.3	Medium effect
Yes	14	0.80 (0.00-6.33)			47.21			
No	172	1.00 (0.80-1.30)			97.27			

Table 4.5-2 Mann Whitney U analysis for demographic & clinical characteristics (n=190) *(Continued)*

Variable	n	Median AED load (95% CI)	Mann Whitney U	P value	Mean Rank	Z value	Approximate r value: z/√n	Cohen Effect Size - r Analysis
Other psychotropics - antipsychotics	190	1.00 (0.80-1.27)	4090.000	0.624		-0.490	0.04	Small effect
Yes	73	1.11 (0.80-1.42)			97.97			
No	117	0.90 (0.67-1.33)			93.96			
Other psychotropics - hypnotics & sedatives	190	1.00 (0.80-1.27)	1462.500	0.112		-1.591	0.1	Small effect
Yes	22	1.43 (0.67-3.17)			113.02			
No	168	0.93 (0.70-1.18)			93.21			
Other psychotropics - anxiolytics	190	1.00 (0.80-1.27)	2310.500	0.329		-0.976	0.07	Small effect
Yes	33	1.30 (0.80-1.76)			103.98			
No	157	0.93 (0.67-1.23)			93.72			
Other psychotropics - antidepressants	190	1.00 (0.80-1.27)	3594.500	0.441		-0.771	0.06	Small effect
Yes	59	1.18 (0.80-1.60)			100.08			
No	131	0.93 (0.67-1.23)			93.44			
Other psychotropics - drugs for dementia	190	1.00 (0.80-1.27)	418.000	0.672		0.423	0.03	Small effect
Yes	4	1.29 (0.00-2.67)			84.00			
No	186	1.00 (0.80-1.27)			95.75			
Other psychotropics - anti-cholinergic drugs	190	1.00 (0.80-1.27)	1377.500	0.165		-1.388	0.1	Small effect
Yes	20	1.34 (0.90-2.73)			111.63			
No	170	0.98 (0.67-1.23)			93.60			

Table 4.5-2 Mann Whitney U Analysis for demographic & clinical characteristics (two groups in variable) (n=190) *(Continued)*

Variable	n	Median AED load (95% CI)	Mann Whitney U	P value	Mean Rank	Z value	Approximate r value: z/√n	Cohen Effect Size - r Analysis
Mental health - psychotic disorder	190	1.00 (0.80-1.27)	1019.500	0.792		-0.263	0.02	Small effect
Yes	12	1.19 (0.60-2.50)			99.54			
No	178	1.00 (0.80-1.27)			95.23			
Mental health - mood disorder	190	1.00 (0.80-1.27)	4416.000	0.601		0.523	0.04	Small effect
Yes	71	0.93 (0.67-1.34)			92.80			
No	119	1.00 (0.80-1.35)			97.11			
Mental health - anxiety disorder	190	1.00 (0.80-1.27)	3989.500	0.839		-0.203	0.02	Small effect
Yes	65	1.07 (0.80-1.53)			96.62			
No	125	0.93 (0.67-1.27)			94.92			
Challenging behaviour	156	1.00 (0.80-1.33)	2946.500	0.588		0.542	0.04	Small effect
Yes	100	0.98 (0.67-1.42)			77.04			
No	56	1.06 (0.75-1.40)			81.12			
Exhibit SIB	157	1.00 (0.80-1.33)	2766.000	0.702		-0.382	0.03	Small effect
Yes	58	1.04 (0.70-1.53)			80.81			
No	99	1.00 (0.67-1.33)			77.94			
Exhibit Aggressive/destructive behaviour	151	1.00 (0.80-1.34)	2557.500	0.476		-0.712	0.06	Small effect
Yes	61	1.17 (0.67-1.60)			79.07			
No	90	0.94 (0.67-1.33)			73.92			

Table 4.5-2 Mann Whitney U Analysis for demographic & clinical characteristics (two groups in variable) (n=190) *(Continued)*

Variable	n	Median AED load (95% CI)	Mann Whitney U	P value	Mean Rank	Z value	Approximate r value: z/√n	Cohen Effect Size - r Analysis
Exhibit stereotyped behaviour	156	1.00 (0.80-1.33)	3311.500	0.338		0.958	0.08	Small effect
Yes	79	0.93 (0.67-1.35)			75.08			
No	77	1.11 (0.80-1.40)			82.01			
Type of seizures	190	1.000 (0.800-1.270)	2690.000	<0.001**		-4.762	0.34	Medium effect
Generalised	102	1.585 (1.000-2.250)			113.13			
Other	88	0.670 (0.600-0.900)			75.07			
Keep seizure record	187	1.000 (0.800-1.300)	1145.000	<0.001**		-4.282	0.31	Medium effect
Yes	158	1.190 (0.930-1.500)			101.25			
No	29	0.400 (0.000-1.000)			54.48			

Cohen (1988) criteria for r: 0.1= small effect, 0.3= medium effect, 0.5=large effect, 0.7=very large effect.

** CAUTION: Levine Statistic - does not satisfy assumptions of equal distributions, an assumption of the Mann Whitney U Test - See Levine Table *Appendices 17 and 19.*

Statistically Significant Results marked in bold and with an asterisk *

4.5.3 Examination of numerical antiepileptic drug load for demographic & clinical characteristics - Kruskal Wallis Test (variables with >2 groups)

Regarding place of residence, a Kruskal Wallis test (*Table 4.5-3*) demonstrated a statistically significant difference (p=0.011) in median AED loads between the mean ranks of at least one pair of groups (H=9.010). Dunn's pairwise comparison tests were carried out for the three pairs of groups: independent/family–residential/campus, independent/family–community group home and residential/campus–community group home. A significantly higher median AED load (p=0.008, adjusted using Bonferroni correction) was found in those living in community group homes compared to those living in independent/family settings. The median AED load for those living in community group homes was 1.27 (95%CI 0.90-2.04, mean rank=108.41) compared to a median AED load of 0.50 (95% CI 0.30-0.80, mean rank=65.58) for those living in independent/family settings. The other groups in the place of residence analysis showed no significant differences. Age group also showed no significant difference in median AED load (H=2.095, p=0.351), with those aged <50 years having the highest median AED load of 1.23 (95% CI 0.60-1.93, mean rank 99.90) and those aged 65+ years having the lowest median AED load (0.82, 95% CI 0.67-1.20, mean rank 85.02). Level of intellectual disability also did not show a significant difference in median AED load.

Table 4.5-3 Kruskal Wallis H analysis for demographic & clinical factors (n=190)

Variable	n	Median AED load (95% CI)	Kruskal Wallis H	P value	Df	Mean Rank
Age	190	1.00 (0.80-1.27)	2.095	0.351	2	
<50 years	20	1.23 (0.60-1.93)				99.90
50-64 years	126	1.00 (0.80-1.42)				98.46
65+ years	44	0.82 (0.67-1.20)				85.02
Place of residence	190	1.00 (0.80-1.27)	9.010	**0.011***	2	
Independent/family	20	0.50 (0.30-0.80)				65.58
Community group home	55	1.27 (0.90-2.04)				108.41
Residential/campus	115	1.00 (0.67-1.33)				94.53
Level of intellectual disability	182	1.00 (0.80-1.30)	1.109	0.574	2	
Mild	29	0.83 (0.40-1.40)				82.14
Moderate	77	1.00 (0.67-1.78)				92.73
Severe/profound	76	1.12 (0.70-1.35)				93.83
Cause of intellectual disability	186	1.00 (0.80-1.27)	8.549	0.014**	2	
Down Syndrome	28	0.71 (0.40-1.00)				71.48
Other aetiology	49	1.57 (1.00-2.13)				108.50
Unknown cause	109	0.87 (0.67-1.27)				92.41
Categorised number of seizure types	190	1.00 (0.80-1.27)	36.992	<0.001**	2	
1	73	1.00 (0.67-1.67)				99.69
2+	32	3.20 (1.50-4.10)				142.75
Unknown number	85	0.67 (0.53-0.93)				74.11

** Does not Satisfy the assumption of equal distributions, so caution with p value - see Levine tables in *Appendices 17 and 19.*

Df= degrees of freedom. **Statistically significant results marked in bold & with an asterisk*.**

4.5.4 Examination of numerical antiepileptic drug load for co-prescribed psychotropic medication with the potential to lower the seizure threshold

A Mann Whitney U test (*Table 4.5-4*) showed a significantly (U=194.000, p=0.027) higher median AED load for participants who report taking lithium (n=5) compared to those not reporting taking lithium (n=185). The median AED load for participants who reported taking lithium was 2.13 (95% CI 1.66-8.33, mean rank 149.20) compared with 0.95 (95% CI 0.75-1.20, mean rank 94.05) for participants not reporting taking lithium. The difference between the groups was small (Cohen effect size r=0.2).

Table 4.5-4 Mann Whitney U analysis for potential seizure threshold-lowering drugs (n=190)

Variable	n	Median AED load (95% CI)	Mann Whitney U	P value	Mean Rank	Z value	Approximate r value: z/√n	Cohen Effect Size- r analysis
Antipsychotics								
Chlorpromazine	190	1.00 (0.80-1.27)	1240.500	0.349		0.937	0.07	Small effect
Yes	12	0.67 (0.53-1.66)			81.13			
No	178	1.00 (0.80-1.30)			96.47			
Haloperidol	190	1.00 (0.80-1.27)	332.500	0.582		0.551	0.04	Small effect
Yes	3	0.90 (0.00-1.87)			78.17			
No	187	1.00 (0.80-1.30)			95.78			
Zuclopenthixol	190	1.00 (0.80-1.27)	387.500	0.257		1.134	0.08	Small effect
Yes	3	0.60 (0.00-1.30)			59.83			
No	187	1.00 (0.80-1.30)			96.07			
Olanzapine	190	1.00 (0.80-1.27)	1887.000	0.236		-1.186	0.09	Small effect
Yes	27	1.33 (0.67-2.04)			107.11			
No	163	0.93 (0.70-1.23)			93.58			
Quetiapine	190	1.00 (0.80-1.27)	773.500	0.799		-0.255	0.02	Small effect
Yes	9	1.33 (0.58-2.68)			100.06			
No	181	1.00 (0.80-1.27)			95.27			
Risperidone	190	1.00 (0.80-1.27)	2037.000	0.637		0.472	0.03	Small effect
Yes	23	0.93 (0.67-1.59)			90.43			
No	167	1.00 (0.80-1.33)			96.20			
Aripiprazole	190	1.00 (0.80-1.27)	393.000	0.566		-0.573	0.04	Small effect
Yes	5	2.13 (0.00-2.73)			109.40			
No	185	1.00 (0.80-1.27)			95.12			

Table 4.5-4 Mann Whitney U analysis for potential seizure threshold-lowering drugs (n=190) *(Continued)*

Variable	n	Median AED load (95%CI)	Mann Whitney U	P value	Mean Rank	Z value	Approximate r value: z/√n	Cohen Effect Size – r analysis
Mood stabilising agent								
Lithium	190	1.00 (0.80-1.27)	194.000	**0.027***		-2.215	0.2	Small effect
Yes	5	2.13 (1.66-8.33)			149.20			
No	185	0.95 (0.75-1.20)			94.05			
Antidepressants								
Citalopram	190	1.00 (0.80-1.27)	208.500	0.133		-1.504	0.1	Small effect
Yes	4	4.63 (0.00-4.96)			136.38			
No	186	1.00 (0.80-1.23)			94.62			
Escitalopram	190	1.00 (0.80-1.27)	1704.000	0.482		0.704	0.05	Small effect
Yes	18	0.87 (0.57-1.73)			86.83			
No	172	1.00 (0.80-1.33)			96.41			
Venlafaxine	190	1.00 (0.80-1.27)	632.000	0.528		-0.631	0.05	Small effect
Yes	8	1.60 (0.00-5.34)			107.50			
No	182	0.98 (0.80-1.23)			94.97			
Paroxetine	190	1.00 (0.80-1.27)	321.500	0.664		0.434	0.03	Small effect
Yes	3	0.67 (0.60-1.42)			81.83			
No	187	1.00 (0.80-1.30)			95.72			
Fluoxetine	190	1.00 (0.80-1.27)	486.000	0.618		-0.498	0.04	Small effect
Yes	6	1.30 (0.00-4.37)			106.50			
No	184	1.00 (0.80-1.23)			95.14			

Table 4.5-4 Mann Whitney U analysis for potential seizure threshold-lowering drugs (n=190) *(Continued)*

Variable	n	Median AED load (95%CI)	Mann Whitney U	P value	Mean Rank	Z value	Approximate r value: z/√n	Cohen Effect Size – r analysis
Antidepressants (cont.)								
Mirtazapine	190	1.00 (0.80-1.27)	1032.000	0.788		0.269	0.02	Small effect
Yes	11	1.07 (0.40-2.00)			91.18			
No	179	1.00 (0.80-1.30)			95.77			
Sertraline	190	1.00 (0.80-1.27)	511.000	0.689		0.400	0.03	Small effect
Yes	5	1.00 (0.25-2.67)			85.80			
No	185	1.00 (0.80-1.30)			95.76			
Trazodone	190	1.00 (0.80-1.27)	542.000	0.490		-0.691	0.05	Small effect
Yes	7	1.80 (0.00-5.25)			109.57			
No	183	1.00 (0.80-1.23)			94.96			

Levene table found in *Appendix 18*. Cohen (1988) criteria for r: 0.1= small effect, 0.3= medium effect, 0.5=large effect, 0.7=very large effect. Due to low numbers of participants being prescribed some potential seizure threshold-lowering drugs (<5), trifluoperazine, flupenthixol, promazine, trimipramine and duloxetine were removed from the table. **Statistically significant results marked in bold & with an asterisk*.**

4.5.5 Examination of numerical antiepileptic drug load for participants reporting if epilepsy limits their ability to do activities

A Mann Whitney U test (*Table 4.5-5*) showed a statistically significant higher median AED load (U=1964.500, p<0.001) for participants reporting that epilepsy limits their ability to do household chores compared to those that say it does not limit this activity. The median AED load for participants reporting that epilepsy limits their ability to do household chores was 3.29 (95%CI 1.23-6.33, mean rank= 147.82) compared to 0.93 (95%CI 0.87-1.17, mean rank 91.34) for those who reported that epilepsy does not limit their ability to do household chores. Other significant differences (U=1541.500, p=0.002) found in the Mann Whitney U test included higher median AED loads (3.40, 95%CI 1.00-6.50, mean rank 146.14) for those who report that epilepsy limits their ability to drive compared to those who report that it does not limit their ability to drive (0.93, 95%CI 0.70-1.18, mean rank 92.39). Due to an inability to satisfy the Levine assumption of equal distributions (*Appendix 18*), the Mann Whitney U test results for epilepsy limiting work, social activities, sports activities, going out alone and none of the above, while significant, need to be interpreted with caution.

Table 4.5-5 Mann Whitney U analysis for participants reporting that epilepsy limits ability to do activities (n=190)

Variable	n	Median (95% CI)	Mann Whitney U	P value	Mean Rank	Z Value	Approximate r value: z/√n	Cohen Effect Size – r analysis
Household chores	190	1.00 (0.80-1.27)	1964.500	**<0.001**		3.703	0.3	Medium effect
Yes	14	3.29 (1.23-6.33)			147.82			
No	176	0.93 (0.67-1.17)			91.34			
Work	190	1.00 (0.80-1.27)	1969.000	<0.001**		3.726	0.3	Medium effect
Yes	14	3.04 (1.23-6.50)			148.14			
No	176	0.92 (0.67-1.17)			91.31			
Social activities	190	1.00 (0.80-1.27)	2483.000	0.001**		3.370	0.3	Medium effect
Yes	20	2.55 (1.23-4.62)			134.65			
No	170	0.92 (0.67-1.16)			90.89			
Sports activities	190	1.00 (0.80-1.27)	1821.000	<0.001**		4.089	0.3	Medium effect
Yes	12	4.20 (2.43-6.50)			158.25			
No	178	0.93 (0.70-1.17)			91.27			
Driving	190	1.00 (0.80-1.27)	1541.500	**0.002***		3.150	0.2	Small effect
Yes	11	3.40 (1.00-6.50)			146.14			
No	179	0.93 (0.70-1.18)			92.39			
Going out alone	190	1.00 (0.80-1.27)	3337.000	<0.001**		4.980	0.4	Medium effect
Yes	25	3.17 (1.73-4.44)			146.48			
No	165	0.83 (0.67-1.00)			87.78			
Other	190	1.00 (0.80-1.27)	688.000	0.063		1.861	0.1	Small effect
Yes	5	2.80 (0.95-6.58)			140.60			
No	185	1.00 (0.75-1.27)			94.28			

Table 4.5-5 Mann Whitney U analysis for participants reporting that epilepsy limits ability to do activities (n=190) *(Continued)*

Variable	n	Median (95% CI)	Mann Whitney U	P value	Mean Rank	Z Value	Approximate r value: z/√n	Cohen Effect
None of the above	190	1.00 (0.80-1.27)	1654.000	<0.001**		-4.755	0.3	Medium effect
Yes	147	0.80 (0.67-1.00)			85.25			
No	43	2.58 (1.35-3.60)			130.53			

** Does not Satisfy assumption of equal distributions so caution with p - see Levine table in *Appendix 18*.
Cohen (1988) criteria for r: 0.1= small effect, 0.3= medium effect, 0.5=large effect, 0.7=very large effect.
S**tatistically significant results marked in bold & with an asterisk***

4.6 Discussion

4.6.1 Main findings

This Chapter examines the use of three AED utilisation methods in older adults with epilepsy and intellectual disability. In total, 40.8% of participants reported taking AED monotherapy, 48% AED polytherapy, and 11.2% reported no AED therapy. Over a quarter of participants with available data were found to have a total AED load ≥2. Almost three-quarters of participants exposed to AED monotherapy reported no seizure in the last year with four in ten participants exposed to AED polytherapy reporting same. A greater number of participants reporting AED polytherapy and having an AED load ≥2 reported getting their epilepsy reviewed by a neurologist compared to participants reporting AED monotherapy or having an AED load <2. Tonic-clonic seizures were the most common seizure type reported, with simple partial and complex partial seizures reported less commonly. A significantly higher prevalence of mood disorder was found in participants reporting AED monotherapy compared to participants reporting AED polytherapy (p=0.001). Two thirds of participants reporting AED monotherapy and six in ten participants reporting AED polytherapy were found to exhibit challenging behaviours.

The majority of participants with both an AED load <2 and ≥2 lived in residential/campus settings. When examining numerical AED load, a significantly higher median AED load was found in participants living in community group homes compared to participants living in independent/family settings (1.27 vs 0.50). We found that almost seven in ten participants with an AED load <2 reported taking AED monotherapy, while all participants with an AED load ≥2 reported taking AED polytherapy. Participants reporting that epilepsy limits their ability to do household chores, work, social activities, and going out alone was significantly associated with exposure to AED polytherapy. Having an AED

load ≥2 was also significantly associated with participants reporting that epilepsy limits their ability to do household chores, work, social activities, sports activities, driving and going out alone. Overall, three quarters of participants reported that they did not receive education to manage their epilepsy. However, a significantly higher median AED load (1.60) was found for participants reporting that they received education to manage their epilepsy compared to those not receiving this education (0.90).

4.6.2 Comparison with previous studies

In this study, 57.6% of participants exposed to AED polytherapy reported at least one seizure in the last year. Similarly, 70.4% of participants with an AED load ≥2 reported at least one seizure in the last year. We found no study in the general or intellectual disability population that we could compare these findings to. Evidence shows that dose titration to maximal levels, together with AED polytherapy may be of limited benefit while creating complications of overtreatment [444]. Only a minority of people benefit from titrating doses to the maximum tolerable levels, thus the majority of people affected are said to be unnecessarily exposed to overtreatment through excessive drug load [444]. Indeed, excessive AED doses and an unnecessarily fast dose titration can increase the risk of serious adverse effects such as Stevens-Johnson or Lyell Syndrome [444].

A higher prevalence of polytherapy was found in females (55.3%) compared to males (44.7%) in this study. An Irish cross-sectional study by O'Dwyer et al. (2018) also found a higher prevalence of polytherapy in females (55.3%) in Wave 1 of this IDS-TILDA cohort [29]. While a greater prevalence of lower AED load (<2) was found in females (61.0%), males and females equally reported a higher AED load (≥2). The median AED load

was found to be numerically greater in males (1.17) compared to females (0.98), but this was not significantly different (p=0.726).

Regarding type of residence, the highest prevalence of polytherapy was found in residential/campus settings (57.4%), which also accounted for the setting with the greatest proportion of participants with an AED load ≥2 (57.4%). O'Dwyer et al. (2018) also found a higher prevalence of polytherapy (61.2%) in residential/campus settings in Wave 1 of this cohort [29]. When examining numerical AED load, the highest median AED load was found in community group homes (1.27) and not in residential/campus settings (1.00) which might have been expected.

With regards to age, the greatest prevalence of polytherapy (69.1%) was found in participants aged 50-64 years, with almost eight in ten participants with an AED load ≥2 also aged 50-64 years. However, the highest median AED load was found in participants aged <50 years (1.23), with a median AED load of 1.00 found in people aged 50-64 years and a median AED load of 0.82 found in people aged 65+ years. Again, we found no study in the general or intellectual disability populations examining AED load with regards to demographic characteristics that we could compare these findings to.

Frequent seizure occurrence in this population group necessitates the easy availability of treatments for status epilepticus. Buccal midazolam was the most common rescue medicine prescribed in this study. Almost two thirds (64.9%) of participants exposed to AED polytherapy reported prescription of buccal midazolam compared to just under half (48.8%) of participants exposed to AED monotherapy. A higher AED load (≥2) was also associated with prescription of buccal midazolam (p<0.001). Unlike in Wave 1 of this IDS-TILDA study [29], rectal diazepam was not prescribed in Wave 3. A randomised controlled trial (RCT) of seizure rescue medications has demonstrated the superiority of buccal

midazolam over rectal diazepam ($p<0.01$), with seizure cessation in 8 minutes with buccal midazolam and 15 minutes with rectal diazepam [419, 445]. Of interest, rates of respiratory depression did not differ between the groups [445].

No AED therapy was reported by one in ten participants in this study, despite one fifth of these reporting at least one seizure in the last year and 13.6% reporting prescription of buccal midazolam. The MRC Multicentre trial for Early Epilepsy and Single Seizures (MESS) showed that early treatment does indeed reduce the risk of a second seizure when compared to no AED treatment or delayed treatment [446]. Immediate treatment was found to increase the time prior to a second seizure, a first occurrence of a tonic-clonic seizure and a significantly reduced time to achieve two-year seizure remission [446]. Thus, it is acceptable practice to treat people at higher risk of recurrence after the first documented seizure [419]. No information is available to explain why participants who report no AED therapy and are still experiencing active seizures do not receive regular AED treatment in this study. Of participants reporting no AED therapy, less than one in ten got their epilepsy reviewed by a neurologist, and over one in five had a severe/profound intellectual disability which may make EEG and other investigations difficult. Other possible reasons could be refusal of treatment, intolerable AED side effects or perhaps a 'wait and see' approach by the treating physician. It is also plausible that participants did not fully report regular AEDs.

The goals of optimum antiepileptic therapy in people with epilepsy include seizure reduction, well tolerated AEDs, easy prescribing, simple treatment regimens, and therapy not associated with teratogenicity, hypersensitivity reactions, or drug-drug interactions [419]. Additionally, no requirement for regular serum level monitoring would be beneficial for people with intellectual disability [279]. In this study, we asked participants whether

epilepsy limits their ability to do some everyday tasks. Of participants taking AED therapy, the majority responded that epilepsy limits none of the tasks listed (75.9%), and this response was significantly (p=0.001) associated with participants reporting AED monotherapy. On the other hand, participants reporting that epilepsy limits their ability to do tasks, for example, household chores, work, social activities, sports activities, going out alone, were significantly more likely to report AED polytherapy and have higher AED loads (≥2). Despite these associations, it is worth noting that 84.3% of participants who report taking AED polytherapy have either a moderate or severe/profound intellectual disability. It is very possible that this question was not fully understood by the participant and that the causation and association lines were blurred. If answered by a proxy, they may be attributing causation to epilepsy when other factors warrant consideration including poor bone health [152], mobility and frailty [447]. Few participants in this study reported that epilepsy limits their ability to do certain tasks making it difficult to do any meaningful analysis to determine if epilepsy related factors such as AED therapy or comorbidity have an impact on daily activities.

4.6.3 Implications for practice

Treating epilepsy in people with intellectual disability is challenging, complicated by high levels of refractory type seizures in this population group, often necessitating polytherapy and high AED loads. Undoubtedly, a balance must be sought between seizure reduction and overtreatment. Slow dose titration facilitates the assessment of AED effects on seizure frequency, and the development of any physical, psychiatric or behavioural side effects [51]. Careful prescribing, titrating and monitoring of AED treatment, together with regular multidisciplinary team reviews is crucial to ensuring people with intellectual disability are

provided with the safest, most effective treatment, with minimal impact on their quality of life.

4.6.4 Comparison of antiepileptic drug utilisation methods

Each of the AED utilisation methods (monotherapy and polytherapy classification, <2/≥2 categorisation, and numerical AED load) outlined in this Chapter offers complementary but more intricate information allowing a thorough investigation of the burden of AEDs in people with epilepsy and intellectual disability. Each method allows us to delve into further detail regarding the utilisation of AEDs. The monotherapy and polytherapy classification allows us to ascertain whether one or multiple AEDs are required for seizure reduction and the demographics/characteristics of the participants in each group. However, this method does not take into consideration the dosage of the AEDs and thus the nuance of high dose monotherapy vs low dose polytherapy is missed. It also fails to allow for meaningful comparison of individual AED regimens when compared with the AED load PDD/DDD concept.

However, the AED load PDD/DDD concept is not without its critics. Some say it assumes linearity of dose-response, when the dose-response relationship is often sigmoid for efficacy and linear or exponential for toxicity [444]. In addition, it is not able to recognise adverse effects associated with specific combinations of AEDs and it does not incorporate any pharmacokinetic or pharmacodynamic interactions with drugs [444]. Renal and hepatic function are also not considered in the WHO DDD classification. However, it allows us to compare the individual AED regimens of participants reporting either AED monotherapy or AED polytherapy, and to evaluate AED load against an overall DDD standard 'maintenance dose'. Categorisng AED load into <2 and ≥2 (adapted from

Lammers et al. (1995) [409]) gave an indication of a low and a high AED load categorisation, and allowed us to use categorical statistical tests like the Chi Square test and Fisher's Exact test to compare demographic and clinical factors. However, the broad categories 0 – 1.99 and 2+ may lead to statistical differences being missed as the majority of participants had an AED load <2.

Examining the PDD/DDD ratio using numerical methods allowed a specific median AED load to be obtained for individual groups (for example male/female), picking up precise differences not achievable by either of the previous methods. Median tests allowed simple comparison of groups (male/female) to understand If higher median AED loads were associated with particular characteristics. Certainly, each method has its own strengths and limitations and the usefulness of individual methods depends on the depth of information required. Numerical AED load is further examined in *Chapter 6* in relation to challenging behaviours.

4.6.5 Strengths

This study used a large, nationally representative sample of older adults with intellectual disability, representative of the older population of people with intellectual disability in Ireland. We obtained thorough medication data for 90.1% of Wave 3 participants which was confirmed by interviewers at the time of interview. The design of the medication record allowed for high quality acquisition of medication data. All participants and/or their proxies received the PIQ which contained the medication record one week prior to the face-to-face interview giving them an opportunity to consult the participants' medication/health records.

4.6.6 Limitations

Due to missing medication data, 19 participants with epilepsy were excluded from this study. We had seizure data for 190 participants, therefore six participants were excluded from the seizure analysis. Six participants were also excluded from the drug load analysis due to missing dose and/or frequency data. Our sample was therefore under-powered to evaluate small sub-groups. Data collected regarding medication use, diagnosis of epilepsy, exhibiting challenging behaviours and concomitant mental health disorders was based on participants' self-report or proxy report which may result in bias. In addition, this study examines older people whose diagnosis of epilepsy may have been made some time ago and we do not know if this diagnosis has been reassessed. However, we found that almost nine in ten people taking an AED in this study report keeping a seizure record. We found low numbers of participants reporting focal seizures, likely due to difficulties in identifying this seizure type in people with intellectual disability. Due to the observational cross-sectional study design, we can only describe associations between variables. The wide range in the categories <2 and ≥2 may lead to statistical differences being missed in some analyses. Some Mann Whitney U tests (denoted **) did not pass the assumption of homogeneity of variance (measured using the Levene test), thus necessitating caution in interpreting significant differences in groups analysed in these tests.

4.7 Conclusion

This Chapter highlights the extensive medication burden carried by people with epilepsy and intellectual disability. Almost half of participants took AED polytherapy with up to five AEDs been taken simultaneously. A quarter of participants were found to have an AED load ≥2 with a maximum participant AED load of 8.33, over eight times the average

maintenance dose. Many of the people taking AED polytherapy and having high AED loads continue to experience seizures. Each of the AED utilisation methods provided different but complementary information illustrating the complexity of treating epilepsy and the potential for overtreatment in people with intellectual disability.

Chapter 5

Antiepileptic drugs, occurrence of seizures and effect of co-administration of potential seizure threshold-lowering psychotropic drugs in adults with intellectual disability who have epilepsy

Monaghan, R., O'Dwyer, M., Luus, R., Mulryan, N., McCallion, P., McCarron, M., Henman, M.C. (2021). Antiepileptic drugs, occurrence of seizures and effect of co-administration of potential seizure threshold-lowering psychotropic drugs in adults with intellectual disability who have epilepsy. *Journal of Applied Research in Intellectual Disabilities* 34; 818-829 http://10.1111/jar.12857 [422]

5.1 Introduction

Epilepsy is a complex neurological disorder and a common condition among people with intellectual disability [33]. It is a spectrum disorder, estimated to encompass > 25 different syndromes and seizure types with variation in severity among individuals [31, 33]. Estimates of the prevalence of epilepsy vary. In people with intellectual disability, this may be the result of underlying population biases and methods employed [28, 35]. The prevalence of epilepsy in people without intellectual disability ranges from 0.6% to 1% [36-38]. In people with intellectual disability, estimates of 14%-44% have been reported [28, 39]. Prevalence rates of epilepsy have shown a strong relationship with level of intellectual disability; those with the most severe intellectual disability having a high prevalence of epilepsy (53%) and those with mild intellectual disability having a lower prevalence (18.9%)[38].

People with intellectual disability are acknowledged to have a lower life expectancy than the general population, with the probability of survival declining with greater severity of intellectual disability [27]. For those with co-existing epilepsy, the risk of mortality increases [46]. Additionally, high rates of refractory epilepsy have been reported in this population [425, 426]. A Swedish study by Forsgren et al. (1990) reported only 32% of epilepsy participants were seizure free in the previous year, while a UK study by Branford et al. (1998) found almost three quarters of participants continued to suffer seizures despite antiepileptic drug (AED) treatment.

Psychopathology is common both in people with epilepsy and in people with intellectual disability [40]. Cognitive and behavioural disturbances in epilepsy are due to a multitude of reasons including underlying neuro-pathologies, neuronal discharges (ictal and inter-ictal), AEDs, and psychosocial issues [448, 449]. Indeed, some studies suggest the

existence of a bidirectional relationship between epilepsy and psychiatric disorders [33, 450]. Psychopathology can be treated with different drugs, with the use of psychotropic drugs being commonplace in adults with intellectual disability [176]. Concern exists regarding overuse of psychotropic drugs, particularly antipsychotics, in this population which are often prescribed for challenging behaviour rather than a psychiatric diagnosis [175].

The pro-convulsive and interactive potential of certain psychotropic drugs, especially the antipsychotic clozapine, has given rise to some concern of psychotropic drugs worsening seizure control [340, 397, 427]. Factors contributing to the risk of seizures include the drug type, dosage, plasma concentration, the patient's own seizure threshold, any seizurogenic conditions e.g. epilepsy, brain injury, and the titration schedule [33, 397]. Long standing concerns regarding antidepressants and antipsychotics in triggering seizures have been consequential in impeding physicians in prescribing these psychotropic drugs to people with epilepsy [338]. However, Kanner et al. (2016) highlight that the reported seizures associated with antidepressants have occurred when taken at high doses and the occurrence of seizures may be the expression of the psychiatric disorder and not an iatrogenic effect of the psychotropic drug [338].

The aim of this study is to examine prevalence and patterns of AED use, frequency of seizures and the influence of co-prescribed psychotropic drugs with the potential to lower the seizure threshold in a nationally representative sample of older adults with intellectual disability who have epilepsy.

5.1.1 *The objectives of this study were:*

I. To describe the demographic characteristics of older adults with intellectual disability reporting a diagnosis of epilepsy and the patterns of their medication use with regards to AEDs and psychotropic drugs.

II. To examine the number and risk categorisation of co-prescribed psychotropic drugs with the potential to lower the seizure threshold and their influence on seizure frequency.

III. To examine the association between seizure frequency and demographic (gender, age, level of intellectual disability, type of residence) and clinical (type of therapy, categorised co-prescribed psychotropic drugs with the potential to lower the seizure threshold, type of seizures) factors.

5.2 Methods

5.2.1 Study design and participants

The data for this study were drawn from the third Wave of data collection, Wave 3 (2016/2017), of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA). IDS-TILDA is a nationally representative, longitudinal study of older adults with intellectual disability in Ireland aimed at investigating the ageing profile, physical and behavioural health, medication use, health service needs, social networks, living situations, community participation, and employment [28]. The original sample (Wave 1) was randomly selected from the National Intellectual Disability Database (NIDD) of Ireland, a database that collates information on people with intellectual disability that use or are entitled to avail of services. Inclusion criteria comprised of age ≥40 years with

intellectual disability (to reflect the lower longevity of people with intellectual disability), to be registered with the NIDD and to provide written consent to participate and/or family/guardian written agreement if required.

At Wave 1 (2009/2010), 753 people aged between 41 and 90 years with intellectual disability were recruited following consent and protocol completion, representing 8.9% of people aged 40 and over who were registered on the 2008 NIDD database [28] . Where an individual was not able to provide consent, a family member or guardian could sign a letter of agreement for their relative to participate. A comparison of demographics showed the IDS-TILDA sample to be representative of this population group [30]. Participants live independently/with family, in community group homes, or in residential/campus settings.

Level of intellectual disability is associated with daily functioning and intelligence quotient scores [8]- mild (50-69), moderate (35-49), severe (20-34) and profound (<20). Overall, 24% of participants had a mild intellectual disability, 46% a moderate intellectual disability, 24% a severe intellectual disability, 5% profound intellectual disability with approximately 5% having an unverified intellectual disability [30]. For this study, 609 people took part in Wave 3, with 44.2% male and 55.8% female. The age range for Wave 3 was 48 to 95 years with a mean of 59.1 years (SD: 8.81). The response rate for Wave 2 (2013/2014) respondents who were alive at Wave 3 was 95.5% [300].

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) standardised reporting guidelines for cross-sectional studies [421]. The IDS-TILDA study received ethics approval from the Faculty of Health Sciences Ethics Committee, Trinity College Dublin and 138 intellectual disability service providers.

5.2.2 Measures

A pre-interview questionnaire (PIQ) was sent to each participant one week before the interview. This allowed participants to prepare and locate any information required (e.g. medication data). At the time of interview, some PIQ entries including medication data were confirmed to improve accuracy.

CAPI (Computer Assisted Personal Interviewing) interviews were completed by trained field workers, experienced in working with people with intellectual disability, utilising small laptops to answer the study questions. Benefits included the automatic rerouting of questions and detection of inadmissible replies. Participants reported that they found CAPI less intimidating compared with a large paper based questionnaire [30]. There were three modes of interview completion: a respondent only interview conducted only with the participant, a proxy interview completed with a family member or carer very familiar with the person, or an interview with the participant and supported by a family member or carer. A combination of these approaches was utilised by a small number of participants.

The questions that were asked in this epilepsy study were asked as part of the overall IDS-TILDA Wave 3 Study. In terms of questions relating to epilepsy and the focus of this study, 20.8% of interviews were self-respondent only, 48.5% used a proxy interview style and 30.7% used a combination of self-respondent and proxy style. To act as a proxy, the individual is required to know the person with intellectual disability for a minimum of 6 months. People with intellectual disability were also involved in the design of pictorial explanations of material including consent forms in a bid to increase the accessibility of the study. Visual aids e.g. show cards were utilised to aid communication and understanding if required.

5.2.3 Reported diagnosis of epilepsy

In Wave 1**,** each participant/proxy was asked in the PIQ if the individual with intellectual disability was ever diagnosed by a doctor/relevant health professional with epilepsy [29]. A diagnosis of epilepsy was then confirmed in person during the face-to-face interview. In subsequent Waves (2 and 3) of the study, each participant/proxy was asked 'since your last interview, has a doctor ever told you that you have epilepsy?'. This allowed for the creation of a variable for prevalence *(Figure 2.6-1)*. Once a condition was confirmed, accuracy was further checked with the question: 'When were you first told by a Doctor that you had epilepsy?' If a case of epilepsy was uncertain, the participant/proxy was invited to confirm the diagnosis with any additional information written in a free text box in the CAPI. Diagnosis data was not available for one (0.2%) participant with medication data (*figure 5.2-1*).

5.2.4 Medication exposure

Participants were asked what medications they take regularly including prescribed, over-the-counter and herbal medicines [140]. Medicines were recorded on the PIQ as either brand or generic name/International non-proprietary name, dose, frequency, route of administration, and date when medication was commenced. All medication data were checked by trained interviewers at the time of interview. Medications were coded using the World Health Organisation Anatomical Therapeutic Chemical Classification (ATC) System by two pharmacists JOC and HA. For Wave 3, medication data was available for 549 (90.1%) participants *(figure 5.2-1)*. Of the 60 participants missing medication data, four (6.7%) participants refused. Fifteen (25%) of these participants and/or proxies did not return the PIQ which contained the participant's medication record detailing medication

usage. Medication data were not available for the remaining 41 (68.3%) participants. Supplements and herbal medicines were excluded from the definition of a medicine. All medication entries were independently reviewed and confirmed by the author (RM).

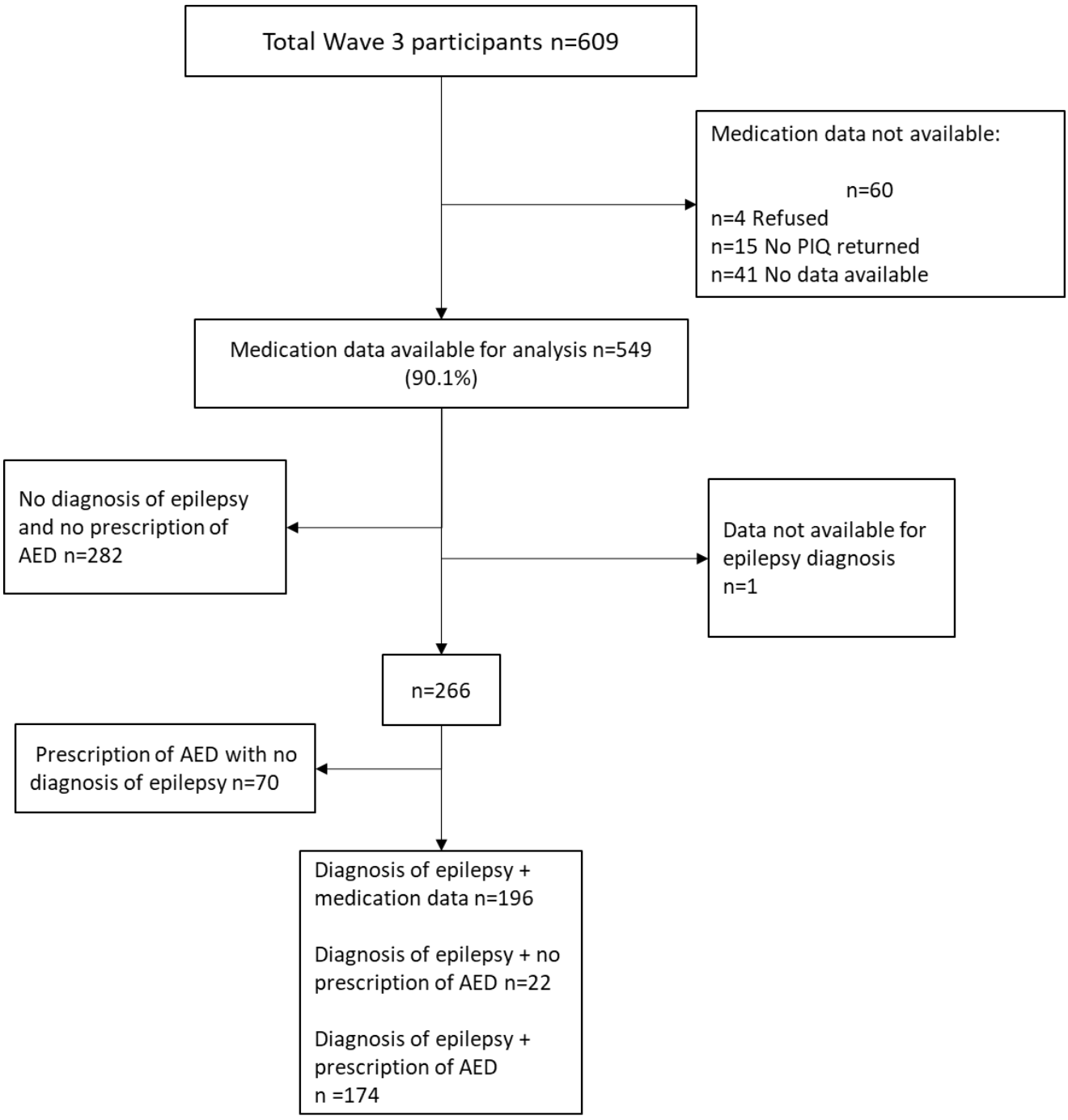


Figure 5.2-1 *Flow chart of epilepsy diagnosis and AED use*

5.2.5 Drug class categorisation

Antiepileptic drugs were defined as those with the ATC code N03A (*Table 3.3-2)*. All AEDs were separated into those taken by a participant with a diagnosis of epilepsy and those without a diagnosis. Psychotropic co-medication was assessed: defined as antipsychotics (N05A), antidepressants (N06A), anxiolytics (N05B), hypnotics & sedatives (N05C), drugs for dementia (N06D), and anti-cholinergic drugs (N04A). Lithium was classified as a mood stabiliser and prochlorperazine was not included in the antipsychotic category as all the doses reported were PRN and fell within the recommended range used for the treatment of Meniere's syndrome, labyrinthitis and nausea and vomiting (10-40mg daily).

Regarding medication with the potential to lower the seizure threshold, antipsychotics, antidepressants and lithium were examined. Clobazam was included in the AED category as it is primarily used for epilepsy. Midazolam was excluded from the N05C class as it is indicated for acute seizure control only [451]. Participant exposure to AEDs was then categorised as 'monotherapy' and 'polytherapy'. Antiepileptic polytherapy was defined as concurrent treatment with two or more regular AEDs. Drugs indicated for the treatment of acute seizures as rescue medication were recorded separately from the other AEDs and included midazolam and lorazepam.

5.2.6 Concurrent medications that may lower the seizure threshold

The prescribing of co-medications that are listed as having the potential to lower the seizure threshold or contraindicated for use in people with epilepsy was examined using the Maudsley Prescribing Guidelines in Psychiatry (2018) *(Appendix 29)* [330] and categorised as low, probably low, moderate, and high risk. For the purposes of analysis, medications classified as low and probably low risk are combined as low risk.

5.2.7 Covariates

Covariates investigated were gender (male/female), age (<50/50-64/65+ years), level of intellectual disability (mild/moderate/severe/profound/unverified), place of residence (independent/family/community group home/residential/campus setting), psychotropic medication classes, comorbid mental health conditions and concurrent psychotropic medications that could potentially lower the seizure threshold. The phrasing of the mental health questions asked in this study can be found elsewhere [176].

Psychotic disorder includes hallucinations, schizophrenia and psychosis. Mood disorder includes depression, manic depression, mood swings, and emotional problems and anxiety disorder includes anxiety and PTSD. However, there were no reports of PTSD in this study. Seizure frequency was categorised as none in the last year and at least one in the last year. The latter category includes daily, weekly (not daily), more than once/month (not weekly) and less than once/month. The categorised seizure type is based on 2017 International League Against Epilepsy (ILAE) classification of seizures [56]. Generalised seizures include tonic-clonic, tonic, clonic, atonic, myoclonic and absence. Focal Seizures include simple partial seizures and complex partial seizures. Residential/campus settings were defined as living arrangements where 10 or more people share a single living unit or where the living arrangements are campus based. Community group homes are in a community setting with staff support for small groups of people with intellectual disabilities.

5.2.8 Statistical analyses

All statistical analyses were carried out using the Statistical Package for Social Sciences, version 25.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at <0.05. Descriptive statistics were used to describe the characteristics of the sample being studied. The Chi-Squared (χ^2) test for independence was utilised to test for significant association between categorical variables. Fisher's Exact test was used to test for significant association between variables where the sample size in subgroups was small (n<5). For assignment of participant risk category for potential seizure threshold-lowering medication when multiple medications were taken, a hierarchical system was used whereby risk was assigned as the highest level of risk of the medication taken e.g. if the participant was taking one low risk and one high risk medication then classified as high risk.

Binary logistic regression was performed to identify factors associated with seizure frequency. In our model, the possible outcomes for the dichotomous dependent variable were no seizures in the last year (reference category) and at least one seizure in the last year. All the variables were entered into the regression model simultaneously. Demographic variables included in the model were gender, age, level of intellectual disability, and place of residence. Clinical variables with significance p<0.10 at bivariate level relating to regular AED medication (type of therapy) and seizures (type of seizures) were included in the model along with the variable - medications categorised by seizure risk - which is of interest in this study. The variable 'number of potential seizure threshold-lowering medications' was not included in the model as it proved highly correlated with the variable 'medications categorised by seizure risk'.

Variables that had small numbers in their subgroups were collapsed. This included type of residence where participants who lived independently or with family were

collapsed with participants living in community group homes. Other variables that were collapsed for this reason were type of therapy where participants taking no AEDs were combined with participants taking monotherapy, type of seizures where participants with focal seizures (n=3) were combined with unknown seizures into a new variable 'other seizures' and risk categorisation of potential seizure threshold-lowering drugs where participants classified as taking moderate risk drugs were combined with participants (n=17) taking high risk drugs.

The variance inflation factor (VIF) was used to test for multicollinearity between independent variables. The VIF for all variables was below the designated threshold of >2.0 indicating no multicollinearity. The logistic regression results are presented as odds ratios with corresponding 95% confidence intervals. To determine the sample size for the logistic regression, we followed the guidelines of Peduzzi et al. (1996) and used n=10k/p where k is the number of covariates (independent variables), p is the smallest of the proportions of negative or positive cases in the population and k/p is the number of events per variable [408]. Seven covariates (k) were included in our model and p (at least one seizure in the last year) was 77/190=0.405. Therefore, the minimum number of cases needed was 173. Our sample for logistic regression (n=182) exceeded this minimum requirement.

5.3 Results

5.3.1 Demographic characteristics with respect to epilepsy diagnosis

In total, 609 people participated in Wave 3, with medication data available for 90.1% (n=549) of participants. Of the 548 participants who provided medication data with confirmed epilepsy status, 44.5% (n=244) reported taking an AED, with 35.8% (n=196) reporting a doctor's diagnosis of epilepsy. Of those with a diagnosis of epilepsy (n=196),

88.8% (n=174) were prescribed a regular AED. A diagnosis of epilepsy without being prescribed a regular AED was reported by 11.2% (n=22) of participants.

Demographic characteristics are presented in *Table 5.3-1.* The majority with epilepsy lived in residential/campus settings (59.2%, n=116) and a significant association was found for reporting epilepsy and place of residence (p<0.001). 66.3% (n=130) of those with epilepsy were aged 50-64 years with 58.2% (n=114) female. There was a significant association at bivariate level between reporting epilepsy and level of intellectual disability (p<0.001). 42.2% (n=79) of those with epilepsy were found to have a severe/profound intellectual disability. 40.8% (n=80) of those with epilepsy were exposed to AED monotherapy and 48.0% (n=94) exposed to AED polytherapy. The most frequently reported AEDs in our study were mood stabilising AEDs - valproic acid, carbamazepine and lamotrigine *(Table 3.3-2)*. Of participants with an epilepsy diagnosis, 39.3% (n=77) were prescribed antipsychotics, 30.6% (n=60) antidepressants and 17.3% (n=34) anxiolytics. In contrast, of those without an epilepsy diagnosis, 47.7% (n=168) were prescribed antipsychotics, 35.2% (n=124) antidepressants and 13.6% (n=48) anxiolytics.

Table 5.3-1 Bivariate analysis of demographic and clinical factors of participants with an epilepsy diagnosis (n=196) and participants without an epilepsy diagnosis (n=352)

Characteristic	All participants with medication data n=548 n (%)	With epilepsy n=196 n (%)	Without epilepsy n=352 n (%)	P value Chi Square
Gender				0.665
Male	236 (43.1)	82 (41.8)	154 (43.8)	
Female	312 (56.9)	114 (58.2)	198 (56.2)	
Age group (years)				0.475
<50	64 (11.7)	21 (10.7)	43 (12.2)	
50-64	345 (63.0)	130 (66.3)	215 (61.1)	
65+	139 (25.4)	45 (23.0)	94 (26.7)	
Level of intellectual disability	n=506	n=187	n=319	**<0.001***
Mild	121 (23.9)	31 (16.6)	90 (28.2)	
Moderate	231 (45.7)	77 (41.2)	154 (48.3)	
Severe/profound	154 (30.4)	79 (42.2)	75 (23.5)	
Place of residence				**<0.001***
Independent	78 (14.2)	20 (10.2)	58 (16.5)	
Community group home	222 (40.5)	60 (30.6)	162 (46.0)	
Residential/campus	248 (45.3)	116 (59.2)	132 (37.5)	
Type of therapy				**<0.001***
AED monotherapy	135 (24.6)	80 (40.8)	55 (15.6)	
AED polytherapy	109 (19.9)	94 (48.0)	15 (4.3)	
No AED therapy	304 (55.5)	22 (11.2)	282 (80.1)	
Comorbid mental health condition				
Psychotic disorder	44 (8.0)	14 (7.1)	30 (8.5)	0.569
Mood disorder	180 (32.8)	74 (37.8)	106 (30.1)	0.068
Anxiety disorder	177 (32.3)	67 (34.2)	110 (31.3)	0.481
Psychotropic medications				
Antipsychotics	245 (44.7)	77 (39.3)	168 (47.7)	0.057
Antidepressants	184 (33.6)	60 (30.6)	124 (35.2)	0.273
Anxiolytics	82 (15.0)	34 (17.3)	48 (13.6)	0.243
Hypnotics & sedatives	51 (9.3)	22 (11.2)	29 (8.2)	0.249
Lithium	16 (2.9)	5 (2.6)	11 (3.1)	0.702
Drugs for dementia	15 (2.7)	11 (5.6)	4 (1.1)	**0.002***
Anti-cholinergic N04A	71 (13.0)	27 (13.8)	44 (12.5)	0.670

n=196: Participants with diagnosis of epilepsy. n=352: Participants with no diagnosis of epilepsy
n= 548: All participants with medication data and confirmed epilepsy status. n=1 individual with medication data excluded from analysis as no confirmed epilepsy status. **Statistically significant results marked in bold and with an asterisk *.**

5.3.2 Relationship between demographic and clinical factors and seizure frequency

When seizure frequency was categorised (*Table 5.3-2*) in participants with epilepsy and seizure data (n=190), 59.5% (n=113) of participants reported no seizure in the last year. Of those reporting at least one seizure in the last year, 61.0% (n=47) were female (p=0.398) and 68.8% (n=53) were prescribed AED polytherapy (p<0.001).

31.1% (n=59) of participants took one potential seizure threshold-lowering medication and 22.1% (n=42) took two or more. 76.2% (n=32) of those taking two or more potentially seizure threshold-lowering medications reported no seizures in the last year (p=0.044). Of those reporting at least one seizure in the last year, 23.4% (n=18) were classified as taking at least one low risk medication whilst 24.7% (n=19) were classified as taking at least one moderate/high risk medication. Moreover, 51.9% (n=40) of those reporting at least one seizure in the last year took no medication with the potential to lower the seizure threshold.

Table 5.3-2 Bivariate analysis of seizure frequency among those with epilepsy (n=190)

Characteristic	Total n=190 n (%)	None in the last year n=113 n (%)	At least one in the last year n=77 n (%)	P value Chi Square
Gender				0.398
Male	81 (42.6)	51 (45.1)	30 (39.0)	
Female	109 (57.4)	62 (54.9)	47 (61.0)	
Age group (years)				0.176
<50	20 (10.5)	12 (10.6)	8 (10.4)	
50-64	125 (65.8)	69 (61.1)	56 (72.7)	
65+	45 (23.7)	32 (28.3)	13 (16.9)	
Type of residence				0.398
Independent/family/community group home	76 (40.0)	48 (42.5)	28 (36.4)	
Residential/campus	114 (60.0)	65 (57.5)	49 (63.6)	
Level of intellectual disability	n=182	n=110	n=72	0.500
Mild	30 (16.5)	21 (19.1)	9 (12.5)	
Moderate	74 (40.6)	43 (39.1)	31 (43.1)	
Severe/profound	78 (42.9)	46 (41.8)	32 (44.4)	
Cause of intellectual disability	n=186	n=111	n=75	0.051
Down Syndrome	28 (15.1)	11 (10.0)	17 (22.7)	
Other aetiology	48 (25.8)	29 (26.1)	19 (25.3)	
Unknown cause	110 (59.1)	71 (63.9)	39 (52.0)	
Types of epilepsy				**<0.001***
Generalised seizures	105 (55.3)	45 (39.8)	60 (77.9)	
Other seizures	85 (44.7)	68 (60.2)	17 (22.1)	
Type of therapy				**<0.001***
No AED therapy/monotherapy	98 (51.6)	74 (65.5)	24 (31.2)	
Polytherapy	92 (48.4)	39 (34.5)	53 (68.8)	
Emergency medicines prescribed				
Buccal midazolam	103 (54.2)	45 (39.8)	58 (75.3)	**<0.001***
Clobazam	3 (1.6)	1 (0.9)	2 (2.6)	0.567 [a]
Lorazepam	1 (0.5)	1 (0.9)	0 (0)	1.000 [a]
Comorbid mental health condition				
Psychotic disorder	13 (6.8)	9 (8.0)	4 (5.2)	0.458
Mood disorder	72 (37.9)	49 (43.4)	23 (29.9)	0.060
Anxiety disorder	66 (34.7)	43 (38.1)	23 (29.9)	0.245

Table 5.3-2 Bivariate analysis of seizure frequency among those with epilepsy (n=190) *(Continued*)

Characteristic	Total n=190 n (%)	None in the last year n=113 n (%)	At least one in the last year n=77 n (%)	P value Chi Square
Categorised total number of potential seizure threshold-lowering psychotropic medications (Median=1, Max=5)				**0.044***
1	59 (31.1)	32 (28.3)	27 (35.1)	
≥2	42 (22.1)	32 (28.3)	10 (13.0)	
No seizure threshold-lowering medication	89 (46.8)	49 (43.4)	40 (51.9)	
Categorised potential seizure threshold-lowering psychotropic medication risk				0.332
Low risk medication	43 (22.6)	25 (22.1)	18 (23.4)	
Moderate/high risk medication	58 (30.5)	39 (34.5)	19 (24.7)	
No seizure threshold-lowering medication	89 (46.8)	49 (43.4)	40 (51.9)	

n=190: participants with seizure data. n=6: participants with epilepsy diagnosis excluded from analysis. [a] Fisher's Exact Test (two-sided). **Statistically significant results marked in bold and with an asterisk *.**

There was no difference in the reporting of seizures between antipsychotics, lithium and antidepressants *(Table 5.3-3).*

Table 5.3-3 Bivariate analysis of potential seizure threshold-lowering psychotropic medications vs seizure frequency (n=190)

	Potential seizure threshold-lowering psychotropic medication	Total n=190 n (%)	None in the last year n=113 n (%)	At least one in the last year n=77 n (%)	P value
	Antipsychotics				
High risk	Chlorpromazine	12 (6.3)	11 (91.7)	1 (8.3)	**0.029***
	Flupentixol, Promazine, Zuclopenthixol	5 (2.6)	4 (80.0)	1 (20.0)	NS
Moderate risk	Olanzapine	29 (15.3)	22 (75.9)	7 (24.1)	0.051[a]
	Quetiapine	9 (4.7)	5 (55.6)	4 (44.4)	1.000
Low risk	Risperidone	23 (12.1)	14 (60.9)	9 (39.1)	0.884[a]
	Aripiprazole, Haloperidol, Trifluoperazine	9 (4.7)	7 (77.8)	2 (22.2)	NS
	Mood Stabiliser				
Moderate risk	Lithium	5 (2.6)	3 (60.0)	2 (40.0)	1.000
	Antidepressants				
High risk	Trimipramine	1 (0.5)	1 (100.0)	0 (0)	1.000
Moderate risk	Trazodone	7 (3.7)	4 (57.1)	3 (42.9)	1.000
	Venlafaxine	8 (4.2)	4 (50.0)	4 (50.0)	0.717
Low risk	Mirtazapine	11 (5.8)	9 (81.8)	2 (18.2)	0.204
	Escitalopram	17 (8.9)	9 (52.9)	8 (47.1)	0.565[a]
	Citalopram, Duloxetine, Fluoxetine, Paroxetine, Sertraline	19 (10.0)	15 (79.0)	4 (21.0)	NS

[a]Chi-squared (χ^2) test. NS (Not significant). n=190 participants with seizure frequency data. Fisher's Exact Test (two-sided).

Statistically significant results marked in bold and with an asterisk *.

5.3.3 Factors associated with seizure frequency

The binary logistic regression model (*Table 5.3-4)* showed that AED polytherapy [OR 4.974 (2.337-10.588), P<0.001], living in a residential/campus setting [OR 2.408 (1.068-5.428), P=0.034] and having generalised seizures [OR 4.940 (2.333-10.461), P<0.001] were significantly associated with reporting at least one seizure in the last year after adjusting for confounders. Participants taking at least one medication classified as moderate/high risk [OR 0.338 (0.141-0.807), P=0.015] were significantly less likely to report at least one seizure in the last year compared to participants taking no seizure threshold-lowering medication. Gender, age, or level of intellectual disability was not significantly associated with reporting at least one seizure in the last year.

Table 5.3-4 Binary logistic regression of factors associated with seizure frequency among older people with intellectual disability (n=182)

Characteristic	Odds ratio (95% CI)	P value
Gender		
Male	1 (reference)	
Female	1.733 (0.832-3.612)	0.142
Age (years)		
<50	1 (reference)	
50-64	1.251 (0.369-4.249)	0.719
65+	0.696 (0.172-2.816)	0.611
Level of intellectual disability		
Mild	1 (reference)	
Moderate	1.315 (0.445-3.889)	0.621
Severe/profound	1.172 (0.381-3.602)	0.781
Type of AED therapy		
No AED/monotherapy	1 (reference)	
Polytherapy	**4.974 (2.337-10.588)**	**<0.001***
Type of residence		
Independent/family/ community group home	1 (reference)	
Residential/campus	**2.408 (1.068-5.428)**	**0.034***
Categorised potential seizure threshold lowering psychotropic medication risk		
No seizure threshold-lowering medications	1 (reference)	
Low risk	0.706 (0.272-1.833)	0.475
Moderate/high risk	**0.338 (0.141-0.807)**	**0.015***
Types of seizures		
Other seizures	1 (reference)	
Generalised seizures	**4.940 (2.333-10.461)**	**<0.001***

Reference category: seizure frequency- none in the last year
Cox & Snell R^2 =0.271 Nagelkerke R^2 = 0.367
Reference groups- male, age <50 years, mild intellectual disability, no AED therapy/monotherapy, independent/family/community group home, taking no seizure threshold-lowering medications and other seizures.
Statistically significant results marked in bold and with an asterisk*.

5.4 Discussion

5.4.1 *Key findings*

To the best of our knowledge, this is the first study to examine the influence on seizure frequency, of risk categorised psychotropic drugs with the potential to lower the seizure threshold in a population of older adults with epilepsy and intellectual disability. We found the prevalence of epilepsy to be 35.8% and 40.5% of those with epilepsy reported at least one seizure in the previous year. A higher proportion of those with epilepsy who reported at least one seizure in the previous year received AED polytherapy and have buccal midazolam prescribed. Over three in ten participants with epilepsy were prescribed one psychotropic medication with the potential to lower the seizure threshold whilst over one in five were prescribed two or more. Participants taking at least one medication classified as moderate/high risk for lowering the seizure threshold were significantly less likely to experience a seizure compared to participants taking no medication of this class after adjusting for confounders. We did not find any association between the reporting of a diagnosis of a mental health condition and epilepsy, or between such a diagnosis and the reporting of seizures among those with epilepsy.

5.4.2 Comparisons with other studies

Both first and second generation antipsychotics have been implicated in raising seizure risk [199, 200]. With first generation antipsychotics, the greatest risk is associated with chlorpromazine [201]. Chlorpromazine was the most frequently co-prescribed high risk psychotropic medicine in our study, but 91.7% of participants taking chlorpromazine reported no seizure in the last year *(Table 5.3-3).* In our study, the maximum daily dose

prescribed was 500mg daily *(Appendix 30)* which is half that of those reported in the studies that raised concerns (>1000mg/day) [452].

Among second generation antipsychotics, we found that over three-quarters of participants taking olanzapine, over half taking quetiapine (both classed as moderate risk) and over 60% taking risperidone (low risk) reported no seizures in the last year *(Table 5.3-3)*. Lertxundi et al. (2013) found that second generation antipsychotics had more frequent spontaneous seizure reports than first generation antipsychotics from analysis of international pharmacovigilance databases (FEDRA, Eudravigilance, and VigiBase) and that olanzapine and quetiapine, may elicit a higher risk than previously thought [200]. Alper et al. (2007) reported higher incidence of seizures with these drugs compared to placebo [199] and olanzapine was reported to be associated with dose dependent electroencephalogram (EEG) slowing or epileptiform abnormalities [390]. The second generation antipsychotic clozapine, classified as high risk, was not prescribed in this study.

Concern surrounding the effect of antidepressants on the seizure threshold emerged from a priori assumption based on uncontrolled, retrospective case reports and EEG studies of patients treated with some psychotropic drugs, especially the tricyclic antidepressants (TCA) [199, 284]. However, a double-blind crossover study of the TCA imipramine showed a decrease in seizures in people suffering absence and myoclonic-astatic seizures [453], and in 1985, a double-blind trial of antidepressants in people with epilepsy compared nomifensine, amitriptyline, and placebo and found no differences in seizure frequency between the groups [454]. The only high risk antidepressant prescribed in our study was the TCA trimipramine and no seizures were reported, while of those classed as moderate risk, trazodone and venlafaxine, 8 out of 15 reported no seizures. Of those classed as low risk, 14 of 47 reported at least one seizure in the last year and studies

involving mirtazapine [194], citalopram [194-196], sertraline [197, 198] and fluoxetine [198] found positive effects on seizure control.

Four antidepressants: clomipramine, bupropion, amoxapine, and maprotiline are reported to be associated with a higher incidence of seizures [199, 360]. High doses of amitriptyline (>200mg) have also been associated with increased seizures [284]. None of these higher risk antidepressants were prescribed in this study. SSRIs (Selective Serotonin Reuptake Inhibitors) and SNRIs (Serotonin Noradrenaline Reuptake Inhibitors) have been recommended as first line in those with a diagnosis of epilepsy [337, 363] and comprise the majority of antidepressants prescribed in our study.

Psychotropic polypharmacy was found to be prevalent with one in five participants taking two or more psychotropic medications with the potential to lower the seizure threshold. However, 76% of these reported no seizures in the last year indicating no cumulative increased seizure risk. Intraclass psychotropic polypharmacy is also prevalent in people with intellectual disability and has been reported, particularly for antipsychotics in this cohort [176], yet there is no discernible trend of an elevated seizure risk. The influence of psychotropic polypharmacy is complex since other psychotropics possess anticonvulsant properties, namely anxiolytics and hypnotics; these may have contributed to a reduction in the occurrence of seizures, although they were prescribed to participants with epilepsy to a lower extent (17.3% and 11.2% respectively) than antipsychotics and antidepressants. Alternatively, the plasma level of some AEDs may be raised because of cytochrome P450 inhibition by antidepressants such as SSRIs [455, 456]. Indeed, 51.9% of participants reporting at least one seizure in the last year took no seizure threshold-lowering psychotropic medication indicating other factors were contributing to seizure risk [397].

5.4.3 Implications for practice

The clinical complexity of prescribing for a person with intellectual disability, epilepsy, and mental health conditions is considerable. Medication information to support prescribing cannot provide detailed guidance where evidence is limited. However, for most psychotropic drugs prescribed appropriately within the therapeutic dose range, seizure incidence is reported to be <0.5% when other risk factors are excluded [41]. In this study, very few drugs classed as high risk were prescribed and recommended doses were used suggesting that prescribers were cautious, yet the use of multiple psychotropics and AEDs suggests that clinical problems were being addressed. The lack of any association between seizure threshold-lowering drugs and seizure occurrence set against the extensive use of AED polytherapy and the substantial reporting of seizures indicates that control of epilepsy in people with intellectual disability remains an unattained goal.

In Ireland, the provision of services for people with intellectual disability varies geographically in scope and scale. Until recently, the specialist care for those with epilepsy was often provided by psychiatrists and although this is changing with neurology teams becoming available in some areas, co-ordination of care will be challenging. One factor adding to the level of challenge is deinstitutionalisation. This is an important policy objective but because of the complex healthcare needs and because of vulnerability, clinically and socially, the professionals providing Primary Care will require both adequate support and resources to manage the risks when the pathways of care are altered. Multiple morbidity and prescribers will necessitate clear and comprehensive networks for communication so that multidisciplinary medication reviews can be conducted regularly, followed up, and communicated to patients and to carers so that harm from polypharmacy can be avoided [457].

5.4.4 Strengths of study

Our study used a large, nationally representative sample of older adults with intellectual disability, representative of the older population of people with intellectual disability in Ireland. We obtained thorough medication data for 90.1% of Wave 3 participants which was confirmed by interviewers at the time of interview. The design of the medication record allowed for high quality acquisition of medication data. All participants and/or their proxies received the PIQ which contained the medication record one week prior to the face to face interview giving them an opportunity to consult the participants' medication/health records.

5.4.5 Limitations of study

Due to missing medication data, 19 participants with epilepsy were excluded from this study. We had seizure data for 190 participants therefore six participants were excluded from the seizure analysis. Our sample was under-powered to evaluate small sub-groups. Data collected regarding medication use, diagnosis of epilepsy, and concomitant mental health conditions was based on participants' self-report or proxy report which may result in bias. Dosage was not taken into account in our risk categorisation. Our study did not take into consideration the risk of drug interactions between AEDs and psychotropic drugs. We found low numbers of participants reporting focal seizures, likely due to difficulties in identifying this seizure type in people with intellectual disability. Due to the observational cross-sectional study design, we can only describe associations between seizure frequency and demographic and clinical factors. This study was not randomised to match the activities of psychotropic medications or AEDs in relation to seizures with controls. In our multivariate analysis, any probable bias was removed where possible by adjusting for

confounders. Nevertheless, residual confounding factors may remain. A further limitation of this study is the possible under-reporting of seizures which may under-represent seizure risk. However, as the majority of participants with epilepsy in our study live in residential/campus settings with nursing supervision, it is unlikely that this occurred frequently. Nevertheless, the possibility that staff may not observe seizures and participants' may not accurately self-report seizures cannot be discounted.

5.5 Conclusion

Our findings suggest psychotropic medication, in therapeutic dosages, recommended to be avoided or used with caution in people with epilepsy did not provoke increased seizure frequency in this intellectual disability cohort. However, a significant proportion of participants continued to report seizures. Intensive management and investigation are required to protect these people from avoidable harm [457]. This study also highlights the significant psychiatric comorbidity associated with a dual diagnosis of epilepsy and intellectual disability and the importance of effective pharmacotherapy.

Chapter 6

The relationship between antiepileptic drug load and challenging behaviours in older adults with intellectual disability and epilepsy

Monaghan, R., O'Dwyer, M., Luus, R., Mulryan, N., McCallion, P., McCarron, M., Henman, M.C. (2021). The relationship between antiepileptic drug load and challenging behaviours in older adults with intellectual disability and epilepsy. *Epilepsy & Behavior* https://doi.org/10.1016/j.yebeh.2021.108191
[458]

6.1 Introduction

The burden of epilepsy is associated with psychiatric, cognitive, and behavioural comorbidity [87, 459], factors more prevalent in people with intellectual disability [87]. Challenging behaviours occur in over 50% of people with intellectual disability, and are severe in 10% [460, 461]. Self-injurious behaviour (SIB), aggression, destruction, disruptive, and stereotyped behaviour are frequently observed, resulting sometimes with the person being excluded from services or activities, or subjected to restrictive practices [462-464]. The aetiology of challenging behaviour is multifactorial, including physical symptoms, for example, constipation, pain; behavioural phenotypes; psychiatric disorders; psychological or social factors; and attention seeking and avoidance behaviours [463]. A meta-analytic study examining risk factors for challenging behaviour in people with intellectual disability found people with severe/profound intellectual disability were more likely to exhibit challenging behaviours (self-injury and stereotypy) compared to those with a mild/moderate level of intellectual disability [104].

Systematic reviews examining epilepsy as a possible marker [462] for challenging behaviours in people with intellectual disability have yielded inconclusive results [87, 462, 465, 466], with some studies showing an increased prevalence in people with epilepsy and additional factors such as seizures of greater frequency and/or severity, medication side effects, and generalised EEG activity [466]. A meta-analysis of studies of adults with intellectual disability showed a significantly higher rate of challenging behaviours in the epilepsy group compared with the non-epilepsy group, and a significantly higher rate of aggression and SIB in the epilepsy group [465]. However, the authors suggested that the effects may not be clinically significant because of small effect sizes [465].

Antiepileptic drugs (AEDs) may also affect mood and behaviour in people with epilepsy [223] and intellectual disability [467]. The psychotropic effects of AEDs arise from the AEDs mechanism of action (GABA or glutamate), underlying neurological condition, and familial or personal history of psychiatric disorders [209, 468]. Antiepileptic drugs with mood stabilising properties (valproic acid, carbamazepine, lamotrigine) [40] are known to have positive effects on mental health and are used in the treatment of bipolar disorder [222]. However, lamotrigine has been reported to cause aggression in people with intellectual disability [231]. Other AEDs associated with a higher risk of precipitating challenging behaviours in people with intellectual disability include clobazam, clonazepam, levetiracetam, phenobarbital, perampanel, topiramate, tiagabine, vigabatrin and zonisamide [465].

It is also suggested that people with epilepsy have a greater susceptibility to adverse behavioural effects of AEDs [222]. Levetiracetam has been known to incite aggressive behaviour and irritability [223]. A systematic review examining the behavioural effects of levetiracetam in adults with epilepsy, cognitive disorders, or an anxiety disorder during clinical trials found adverse behavioural effects occurred significantly more frequently among patients with epilepsy compared to patients with cognition or anxiety difficulties being treated with levetiracetam [469].

Negative behavioural effects of AEDs may be associated with a higher AED load [467]. Total drug load has been defined as *"the amount of drug exposure for a certain indication"* [266]. Total AED load can be quantified as the sum of the prescribed daily dose (PDD) divided by the defined daily dose (DDD) (average maintenance dose) ratios (PDD/DDD) for each AED prescribed [443]. Use of AED polytherapy and high doses with rapid titration is associated with greater adverse cognitive and behavioural effects [264,

265]. Indeed, consensus guidelines rank the impact of AEDs on behaviour and cognition as second out of 11 priority areas [164].

The aim of this study is to examine the prevalence of challenging behaviours and its relationship with AEDs and AED load, in older adults with intellectual disability who report a diagnosis of epilepsy.

6.1.1 The objectives of this study were:

I. To describe the demographic characteristics of older adults with intellectual disability reporting a diagnosis of epilepsy and exhibiting challenging behaviours.
II. To examine the clinical characteristics of participants in this epilepsy cohort, exhibiting SIB, aggressive/destructive and/or stereotyped behaviour, and the patterns of AED use, type of AED therapy, AED load, and co-prescribed psychotropic drugs.
III. To examine the relationship between AED load and demographic and clinical characteristics and investigate its association with exhibiting SIB, aggressive/ destructive and stereotyped behaviour.

6.2 Methods

6.2.1 Study design

The data for this study were drawn from Wave 3 (2016/2017) of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA). IDS-TILDA is a nationally representative, longitudinal study of older adults with intellectual disability in Ireland aimed at investigating the ageing profile, physical and behavioural health, medication use,

health service needs, social networks, living situations, community participation, and employment [28]. The original sample (Wave 1) was randomly selected using the National Intellectual Disability Database (NIDD) of Ireland, a database that gathers information on people with intellectual disability that use or are entitled to avail of services. Inclusion criteria consisted of age ≥40 years with intellectual disability (to reflect the lower longevity of people with intellectual disability), to be registered with the NIDD, and to provide written consent to participate and/or family/guardian written agreement if required.

6.2.2 Participants

A total of 753 people aged between 41 and 90 years with intellectual disability were recruited in Wave 1 (2009/2010) following consent and protocol completion, representing 8.9% of people aged 40 years and over who were registered on the 2008 NIDD database [28]. If an individual could not provide consent themselves, a family member or guardian could sign a letter of agreement for their relative to participate. McCarron et al. (2011) undertook a comparison of demographics, showing the IDS-TILDA sample to be representative of this population group [30]. Level of intellectual disability is associated with intelligence quotient scores [318] - mild (50-69), moderate (35-49), severe (20-34) and profound (<20). Case notes for each participant where possible, confirmed the correct classification. For this study, the number of people taking part in Wave 3 was 609 with 44.2% male and 55.8% female [300]. The age range for Wave 3 was 48 to 95 years with a mean of 59.1 years (SD: 8.81) [300]. Overall in Wave 3, 24.8% had a mild intellectual disability, 46.2% a moderate intellectual disability and 29.1% a severe/profound intellectual disability [300]. Participants live independently/with family, in community

group homes, or in residential/campus settings. The response rate for Wave 2 (2013/2014) respondents who were alive at Wave 3 was 95.5% [300].

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) standardised reporting guidelines for cross-sectional studies [470]. The IDS-TILDA study received ethics approval from the Faculty of Health Sciences, Ethics Committee at Trinity College Dublin and 138 intellectual disability service providers. To comply with the General Data Protection Regulation (GDPR) and the Irish Health Research Regulations (2018), a consent declaration waiver was obtained for the study from the Irish Health Research Consent Declaration Committee (HRCDC), for any data supplied in the past or future by people unable to consent themselves.

6.2.3 Measures

A pre-interview questionnaire (PIQ) was sent to each participant one week prior to the interview taking place. This gave participants time to prepare and locate any information that may be needed (e.g. medication data), enhancing the reliability of the data. CAPI (Computer Assisted Personal Interviewing) interviews were completed by trained field workers, experienced in working with people with intellectual disability, utilising laptops to answer the study questions. Advantages included the automatic rerouting of questions and detection of inadmissible replies. Different interviewing styles were undertaken by participants depending on their level of intellectual disability and capacity to communicate. There were three styles of interviewing; self-report, proxy assisted (where the person with intellectual disability answered some but not all questions), and proxy only, where the carer/support person answered the questions on the persons' behalf. To act as a proxy, the individual was required to know the person with intellectual disability for a minimum

of six months. In terms of questions relating to epilepsy and the focus of this study, 20.8% of interviews were self-report only, 48.5% used a proxy interview style and 30.7% used a combination of self-report and proxy style [422].

6.2.4 Report of a diagnosis of epilepsy

During Wave 1 data collection, each participant/proxy was asked in the PIQ if the individual with intellectual disability was ever diagnosed by a doctor/relevant health professional with epilepsy. In the face-to-face interview, confirmation of a report of a diagnosis of epilepsy and medications in the PIQ were made. In successive Waves (2 and 3) of the study, each participant/proxy was asked 'since your last interview, has a doctor ever told you that you have epilepsy?'. Consequently, a variable for prevalence was created [422]. Following reported epilepsy diagnosis confirmation, subsequent questions were asked regarding the reported diagnosis e.g. 'When were you first told by a Doctor that you had epilepsy?'. Additional free text detailed and confirmed any additional information. Reported epilepsy diagnosis data was not available for one (0.2%) participant with medication data (*Figure 6.2-1*) [422].

6.2.5 Medication exposure

Participants were asked which medications they take on a regular basis including prescribed, over-the-counter and herbal medicines [140]. Medicines were recorded on the PIQ as either brand or generic name/International non-proprietary name, dose, frequency, route of administration, and date when medication was commenced. At the time of interview, trained interviewers checked all medication data for accuracy. Medications were coded using the World Health Organisation Anatomical Therapeutic Chemical

Classification (ATC) System by two pharmacists JOC and HA [422]. For Wave 3, medication data was available for 549 (90.1%) participants (*Figure 6.2-1*). Of the 60 participants missing medication data, 4 (6.7%) participants refused to provide this data. 15 (25%) participants and/or proxies did not return the PIQ which contained the medication record detailing the participants' medication usage. Medication data was not available for the remaining 41 (68.3%) participants [422]. The author (RM) reviewed and confirmed all medication entries in this study.

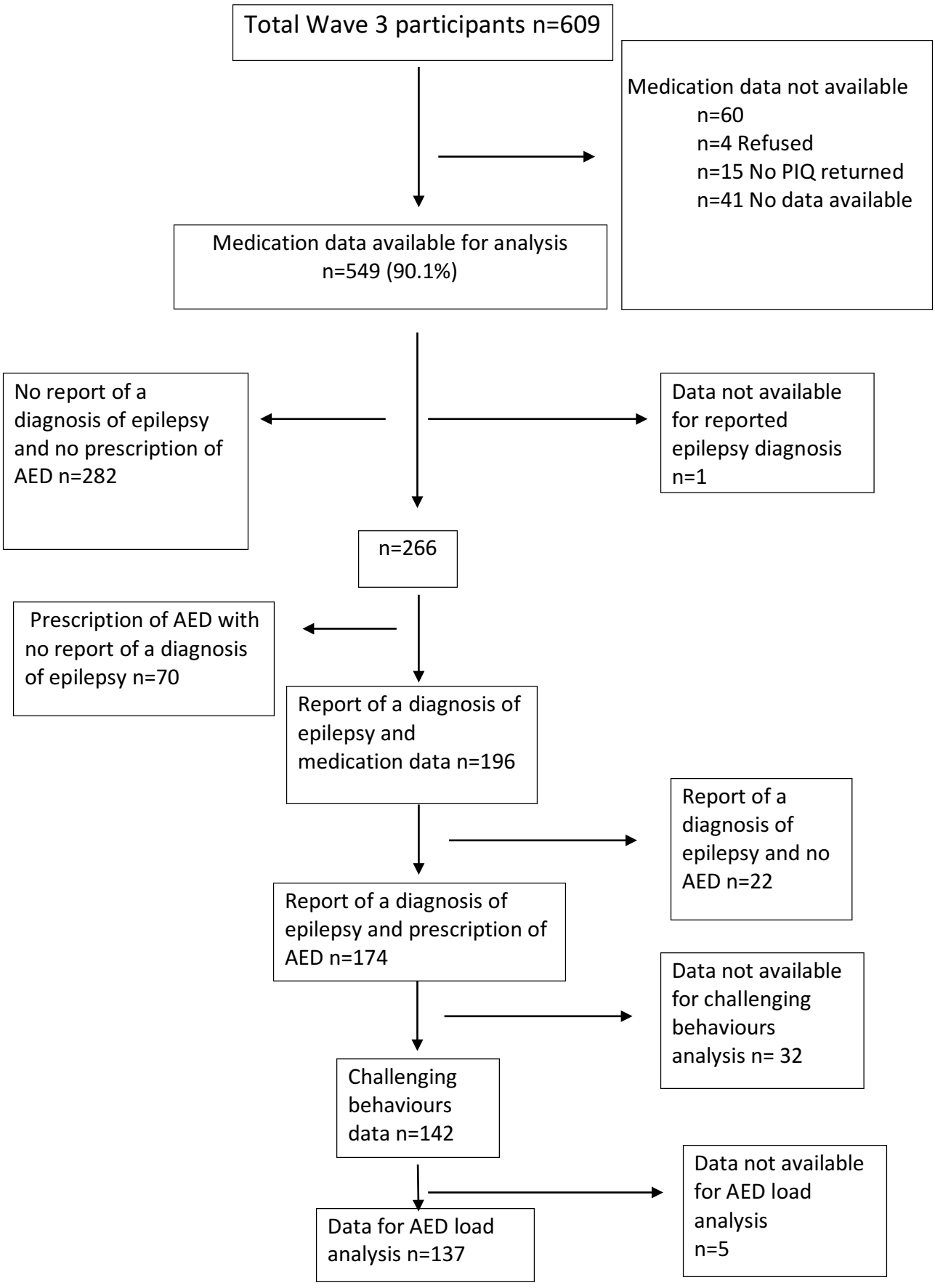


Figure 6.2-1 Flow chart of epilepsy diagnosis, challenging behaviour and AED use

6.2.6 Drug class categorisation

Antiepileptic drugs were defined as those with the ATC code N03A. All AEDs were split into those taken by a participant with a reported diagnosis of epilepsy and those without a reported diagnosis [422]. Clobazam was included in the AED category as it is primarily used for epilepsy. Midazolam was excluded from the N05C class as it is used for acute seizure control only [451]. Regular AEDs were then categorised into number of AEDs prescribed and subsequently into 'monotherapy' and 'polytherapy' [422]. Antiepileptic polytherapy was defined as concurrent treatment with two or more regular AEDs. Drugs indicated for the emergency treatment of acute seizures were recorded separately from the other AEDs and included midazolam. Psychotropic co-medication examined were antipsychotics (N05A), antidepressants (N06A), anxiolytics (N05B), hypnotics & sedatives (N05C), drugs for dementia (N06D), and anti-cholinergic drugs (N04A). Lithium was classified as a mood stabiliser and prochlorperazine was not included in the antipsychotic category as all the doses reported in this study fell within the recommended range used for the treatment of Meniere's syndrome, labyrinthitis and nausea and vomiting (10-40mg daily).

6.2.7 Antiepileptic drug load

The AED PDD/DDD ratio [266, 267] was calculated for all participants with medication data taking a regular AED. Due to incomplete dosage data for six participants (excluded from analysis), this ratio was calculated for 96.6% (168/174) of those with a reported diagnosis of epilepsy and taking a regular AED in this study. The PDD/DDD ratio is the ratio of prescribed daily dose (PDD) to defined daily dose (DDD) [40]. The DDD is the assumed average maintenance daily dose, for a drug taken for its main indication in adults [40] *(Appendix 26).* The PDD is the actual prescribed daily dose. A PDD/DDD ratio can be used

as a measure of drug load [40]. This analysis was completed using Microsoft Excel and a cumulative ratio of all AEDs being taken, calculated.

$$total\ drug\ load = \sum_i \frac{PDD_i}{DDD_i}$$

Numerical descriptive measures, namely median and interquartile range (IQR), of the total AED load variable were obtained and analysed.

6.2.8 Challenging behaviours

The Behaviour Problems Inventory-Short Form (BPI-S), an informant based questionnaire, was used to assess challenging behaviours [95]. The instrument examines three subtypes of challenging behaviours; self-injurious behaviour (SIB) (8 items), aggressive/destructive behaviour (10 items) and stereotyped behaviour (12 items) [405] (*Appendix 31*). A study investigating reliability and factorial validity of the BPI-S found acceptable reliability regarding internal consistency, inter-rater agreement and test-retest reliability [405]. This section was completed by the carer/key worker/support person who knew the person with intellectual disability very well (minimum of 6 months). This data was collected via the PIQ, giving the informant time to fill out the information required prior to the CAPI interview. Broad definitions of each type of behaviour were given in the PIQ (*Appendix 38*).

Individuals providing this data were instructed to describe behaviours in the person with intellectual disability during the previous two months:

1. How often a described behaviour typically occurs.
2. How serious a problem the behaviour is.

If the behaviour did not occur during the previous two months and therefore, posed no problem, they were instructed to check “never/no problem”. If the behaviour had occurred, they were asked to rate the approximate frequency of its occurrence and its

severity. Each level of severity (mild/moderate/severe) was clearly defined. They were not required to provide a severity level for stereotyped behaviour and no scale/severity definition was provided. For the purpose of this study, a positive response to frequency indicated the presence of challenging behaviours. This allowed for the creation of a variable (YES/NO) for individual types of behaviours which were grouped into SIB, aggressive/destructive and stereotyped behaviour per the BPI-S scale [95] and then grouped into overall presence of challenging behaviours.

6.2.9 Covariates

Covariates investigated were gender (male/female), age (<50/50-64/65+ years), level of intellectual disability (mild/moderate/severe/profound/unverified), place of residence (independent/family/community group home/residential/campus), cause of intellectual disability (Down Syndrome/other aetiology/unknown cause), psychotropic medications (antipsychotics/antidepressants/lithium/anxiolytics/hypnotics and sedatives/drugs for dementia/anti-cholinergic), comorbid mental health conditions, any challenging behaviours, categorised challenging behaviours (SIB/aggressive/destructive/stereotyped behaviour), type of seizures (generalised/other), seizure frequency (none in the last year/at least one in the last year), and AEDs. Psychotic disorder includes reported doctor's diagnosis of hallucinations, schizophrenia, and psychosis. Mood disorder includes reported doctor's diagnosis of depression, manic depression, mood swings, and emotional problems and anxiety disorder includes reported doctor's diagnosis of anxiety and Post Traumatic Stress Disorder (PTSD), although there were no reports of PTSD in this study [422].

Mood stabilising AEDs include valproic acid, carbamazepine and lamotrigine. The categorised seizure type was based on the 2017 International League Against Epilepsy

(ILAE) classification of seizures [56]. Generalised seizures include tonic-clonic, tonic, clonic, atonic, myoclonic and absence. Focal seizures include simple partial seizures and complex partial seizures. 'Other' seizure category includes both focal and unknown seizures due to low numbers of reported focal seizures (n=3). Residential/campus settings were defined as living arrangements where 10 or more people share a single living unit or where the living arrangements are campus based. Community group homes are in a community setting with staff support for small groups of people with intellectual disabilities.

6.2.10 Statistical analyses

Descriptive statistics described the characteristics of the population being studied. The Chi Squared (χ^2) test for independence was used to test for significant association between categorical variables at bivariate level. Fisher's Exact test was used to test for significant association between categorical variables where the sample size in subgroups was small ($n<5$). To control for problems associated with multiple comparisons, thereby increasing the likelihood of Type 1 error (rejecting the null hypothesis when it is true and the false discovery rate), a Bonferroni correction was applied to all bivariate Chi Squared/Fisher's Exact tests [406]. Variables that had small numbers in their subgroups were collapsed. This included type of residence, where participants who lived independently or with family were collapsed with participants living in community group homes. Participants with severe intellectual disability and profound intellectual disability were collapsed into a single group of severe/profound intellectual disability. The Kolmogorov-Smirnov test and Shapiro-Wilk test were used to assess if the numerical variable for AED load (PDD/DDD) was normally distributed. As the AED load data significantly deviated from a normal distribution, the non-parametric test, Mann Whitney U, was used to analyse the numerical

data for AED load. Descriptive statistics, including medians (with 95% CI) and interquartile range (IQR) were used to describe the groups. Levene's test for homogeneity of variance was used to assess this assumption for non-parametric tests.

Three binary logistic regressions were performed to identify factors associated with exhibiting (a) SIB, (b) aggressive/destructive behaviour and (c) stereotyped behaviour. In the three models, the possible outcomes for the dichotomous dependent variable were exhibiting (a) SIB yes/no, (b) aggressive/destructive behaviour yes/no or (c) stereotyped behaviour yes/no. All the variables were entered into each regression model simultaneously. Demographic variables included in each of the models were age, level of intellectual disability and place of residence. AED load was included in the models as this was of interest in the study and following positive associations found in non-parametric tests undertaken. Small case numbers prohibited other demographic (for example, gender) and clinical variables (for example, type of seizures) from being included. The variance inflation factor (VIF) was utilised to test for multicollinearity between independent variables. All variables were found to have a VIF below the designated threshold of >2 indicating no multicollinearity. The logistic regression results are presented as odds ratios with corresponding 95% confidence intervals.

The sample size for the logistic regression was determined using the guidelines of Peduzzi et al. (1996), namely that n=10k/p where k is the number of covariates (independent variables), p is the smallest of the proportions of negative or positive cases in the population and k/p is the number of events per variable [408]. Four covariates (k) were included in the three models and p was (a) SIB (exhibit)- 52/141=0.369, (b) aggressive/destructive behaviour (exhibit)- 54/137=0.394, and (c) stereotyped behaviour (do not exhibit)- 70/141=0.496. Therefore, the minimum numbers of cases needed ranged

from n=81-108. The samples used here for each logistic regression (n=125-129) exceeded these minimum requirements. All statistical analyses were carried out using the Statistical Package for Social Sciences, version 25.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at <0.05.

6.3 Results

6.3.1 Demographic & clinical characteristics of participants

Of participants with a reported diagnosis of epilepsy, taking at least one regular AED and having completed BPI-S (n=142), challenging behaviours were found to be exhibited by 62.7% (n=89) *(Table 6.3-1*). The level of intellectual disability was found to be significantly associated with exhibiting challenging behaviours (p<0.001) with a higher prevalence of challenging behaviours associated with greater severity of intellectual disability. Most participants (70.8%, 63 of 89) exhibiting challenging behaviours lived in a residential/campus setting. Of those exhibiting challenging behaviours, 52.8% reported taking AED polytherapy. The median AED load for participants exhibiting challenging behaviours was 1.26 (95%CI 0.93-1.66) compared with 1.30 (95%CI 0.80-1.76) for participants not exhibiting challenging behaviours. Of those exhibiting challenging behaviours, 39.3% (n=35) reported suffering from a mood disorder and 7.9% (n=7) a psychotic disorder. Reporting an anxiety disorder was found to be significantly associated with exhibiting challenging behaviours (41.6%, n=37, p=0.022). Half of the participants (49.4%, n=44) exhibiting challenging behaviours reported prescription of antipsychotics compared to a quarter (24.5%, n=13) of participants not exhibiting challenging behaviours (p=0.003).

Table 6.3-1 - Bivariate analysis of exhibiting challenging behaviours among those with a reported epilepsy diagnosis, taking a regular AED & completed BPI-S (n=142)

Characteristic	Total n=142	Exhibit challenging behaviours n=89	Does not exhibit challenging behaviours n=53	P value
Gender				0.043
Male	61 (43.0)	44 (49.4)	17 (32.1)	
Female	81 (57.0)	45 (50.6)	36 (67.9)	
Age				0.203
<50 years	16 (11.3)	13 (14.6)	3 (5.7)	
50-64 years	95 (66.9)	59 (66.3)	36 (67.9)	
65+ years	31 (21.8)	17 (19.1)	14 (26.4)	
Level of intellectual disability	n=134	n=85	n=49	**<0.001***
Mild	21 (15.7)	6 (7.1)	15 (30.6)	
Moderate	53 (39.6)	31 (36.5)	22 (44.9)	
Severe/profound	60 (44.8)	48 (56.5)	12 (24.5)	
Place of residence				0.003
Independent/ family/community group home	55 (38.7)	26 (29.2)	29 (54.7)	
Residential/campus	87 (61.3)	63 (70.8)	24 (45.3)	
Cause of intellectual disability	n=140	n=87	n=53	0.397
Down Syndrome	19 (13.6)	14 (16.1)	5 (9.4)	
Other aetiology	38 (27.1)	21 (24.1)	17 (32.1)	
Unknown aetiology	83 (59.3)	52 (59.8)	31 (58.5)	
Type of seizures				0.935
Generalised	81 (57.0)	51 (57.3)	30 (56.6)	
Other	61 (43.0)	38 (42.7)	23 (43.4)	
Seizure frequency	n=139	n=87	n=52	0.208
None in the last year	79 (56.8)	53 (60.9)	26 (50.0)	
At least one in the last year	60 (43.2)	34 (39.1)	26 (50.0)	
Type of therapy				0.380
Monotherapy	63 (44.4)	42 (47.2)	21 (39.6)	
Polytherapy (Median=2, Max=5)	79 (55.6)	47 (52.8)	32 (60.4)	
Median AED load (PDD/DDD) (95% CI) (n=137)	1.30 (1.00-1.53)	1.26 (0.93-1.66)	1.30 (0.80-1.76)	0.984[b]
Mood stabilising AED				1.000 [a]
Yes	129 (90.8)	81 (91.0)	48 (90.6)	
No	13 (9.2)	8 (9.0)	5 (9.4)	

Table 6.3-1 - Bivariate analysis of exhibiting challenging behaviours among those with a reported epilepsy diagnosis, taking a regular AED & completed BPI-S (n=142*) (Continued)*

Characteristic	Total n=142	Exhibit challenging behaviours n=89	Does not exhibit challenging behaviours n=53	P value
Comorbid mental health disorder				
Psychotic disorder	11 (7.7)	7 (7.9)	4 (7.5)	1.000 [a]
Mood disorder	48 (33.8)	35 (39.3)	13 (24.5)	0.071
Anxiety disorder	49 (34.5)	37 (41.6)	12 (22.6)	**0.022***
Co-prescribed psychotropic drugs				
Antipsychotics	57 (40.1)	44 (49.4)	13 (24.5)	0.003
Antidepressants	45 (31.7)	28 (31.5)	17 (32.1)	0.939
Anxiolytics	25 (17.6)	20 (22.5)	5 (9.4)	0.048
Hypnotics & sedatives	19 (13.4)	13 (14.6)	6 (11.3)	0.578
Lithium	4 (2.8)	4 (4.5)	0 (0)	0.297 [a]
Drugs for dementia	4 (2.8)	3 (3.4)	1 (1.9)	1.000 [a]
Anti-cholinergic (N04A)	16 (11.3)	11 (12.4)	5 (9.4)	0.594

P value: Chi Square, [a] Fisher Exact Test (2 sided). [b] Mann Whitney U mean rank- exhibit challenging behaviour = 68.95 (n=86), do not exhibit challenging behaviour = 69.09 (n=51).

P value: for Chi-Square Test after applying Bonferroni correction α=0.05/20= 0.0025 thus p<0.0025 for significance.

Statistically significant results (after applying Bonferroni correction) marked in bold and with an asterisk *

6.3.2 Demographic & clinical characteristics of participants with categorised challenging behaviours

Participants exhibiting SIB (61.5%, n=32, p=0.001) or stereotyped behaviour (59.7%, n=40, p<0.001) were more likely to have a severe/profound level of intellectual disability (*Table 6.3-2*). Over 70% of participants exhibiting each behaviour type lived in residential/campus settings. The highest median AED load was found in participants exhibiting aggressive/destructive behaviour (1.47, 95%CI 1.00-2.13) with the lowest median AED load found in participants exhibiting stereotyped behaviour (1.09, 95%CI 0.70-1.57). Antipsychotics were reported for over half of participants exhibiting categorised challenging behaviours with 55.8% (n=29) of those exhibiting SIB (P=0.005), 57.4% (n=31) exhibiting aggressive/destructive behaviour (p=0.001) and 53.5% (n=38) exhibiting stereotyped behaviour (p=0.001) reporting prescription of antipsychotics.

Table 6.3-2 - Bivariate analysis of demographic & clinical factors among those with a report of an epilepsy diagnosis, taking a regular AED and exhibiting SIB (n=141), aggressive/destructive behaviour (n=137) and stereotyped behaviour (n=141)

Characteristic	Total SIB n=141	Exhibit SIB n=52	P value	Total aggressive/ destructive behaviour n=137	Exhibit aggressive/ destructive behaviour n=54	P value	Total stereotyped behaviour n=141	Exhibit stereotyped behaviour n=71	P value
Gender			0.379			0.333			0.049
Male	61 (43.3)	20 (38.5)		59 (43.1)	26 (48.1)		60 (42.6)	36 (50.7)	
Female	80 (56.7)	32 (61.5)		78 (56.9)	28 (51.9)		81 (57.4)	35 (49.3)	
Age			0.460			0.831			0.218
<50 years	16 (11.3)	8 (15.4)		15 (10.9)	7 (13.0)		16 (11.3)	11 (15.5)	
50-64 years	94 (66.7)	32 (61.5)		91 (66.4)	35 (64.8)		94 (66.7)	47 (66.2)	
65+ years	31 (22.0)	12 (23.1)		31 (22.6)	12 (22.2)		31 (22.0)	13 (18.3)	
Level of intellectual disability	n=133	n=52	**0.001***	n=129	n=52	0.293	n=133	n=67	**<0.001***
Mild	21 (15.8)	2 (3.8)		21 (16.3)	6 (11.5)		21 (15.8)	3 (4.5)	
Moderate	54 (40.6)	18 (34.6)		53 (41.1)	20 (38.5)		53 (39.8)	24 (35.8)	
Severe/profound	58 (43.6)	32 (61.5)		55 (42.6)	26 (50.0)		59 (44.4)	40 (59.7)	
Place of residence			0.025			0.025			0.003
Independent/ family/ community group home	55 (39.0)	14 (26.9)		54 (39.4)	15 (27.8)		55 (39.0)	19 (26.8)	
Residential/campus	86 (61.0)	38 (73.1)		83 (60.6)	39 (72.2)		86 (61.0)	52 (73.2)	
Cause of intellectual disability	n=139	n=51	0.246	n=136	n=53	0.115	n=140	n=71	0.195
Down Syndrome	18 (12.9)	4 (7.8)		18 (13.2)	4 (7.5)		19 (13.6)	12 (16.9)	
Other aetiology	37 (26.6)	12 (23.5)		37 (27.2)	12 (22.6)		38 (27.1)	15 (21.1)	
Unknown aetiology	84 (60.4)	35 (68.6)		81 (59.6)	37 (69.8)		83 (59.3)	44 (62.0)	
Type of seizures			0.217			0.737			0.560
Generalised	80 (56.7)	26 (50.0)		76 (55.5)	29 (53.7)		80 (56.7)	42 (59.2)	
Other	61 (43.3)	26 (50.0)		61 (44.5)	25 (46.3)		61 (43.3)	29 (40.8)	

Table 6.3-2 - Bivariate analysis of demographic & clinical factors among those with a report of an epilepsy diagnosis, taking a regular AED and exhibiting SIB (n=141), aggressive/destructive behaviour (n=137) and stereotyped behaviour (n=141) (*Continued*)

Characteristic	Total SIB n=141	Exhibit SIB n=52	P value	Total aggressive/ destructive behaviour n=137	Exhibit aggressive/ destructive behaviour n=54	P value	Total stereotyped behaviour n=141	Exhibit stereotyped behaviour n=71	P value
Seizure frequency	n=138	n=51	0.011	n=134	n=52	0.370	n=138	n=70	0.041
None in the last year	78 (56.5)	36 (70.6)		76 (56.7)	32 (61.5)		79 (57.2)	46 (65.7)	
At least one in the last year	60 (43.5)	15 (29.4)		58 (43.3)	20 (38.5)		59 (42.8)	24 (34.3)	
Type of therapy			0.217			0.819			0.267
Monotherapy	61 (43.3)	26 (50.0)		60 (43.8)	23 (42.6)		63 (44.7)	35 (49.3)	
Polytherapy	80 (56.7)	26 (50.0)		77 (56.2)	31 (57.4)		78 (55.3)	36 (50.7)	
Median AED load (PDD/DDD) (95%CI)	1.32 (1.00-1.57)	1.35 (0.95-1.66)	0.838[b]	1.32 (1.00-1.57)	1.47 (1.00-2.13)	0.090[c]	1.29 (1.00-1.50)	1.09 (0.70-1.57)	0.379[d]
Mood stabilising AED			1.000[a]			0.601			0.368
Yes	128 (90.8)	47 (90.4)		124 (90.5)	48 (88.9)		128 (90.8)	66 (93.0)	
No	13 (9.2)	5 (9.6)		13 (9.5)	6 (11.1)		13 (9.2)	5 (7.0)	
Comorbid mental health disorder									
Psychotic disorder	11 (7.8)	4 (7.7)	1.000[a]	11 (8.0)	4 (7.4)	1.000[a]	11 (7.8)	6 (8.5)	0.772
Mood disorder	49 (34.8)	24 (46.2)	0.030	46 (33.6)	26 (48.1)	0.004	48 (34.0)	32 (45.1)	0.005
Anxiety disorder	49 (34.8)	24 (46.2)	0.030	46 (33.6)	24 (44.4)	0.030	49 (34.8)	31 (43.7)	0.025
Co-prescribed psychotropic drugs									
Antipsychotics	57 (40.4)	29 (55.8)	0.005	55 (40.1)	31 (57.4)	**0.001***	57 (40.4)	38 (53.5)	**0.001***
Antidepressants	46 (32.6)	17 (32.7)	0.989	44 (32.1)	24 (44.4)	0.013	45 (31.9)	20 (28.2)	0.337
Anxiolytics	25 (17.7)	11 (21.2)	0.416	24 (17.5)	15 (27.8)	0.011	25 (17.7)	16 (22.5)	0.132
Hypnotics & sedatives	19 (13.5)	10 (19.2)	0.126	19 (13.9)	9 (16.7)	0.445	19 (13.5)	11 (15.5)	0.480
Lithium	4 (2.8)	3 (5.8)	0.142[a]	4 (2.9)	4 (7.4)	0.023[a]	4 (2.8)	3 (4.2)	0.620[a]
Drugs for dementia	4 (2.8)	1 (1.9)	1.000[a]	4 (2.9)	2 (3.7)	0.647[a]	4 (2.8)	2 (2.8)	1.000[a]
Anti-cholinergic N04A	15 (10.6)	8 (15.4)	0.162	14 (10.2)	7 (13.0)	0.392	16 (11.3)	9 (12.7)	0.616

P value: Chi Square Test, [a] Fisher Exact Test (2 sided). P value: for Chi Square Test and applying Bonferroni correction α=0.05/20= 0.0025 thus p<0.0025 for significance.

Statistically significant results (after applying Bonferroni) marked in bold and with an asterisk *

[b] SIB Mann Whitney U Test: Exhibit mean rank= 69.39 (n=51), do not exhibit mean rank= 67.96 (n=85). Do not exhibit SIB median AED load: 1.30 (95%CI 0.80-1.87).

[c] Aggressive/Destructive Behaviour Mann Whitney U Test: Exhibit mean rank=73.62 (n=51), do not exhibit mean rank= 62.02 (n=81). Do not exhibit aggressive/destructive behaviour median AED load 1.11 (95%CI 0.80-1.57).

[d] Stereotyped Behaviour Mann Whitney U Test: Exhibit mean rank=65.53 (n=68), do not exhibit mean rank=71.47 (n=68). Do not exhibit stereotyped behaviour median AED load 1.30 (95%CI 1.00-2.25).

6.3.3 Relationship between antiepileptic drug load, demographic, and clinical characteristics with regards to exhibiting SIB, aggressive/destructive, and stereotyped behaviour

A significantly higher median AED load was found for participants with a severe/profound intellectual disability exhibiting aggressive/destructive behaviour (p=0.001) (1.55, 95%CI 1.33-3.34) (*Appendix 36*) and SIB (p=0.048) (1.42, 95%CI 1.00-1.67) (*Appendix 35*), compared to not exhibiting aggressive/destructive behaviour (0.64, 95%CI 0.53-1.30) and SIB (0.71, 95% CI 0.53-1.47). A significantly higher median AED load (p=0.007) was also found for participants taking AED monotherapy and exhibiting SIB (0.67, 95%CI 0.60-0.93) compared to not exhibiting SIB (0.57, 95%CI 0.40-0.67).

In addition, a significantly higher median AED load (p=0.006) was found for participants reporting at least one seizure in the last year and exhibiting aggressive/destructive behaviour (3.62, 95%CI 2.67-5.07), compared to not exhibiting aggressive/destructive behaviour (1.75, 95%CI 1.17-2.73). Participants not reporting antipsychotics and antidepressants and exhibiting aggressive/destructive behaviour were found to have significantly (p= 0.042 and p=0.005, respectively) higher median AED loads (2.27, 95%CI 1.17-3.62 and 2.00, 95%CI 1.00-3.60, respectively) compared to those not exhibiting aggressive/destructive behaviour (1.00, 95%CI 0.67-1.76 and 0.84, 95%CI 0.67-1.40, respectively).

The median AED loads of participants reporting antipsychotic medications and exhibiting SIB (1.00 95%CI 0.70-1.57), aggressive/destructive (1.07 95%CI 0.80-1.87) and stereotyped behaviour (1.09 95%CI 0.67-1.66) (*Appendix 37*) were not significantly different from those not exhibiting these behaviours (SIB 1.32 95%CI 0.87-2.43;

aggressive/destructive behaviour 1.30 95%CI 0.75-1.73; stereotyped behaviour 1.30 95%CI 0.87-2.43, respectively).

6.3.4 Factors associated with exhibiting SIB, aggressive/destructive & stereotyped behaviour

Binary logistic regression models (*Table 6.3-3*) demonstrated that having a severe/profound intellectual disability [OR 9.528 (95% CI: 1.904-47.681), p=0.006] was significantly associated with exhibiting SIB. Living in a residential/campus setting [OR 3.098 (95% CI: 1.267-7.577), p=0.013] and having a higher AED load [OR 1.298 (95% CI: 1.013-1.662), p=0.039] were significantly associated with exhibiting aggressive/destructive behaviour after adjusting for confounders. Having a moderate [OR 4.281 (95% CI: 1.060-17.294), p=0.041] or severe/profound intellectual disability [OR 8.113 (95% CI: 1.969-33.430), p=0.004], and living in a residential/campus setting [OR 2.897 (95% CI: 1.214-6.911), p=0.017] were associated with exhibiting stereotyped behaviour. Age was not found to be associated with exhibiting SIB, aggressive/destructive behaviour or stereotyped behaviour (*Table 6.3-3*).

Table 6.3-3 - Binary logistic regression of factors associated with exhibiting SIB, aggressive/destructive and stereotyped behaviour among older people with intellectual disability

	Self-Injurious behaviour (SIB) n=129		Aggressive/destructive behaviour n=125		Stereotyped behaviour n=129	
Characteristic	**Odds ratio (95%CI)**	**P Value**	**Odds ratio (95%CI)**	**P Value**	**Odds ratio (95%CI)**	**P Value**
Age						
<50 years	1 (Reference)		1 (Reference)		1 (Reference)	
50-64 years	0.659 (0.195-2.231)	0.503	0.592 (0.154-2.277)	0.446	0.341 (0.086-1.343)	0.124
65+ years	0.813 (0.199-3.324)	0.773	0.969 (0.218-4.313)	0.967	0.220 (0.047-1.035)	0.055
Level of intellectual disability						
Mild	1 (Reference)		1 (Reference)		1 (Reference)	
Moderate	4.018 (0.818-19.741)	0.087	0.969 (0.294-3.192)	0.959	4.281 (1.060-17.294)	**0.041***
Severe/profound	9.528 (1.904-47.681)	**0.006***	1.098 (0.320-3.760)	0.882	8.113 (1.969-33.430)	**0.004***
Type of residence						
Family/independent/ community group home	1 (Reference)		1 (Reference)		1 (Reference)	
Residential/campus	1.403 (0.591-3.331)	0.442	3.098 (1.267-7.577)	**0.013***	2.897 (1.214-6.911)	**0.017***
AED load	0.952 (0.749-1.209)	0.686	1.298 (1.013-1.662)	**0.039***	0.915 (0.714-1.173)	0.484

Reference groups - <50 years, mild intellectual disability, family/independent/community group home.

Statistically significant results marked in bold and with an asterisk*.

SIB: Reference category: Does not exhibit SIB

Cox & Snell R^2 0.125, Nagelkerke R^2 0.170

Aggressive/Destructive Behaviour: Reference category: Does not exhibit aggressive/destructive behaviour

Cox & Snell R^2 0.099, Nagelkerke R^2 0.134

Stereotyped Behaviour: Reference category: Does not exhibit stereotyped behaviour.

Cox & Snell R^2 0.191, Nagelkerke R^2 0.255

6.4 Discussion

6.4.1 Main findings from paper

To our knowledge, this is the first study examining AED load (PDD/DDD) and challenging behaviours in older adults with intellectual disability and a diagnosis of epilepsy. Almost two-thirds of participants with epilepsy and available information reported exhibiting challenging behaviours with an increased prevalence among those with greater severity of intellectual disability. Aggressive/destructive and stereotyped behaviours were associated with living in residential/campus settings, adjusting for confounders. Over half of participants exhibiting challenging behaviours reported taking AED polytherapy. The highest median AED load was found in participants exhibiting aggressive/destructive behaviour. Participants with a severe/profound intellectual disability exhibiting SIB and aggressive/destructive behaviour had significantly higher median AED loads compared to participants not exhibiting these behaviours. Higher AED load was associated with exhibiting aggressive/destructive behaviour after adjusting for confounders.

6.4.2 Comparison with other studies

Many AEDs have been associated with adverse behavioural effects in people with epilepsy, although there is little evidence from randomised controlled trials [471, 472]. A report examining behavioural disorder in people with intellectual disability and epilepsy concluded that AEDs may provoke either positive or negative behavioural side effects in people with intellectual disability [467]. Antiepileptic drug polytherapy has also been associated with drug related behavioural problems like irritability and aggressive behaviour [210, 473]. In this study, we did not find a significant association between AED use (monotherapy or polytherapy) and reporting challenging behaviours. A higher prevalence

of challenging behaviours has been found in some studies of people with intellectual disability and epilepsy who take AED polytherapy [465, 474]. However, a meta-analysis examining this association did not find a definite correlation between the rate of challenging behaviours and polytherapy with AED medications [465].

Increased levels of refractory epilepsy [425] in this population group often necessitate use of high AED doses and polytherapy, thus contributing to higher AED loads [271] and increasing the risk of adverse effects [475]. We found higher median AED loads (PDD/DDD) were associated with exhibiting both SIB and aggressive/destructive behaviour among specific subgroups when comparing demographic and clinical characteristics. While high AED doses and polytherapy might be expected among participants reporting increased seizure frequency, we also found that a higher median AED load in this subgroup was associated only with participants exhibiting aggressive/destructive behaviour. Significantly higher median AED loads were also found in participants taking AED monotherapy and exhibiting SIB compared to not exhibiting SIB, requiring caution in all therapy regimens. Taking antipsychotics or antidepressants was not associated with a higher median AED load across all behaviour types.

Furthermore, in participants with the most severe intellectual disability, where the greatest prevalence of challenging behaviours were found (56.5%), significantly higher median AED loads were found among participants exhibiting both SIB and aggressive/destructive behaviour compared to participants with severe/profound intellectual disability not exhibiting these behaviours (SIB and aggressive/destructive behaviour, respectively) indicating a higher AED load (PDD/DDD) may be an increased risk for some behavioural problems in people with greater severity of intellectual disability. The overall median AED load for participants exhibiting challenging behaviour was found to be

lower than for participants not exhibiting challenging behaviour due to lower AED loads for stereotyped behaviour.

We did not find any study allowing direct comparisons of AED load (PDD/DDD) and challenging behaviour, either in people with intellectual disability or in the general population. Mood stabilising AEDs were widely prescribed to participants exhibiting challenging behaviours in this study, but they are recognised first line treatments for many seizure types. It is plausible that the mood stabilising properties of some AEDs were exploited and the association between AED load and some behaviours may occur as the presence of behaviours prompts a response, and one response is to prescribe. However, although a systematic review found behavioural improvement with the use of some antiepileptic medication [476], this was in 2008, and there is still little high quality evidence to support their use.

Therefore, our findings pose the question of whether the presence of challenging behaviours in people with epilepsy and intellectual disability leads to greater prescribing of some AEDs for their mood stabilising properties, thus contributing to higher AED loads; or if the dosages of AED medication required to treat refractory seizures produces high AED loads, leading to greater levels of challenging behaviours. Polytherapy and high AED dosages have also been found to be associated with numerous comorbidities including poor bone health [153], fracture risk [258] and adverse cognitive effects [261] necessitating greater caution.

6.4.3 Implications for practice

Numerous factors can impact on behavioural outcomes, including the level of intellectual disability [88], AED type [223], dosage [477], titration speed [477], epilepsy diagnosis [469],

polytherapy [474, 477, 478], previous psychiatric illness [479] and individual patient tolerability [223, 480], therefore making it difficult to determine those that are associated and the nature of the association. Identifying possible adverse effects of AEDs (which may present as challenging behaviours) in people with intellectual disability is a substantial challenge, due in part to limited verbal and communication skills [143, 157, 212], particularly in people with severe/profound intellectual disability, those who are probably most at risk [104]. To add to the complexity, high levels of psychotropic prescribing are found in people with intellectual disability, often to treat behavioural rather than psychiatric problems [175] leading to an increased likelihood for drug-drug interactions with AEDs and adverse effects, meriting increased vigilance for breakthrough behavioural problems and avoidance of high dosages.

Residential/campus settings are most strongly associated with these issues, necessitating the provision of long-term care that is complex, burdensome and resource intensive. In this study, residential/campus settings were the most common type of residence for people exhibiting challenging behaviours (70.8%), and were associated with exhibiting both aggressive/destructive and stereotyped behaviours. Moreover, as people with intellectual disability living in community-based settings get older, their care needs grow in complexity. For those with a diagnosis of epilepsy, regular and comprehensive assessment of their needs is warranted to enable them to live in a type of setting that protects both them and others, yet offering them the greatest amount of freedom.

6.4.4 Strengths of study

Our study used a large, nationally representative sample of older Irish adults with intellectual disability and representative of the older population of people with intellectual

disability in Ireland. Detailed medication data for 90.1% of Wave 3 participants was obtained which was confirmed by interviewers at the time of the interview. The design of the medication record allowed for high quality acquisition of medication data. All participants and/or their proxies received the PIQ which contained the medication record/challenging behaviours section one week prior to the face-to-face interview giving them an opportunity to consult the participants' medication/health records. A stringent VIF cutoff threshold (<2) was employed to rule out multicollinearity between variables in the regression analysis, contributing to the strength of the study.

6.4.5 Limitations of study

Data were not available concerning medications for 19 participants, for 32 participants regarding challenging behaviours and regarding AED load for six participants, therefore, our sample was under-powered to evaluate small sub-groups. As a result, associations found in this study are based on small group sizes. Liver and/or renal function was not taken into consideration for AED load PDD/DDD ratio. We found low numbers of participants reporting focal seizures, which necessitated grouping focal with unknown seizures. Due to the observational cross-sectional study design, we can only describe associations between challenging behaviours and demographic and clinical factors. This study was not randomised to match the activities of AEDs in relation to challenging behaviours with controls. In our multivariate analysis, any probable bias was removed where possible by adjusting for confounders. Nevertheless, residual confounding factors may remain. Additionally, due to small sample sizes for our binary logistic regression, we were limited to examining four predictors.

6.5 Conclusion

Our findings suggest that challenging behaviours are a considerable problem for older people with intellectual disability and a diagnosis of epilepsy. Significantly higher median AED loads were found in some subgroups, including those with severe/profound intellectual disability who exhibit SIB and aggressive/destructive behaviour, raising the question as to whether AED load is a precipitating factor or a consequence in these people. However, a large number of possible contributory and interacting factors exist, thus larger, better powered studies are needed to discern if AED load contributes to behavioural problems in sub groups with different seizure types, and to enable different causal factors to be assessed. In addition, more discriminatory and easy to use tools are required to enable regular comprehensive reviews to be performed, considering 1) the epilepsy and its impact; 2) the behaviours and potential associated factors; 3) the AED(s) used to treat the epilepsy; 4) any AED(s) used for behavioural problems; and 5) any psychotropic drugs prescribed, particularly those without a clear indication.

Chapter 7

Psychotropic pharmacotherapy in older adults with intellectual disability reporting mental health disorders - an observational cross-sectional study

7.1 Introduction

Mental illness is a common comorbidity in adults with intellectual disability, surpassing levels found in the general population [481, 482]. Various methodological constraints in studies, including definitions of intellectual disability and mental health problems, representativeness of study samples, assessment of cases, and diagnostic criteria have led to extensive differences in prevalence rates of mental health disorders [84], with a range of 7% to 97% reported [483]. A Scottish population based study of adults aged 16 years and over by Cooper et al. (2007) found a point prevalence rate of mental illness of 40.9% in people with intellectual disability, reducing to 22.4% when autism and challenging behaviour are excluded [483]. In adults with intellectual disability, autism, depression, anxiety disorders, behavioural issues, and schizophrenia account for some of the most commonly found disorders within the psychiatric spectrum [6]. An increased prevalence of mental illness is also associated with greater severity of intellectual disability [481].

Psychiatric comorbidity in people with intellectual disability is regularly treated with psychotropic medications, which are often prescribed appropriately and are evidenced based [147]. However, few sections of society have experienced a greater overmedication trend than people with intellectual disability [177]. The inappropriate use of psychotropic medications together with widespread polypharmacy in this population group is undoubtedly a cause of concern [178]. An Irish cross-sectional study from IDS-TILDA by O'Dwyer et al. (2017) of 753 people aged 41-90 years, examined psychotropic medication use in older adults with intellectual disability and found a 59.1% prevalence of psychotropic prescribing, of which 66.2% of participants reported psychotropic polypharmacy [176]. Similar to many studies, antipsychotics were found to be the most

frequently prescribed psychotropic class among 43% of their study participants [176]. However, psychotropic polypharmacy, either intra-class or inter-class polypharmacy is often justified in some clinical cases and considered to be 'rational polypharmacy' [147].

A UK cohort study of 33,016 adults with intellectual disability by Sheehan et al. (2015) found that rates of prescribing of antipsychotics (21%) to people with intellectual disabilities greatly exceeded the rates of reported psychotic disorder (schizophrenia 4%, psychosis/other 2%) [175]. In addition, O'Dwyer et al. (2019) in Wave 2 of IDS-TILDA (n=677) found that 45.1% of participants reported use of antipsychotics, and of those who reported antipsychotic use who had diagnosis information (n=282), only 25.9% reported a psychotic disorder [484]. Antipsychotics are often utilised in the treatment of challenging behaviour, particularly aggressive or disruptive behaviour [175, 484, 485], despite limited evidence to substantiate their use [486].

A review by Ji and Findling (2016) of evidence based pharmacotherapy options for mental health problems in people with intellectual disability found that adverse effects of psychotropic medications are reported to be more common in people with intellectual disability than in the general population [178]. Atypical antipsychotic prescribing has surpassed that of typical antipsychotics in recent decades due to a reduction in the risk of extrapyramidal side effects and the mood stabilising properties of atypical antipsychotics [487, 488]. Nonetheless, atypical antipsychotics have also been associated with an increased risk in older people due to adverse cerebrovascular events, including stroke [489]. A UK observational study by Frighi et al. (2011) comparing 138 antipsychotic treated people and 64 antipsychotic naive people with intellectual disability, found antipsychotics at low doses were generally safe in people with intellectual disability in relation to metabolic adverse effects, but they found a trend towards a higher rate of type 2 diabetes

in the antipsychotic group [490]. This study also found a total of 100% and 70% of participants on amisulpride/sulpiride and risperidone respectively had hyperprolactinaemia with secondary hypogonadism in 77% and 4% of affected women and men [490].

The aim of this study is to examine the prevalence and factors associated with reporting a mental health disorder, psychotropic pharmacotherapy and psychotropic polypharmacy in a representative sample of older adults with intellectual disability.

7.1.1 The objectives of this study were:

I. To describe the demographic and clinical characteristics of older adults with intellectual disability reporting a mental health disorder.

II. To examine the prevalence and patterns of psychotropic medication use amongst participants reporting a mental health disorder and specifically, psychotic, mood, and anxiety disorders.

III. To examine the association between inter-class and intra-class psychotropic polypharmacy with regards to reporting a mental health disorder and exhibiting challenging behaviours.

IV. To determine the association between demographic (gender, age, level of intellectual disability, type of residence) and clinical characteristics (reporting a mental health disorder, exhibiting challenging behaviour, epilepsy diagnosis) and exposure to inter-class psychotropic polypharmacy.

7.2 Methods

7.2.1 Study design

The data for this study were drawn from Wave 3 (2016/2017) of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA). The original sample (Wave 1) was randomly selected from the National Intellectual Disability Database (NIDD) of Ireland, a database that collates information on people with an intellectual disability that use or are entitled to avail of services. Inclusion criteria comprised of age ≥40 years with intellectual disability (to reflect the lower longevity of people with intellectual disability), to be registered with the NIDD and to provide written consent to participate and/or family/guardian written agreement if required. Further details on study design can be found in *Chapter 2, section 2.*

7.2.2 *Participants*

At Wave 1 (2009/2010), a total of 753 people aged between 41 and 90 years with an intellectual disability were recruited following consent and protocol completion, representing 8.9% of people aged 40 years and over who were registered on the 2008 NIDD database [28]. Where an individual was not in a position to provide consent, a family member or guardian could sign a letter of agreement for their relative to participate. A comparison of demographics by McCarron et al. (2011) showed the IDS-TILDA sample to be representative of this population group [30]. Further information regarding participants can be found in *Chapter 2, sections 2 and 3*.

7.2.3 Measures

A pre-interview questionnaire (PIQ) was sent to each participant one week before the interview took place. This allowed participants to prepare and locate any information that may be required (for example, medication data). This also helped to enhance the reliability of the data. CAPI (Computer Assisted Personal Interviewing) interviews were completed by trained field workers, experienced in working with people with intellectual disability, utilising laptops to answer the study questions. Further information regarding data collection can be found in *Chapter 2, section 5*.

7.2.4 Reported diagnosis of mental health disorder

Participants were asked in the CAPI *"what type of emotional, nervous, or psychiatric problems do/does you/he/she have?"* The following options were given in the CAPI: Hallucinations, anxiety, depression, emotional problems, schizophrenia, psychosis, mood swings, manic depression, post-traumatic stress disorder (PTSD), something else, unclear response, don't know, and refused to answer. If a participant reported a recognised mental health disorder (n=5) in the 'something else category' that was not captured in the options listed above, for example, obsessive compulsive disorder (OCD) or a personality disorder, this was captured in a new variable for overall mental health disorder created by the author (RM). Behavioural responses were not included in the definition of a mental health disorder as challenging behaviour was assessed separately in the Behaviour Problems Inventory-Short Form (BPI-S) [95]. Responses for unclear response, don't know, refused to answer and queried were excluded from the analysis together with any 'disputes'.

For the purposes of analysis in this study, three categories of mental health disorder were created by grouping the above mental health disorders. Psychotic disorder includes

psychosis, hallucinations, and schizophrenia. Mood disorder includes depression, manic depression, mood swings, and emotional problems and anxiety disorder includes anxiety and PTSD although no participant reported PTSD in this study *(Figure 7.2-1).*

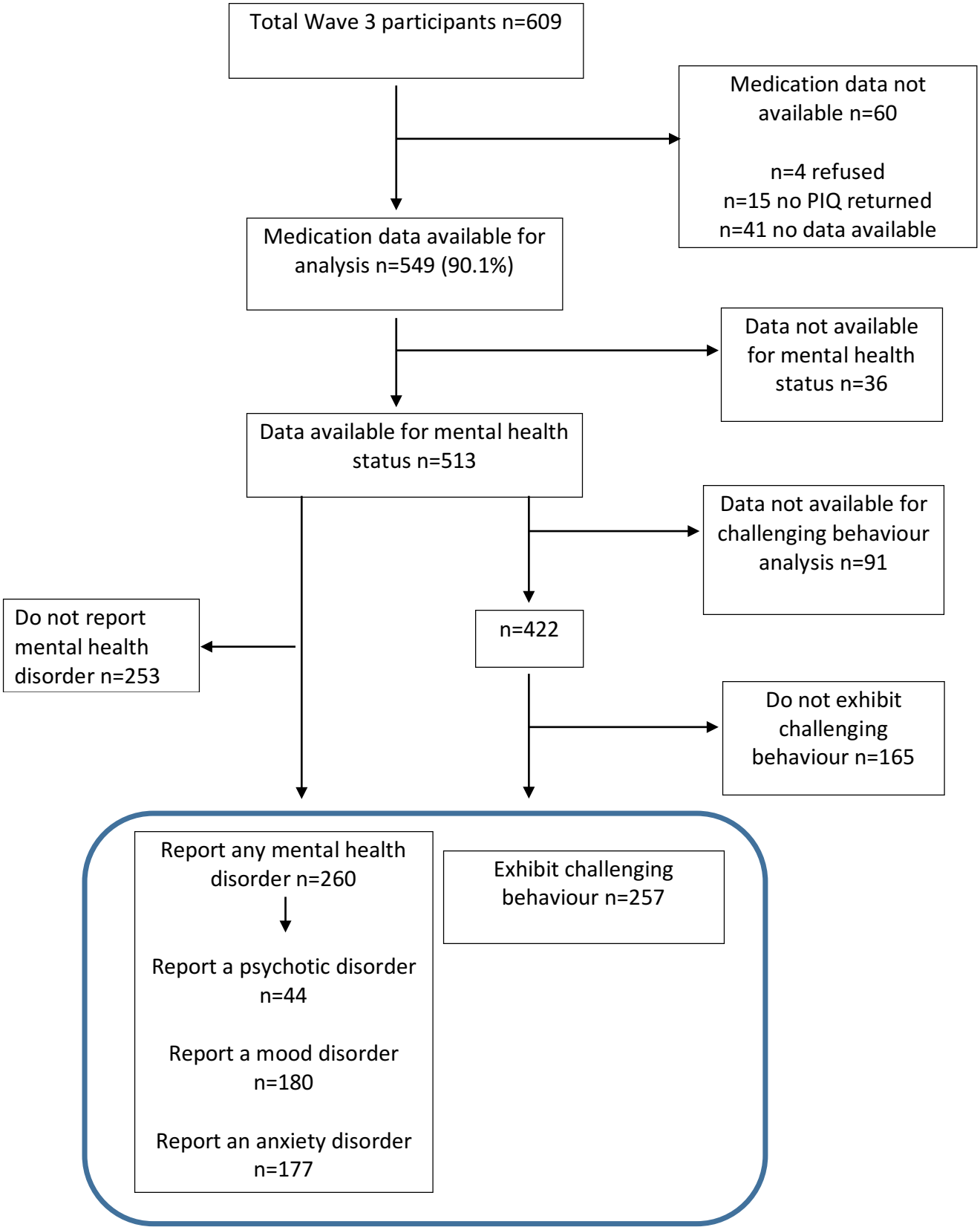
7.2.5 Challenging behaviour

The Behaviour Problems Inventory-Short Form (BPI-S), an informant based questionnaire, was used to assess challenging behaviours [95]. This instrument examines three subtypes of challenging behaviours; self-injurious behaviour (SIB) (8 items), aggressive/destructive behaviour (10 items) and stereotyped behaviour (12 items) [405] (*Appendix 48).* The carer/key worker/support person who knew the person with intellectual disability very well (minimum of 6 months) completed this questionnaire. This data was collected via the PIQ, giving the informant time to fill out the information required prior to the CAPI interview. Further information regarding assessing challenging behaviours can be found in *Chapter 2, section 11*.

7.2.6 Medication exposure

Participants were asked what medications they take on a regular basis including prescribed, over-the-counter and herbal medicines [140]. Medicines were recorded on the PIQ as either brand or generic name/International non-proprietary name, dose, frequency, route of administration, and date when medication was commenced. All medication data were checked by trained interviewers at the time of interview. Medications were coded using the World Health Organisation Anatomical Therapeutic Chemical Classification (ATC) System by two pharmacists JOC and HA. All medication entries input into the statistics

software were independently reviewed and confirmed by the author (RM). Further information regarding medication exposure can be found in *Chapters 2 and 3*.



Study Population

Figure 7.2-1 Flow chart of mental health diagnosis and exhibiting challenging behaviour

7.2.7 Drug class categorisation

Psychotropic medication were the focus of this study, defined as antipsychotics (N05A), antidepressants (N06A), antiepileptics (N03A), anxiolytics (N05B), and hypnotics and sedatives (N05C). Other CNS medication examined included drugs for dementia (N06D), and anti-cholinergic drugs (N04A). Subcategories of each psychotropic class were assessed: atypical/typical antipsychotics, mood stabilising AED (valproic acid/carbamazepine/ lamotrigine), SSRI/SNRI/TCA/other antidepressants, anxiolytic benzodiazepines/other anxiolytics, non-benzodiazepine hypnotics (Z drugs)/prolonged acting/short acting hypnotics. The category taking 'any psychotropic medication' includes at least one of the following: antipsychotic, antidepressant, anxiolytic, hypnotics and sedatives, lithium and mood stabilising AEDs (without an epilepsy diagnosis). Further information regarding drug classes can be found in *Chapters 2 and 3*. *Appendix 49* shows the various psychotropic medication classes and subgroups analysed in this study.

7.2.8 Psychotropic polypharmacy

Psychotropic polypharmacy (inter-class) was defined as the concurrent use of two or more psychotropic medications (antipsychotics, antidepressants, anxiolytics, hypnotics and sedatives, lithium and mood stabilising AEDs (without an epilepsy diagnosis)) in one individual per O'Dwyer et al. (2017) [176]. Inter-class psychotropic polypharmacy implies between classes of psychotropic medication. Intra-class psychotropic polypharmacy implies the same class of psychotropic medication. Intra-class psychotropic polypharmacy was examined for antipsychotics, antidepressants, mood stabilising AEDs (without epilepsy diagnosis), anxiolytics and hypnotics and sedatives.

7.2.9 Covariates

Covariates investigated were gender (male/female), age (<50/50-64/65+ years), level of intellectual disability (mild/moderate/severe/profound/unverified), place of residence (independent/family/community group home/residential/campus setting), cause of intellectual disability (Down Syndrome/other aetiology/unknown aetiology), diagnosis of epilepsy, any psychotropic medication, individual psychotropic medication classes, psychotropic polypharmacy, mental health disorder, categorised mental health disorders (psychotic/mood/anxiety disorder), challenging behaviour (Yes/No), get psychiatric/ psychological treatment, psychiatric treatment from psychiatrist/GP/other, psychological treatment from psychologist/counsellor/CNS/other. Residential/campus settings were defined as living arrangements where ten or more people share a single living unit or where the living arrangements are campus based. Community group homes are in a community setting with staff support for small groups of people with intellectual disabilities. Living independently/with family means living by oneself or with family in the community.

7.2.10 Statistical analyses

Descriptive statistics described the characteristics of the population being studied. The Chi Square (χ^2) test for independence was used to test for significant association between categorical variables at bivariate level. Fisher's Exact test was used to test for significant association where the sample size in subgroups was small (n<5). To control for problems associated with multiple comparisons, thereby increasing the likelihood of Type 1 error (rejecting the null hypothesis when it is true and the false discovery rate), a Bonferroni correction was applied to Chi Square/Fisher's Exact tests where necessary [406]. Binary logistic regression was performed to identify factors associated with exposure to inter-

class psychotropic polypharmacy. The possible outcomes for the dichotomous dependent variable was exposure and no exposure to inter-class psychotropic polypharmacy. All the variables were entered into the regression model simultaneously. Demographic variables included in the model were gender, age, level of intellectual disability and place of residence. Clinical variables associated with mental health with significance $p<0.01$ at bivariate level (mental health diagnosis, exhibit challenging behaviour) and diagnosis of epilepsy (highly prevalent in this cohort) were included.

The variance inflation factor (VIF) was used to test for multicollinearity between independent variables. The VIF for all variables was below the designated threshold of >2.0 indicating no multicollinearity. The logistic regression results are presented as odds ratios with corresponding 95% confidence intervals. To determine the sample size for the logistic regression, we followed the guidelines of Peduzzi et al (1996) where n=10k/p. K is the number of covariates (independent variables), p is the smallest of the proportions of negative or positive cases in the population and k/p is the number of events per variable [408]. Seven covariates (k) were included in our model and p – exposure to inter-class psychotropic polypharmacy was 181/513= 0.353. Therefore, the minimum number of cases needed was n=198. Our sample for logistic regression (n=386) exceeded this minimum requirement.

All statistical analyses were carried out using the Statistical Package for Social Sciences, version 25.0 (SPSS Inc., Chicago, IL, USA).

7.3 Results

7.3.1 Demographic and clinical characteristics of participants

Demographic and clinical characteristics of participants with regards to reporting a mental health disorder are presented in *Table 7.3-1*. In total, 50.7% (n=260) of all participants in Wave 3 with medication and mental health data (n=513) reported a mental health disorder with 56.9% (n=148) female and 43.1% (n=112) male. Of those reporting a mental health disorder, 60.0% (n=156) were aged 50-64 years, with 18.4% (n=45) having a mild intellectual disability, 44.7% (n=109) a moderate intellectual disability, and 36.9% (n=90) a severe/profound intellectual disability. Over half (56.9%, n=148) of participants reporting a mental health disorder lived in a residential/campus setting. Almost three quarters (74.3%, n=159) of those reporting a mental health disorder and having behavioural (BPI-S) data were found to exhibit challenging behaviours with 38.8% (n=83) exhibiting SIB, 50.5% (n=108) exhibiting aggressive/destructive behaviour and 61.7% (n=132) exhibiting stereotyped behaviour ($p<0.001$). Of participants not reporting a mental health disorder, 47.1% (n=98) exhibited challenging behaviour.

With regards to use of psychotropic medication by participants reporting a mental health disorder, 71.2% (n=185) reported being prescribed antipsychotics, 50.4% (n=131) antidepressants, 24.2% (n=63) anxiolytics, and 14.2% (n=37) hypnotics and sedatives. In contrast, of participants not reporting a mental health disorder, 18.2% (n=46) reported being prescribed antipsychotics, 15.8% (n=40) antidepressants, 7.1% (n=18) anxiolytics, and 5.5% (n=14) hypnotics and sedatives. Of those reporting a mental health disorder who responded (n=250), 82.4% (n=206) reported receiving psychiatric treatment since their Wave 2 interview, with 98.5% (n=203) reporting receiving psychiatric treatment from a psychiatrist and 15.5% (n=32) from a GP.

Table 7.3-1 Bivariate analysis of demographic and clinical characteristics of participants with (n=260) and without (n=253) a mental health disorder (n=513)

Characteristic	All participants with medicine data and confirmed mental health status n=513 n (%)	Reported mental health disorder n=260 n (%)	No reported mental health disorder n=253 n (%)	P value
Gender				0.717
Male	225 (43.9)	112 (43.1)	113 (44.7)	
Female	288 (56.1)	148 (56.9)	140 (55.3)	
Age				0.071
<50 years	62 (12.1)	30 (11.5)	32 (12.6)	
50-64 years	327 (63.7)	156 (60.0)	171 (67.6)	
65+ years	124 (24.2)	74 (28.5)	50 (19.8)	
Level of intellectual disability	n=473	n=244	n=229	0.006
Mild	109 (23.0)	45 (18.4)	64 (27.9)	
Moderate	217 (45.9)	109 (44.7)	108 (47.2)	
Severe/profound	147 (31.1)	90 (36.9)	57 (24.9)	
Place of residence				**<0.001***
Independent	77 (15.0)	17 (6.5)	60 (23.7)	
Community group home	204 (39.8)	95 (36.5)	109 (43.1)	
Residential/campus	232 (45.2)	148 (56.9)	84 (33.2)	
Report exhibiting challenging behaviour	n=422	n=214	n=208	**<0.001***
Yes	257 (60.9)	159 (74.3)	98 (47.1)	
No	165 (39.1)	55 (25.7)	110 (52.9)	
Type of challenging behaviours	n=422	n=214	n=208	
Self-Injurious behaviour (SIB)	134 (31.8)	83 (38.8)	51 (24.5)	**0.002***
Aggressive/destructive behaviour	154 (36.5)	108 (50.5)	46 (22.1)	**<0.001***
Stereotyped behaviour	194 (46.0)	132 (61.7)	62 (29.8)	**<0.001***
Diagnosis of epilepsy				0.218
Yes	188 (36.6)	102 (39.2)	86 (34.0)	
No	325 (63.4)	158 (60.8)	167 (66.0)	
Take any psychotropic				**<0.001***
Yes	313 (61.0)	233 (89.6)	80 (31.6)	
No	200 (39.0)	27 (10.4)	173 (68.4)	

Table 7.3-1 Bivariate analysis of demographic and clinical characteristics of participants with (n=260) and without (n=253) a mental health disorder (n=513) (*Continued*)

Characteristic	All participants with medicine data and confirmed mental health status n=513 n (%)	Reported mental health disorder n=260 n (%)	No reported mental health disorder n=253 n (%)	P value
Psychotropic medications				
Antipsychotics	231 (45.0)	185 (71.2)	46 (18.2)	**<0.001***
Antidepressants	171 (33.3)	131 (50.4)	40 (15.8)	**<0.001***
Mood stabilising AED (no epilepsy diagnosis)	48 (9.4)	38 (14.6)	10 (4.0)	**<0.001***
Anxiolytics	81 (15.8)	63 (24.2)	18 (7.1)	**<0.001***
Hypnotics & sedatives (including melatonin)	51 (9.9)	37 (14.2)	14 (5.5)	**0.001***
Other CNS medication				
All antiepileptics (AED)	229 (44.6)	139 (53.5)	90 (35.6)	**0.001***
Drugs for dementia	15 (2.9)	7 (2.7)	8 (3.2)	0.752
Anti-cholinergic N04A	68 (13.3)	61 (23.5)	7 (2.8)	**<0.001***
Since last interview, did you get psychiatric treatment?	n=259	n=250	n=9	0.064 [a]
Yes	211 (81.5)	206 (82.4)	5 (55.6)	
No	48 (18.5)	44 (17.6)	4 (44.4)	
Who gives you psychiatric treatment?	n=211	n=206	n=5	
Psychiatrist	208 (98.6)	203 (98.5)	5 (100.0)	1.000 [a]
GP	32 (15.2)	32 (15.5)	0 (0)	1.000 [a]
Other	5 (2.4)	5 (2.4)	0 (0)	1.000 [a]
Since last interview, did you get psychological treatment? (Counselling/behavioural support)	n=258	n=249	n=9	0.117 [a]
Yes	68 (26.4)	68 (27.3)	0 (0)	
No	190 (73.6)	181 (72.7)	9 (100.0)	

p=Chi Square, [a] Fisher's Exact Test. P value: after applying Bonferroni correction α=0.05/23= 0.0022, thus p<0.0022 for significance. Due to low numbers of participants reporting who gives them psychological treatment in some categories (<5), Clinical Nurse Specialist (CNS) was removed from table. Lithium (n=14), Psychologist (n=54), Counsellor (n=8) and other (n=7) giving psychological treatment were also removed from the table due to low numbers in the 'no reported mental health disorder category'. Free text responses for others who give psychiatric treatment include staff members, MDT and behaviour team. **Statistically significant results marked in bold and with an asterisk***

The study cohort's composition in terms of reporting mental health disorders, epilepsy and challenging behaviours can be seen in *Figure 7.3-1*. Of 513 participants in the study with confirmed mental health status and medication data, 12.3% (n=63) reported having a mental health disorder, epilepsy and challenging behaviour. Missing data in the challenging behaviour category (n=91) with regards to reporting a mental health disorder and epilepsy is presented.

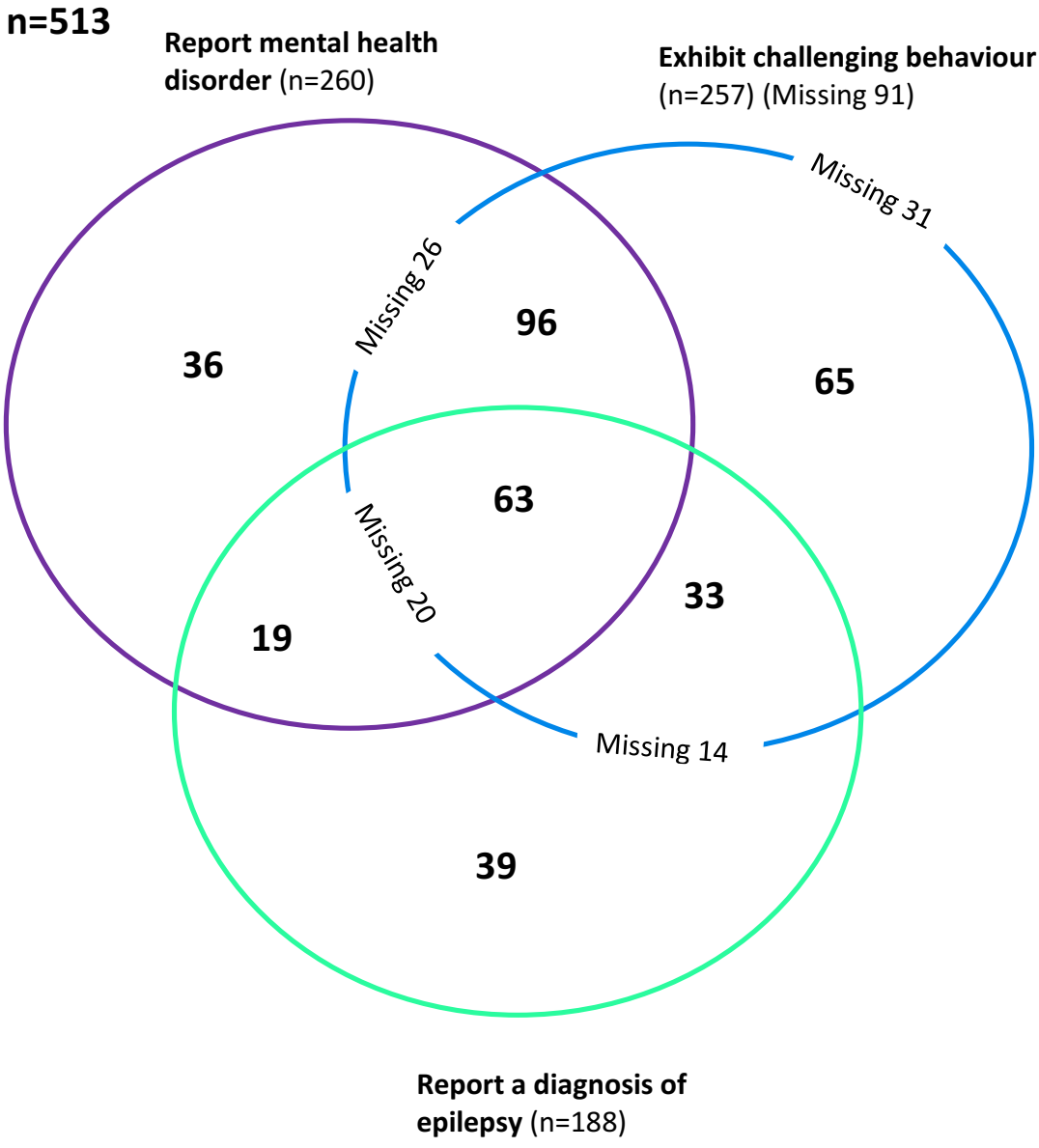


Figure 7.3-1 Venn diagram of participants reporting a mental health disorder, epilepsy and challenging behaviour.

7.3.2 Psychotropic pharmacotherapy

Of participants with medication and mental health data (n=513), 61% (n=313) reported prescription of any psychotropic medication with 35.3% (n=181) reporting being exposed to inter-class psychotropic polypharmacy. Over three in ten participants in the study reported a mood disorder (35.1%, n=180) or an anxiety disorder (34.5%, n=177), with 8.6% (n=44) reporting a psychotic disorder. When considering those who reported a mental health disorder (n=260), nine in ten (89.6%, n=233) participants reported taking psychotropic medication, with over half being exposed to inter-class psychotropic polypharmacy (56.5%, n=147) *(Table 7.3-2)*. Of participants reporting a psychotic disorder (n=44), 77.3% (n=34) reported being exposed to inter-class psychotropic polypharmacy ($p<0.001$).

Antipsychotics were found to be the most commonly reported psychotropic class in participants reporting a mental health disorder (71.2%, n=185). Antidepressants (50.4%, n=131) were also frequently prescribed to those reporting a mental health disorder. In contrast, anxiolytics (24.2%, n=63) and hypnotics and sedatives (14.2%, n=37) were prescribed less frequently. A higher prevalence of atypical antipsychotic prescribing was found in participants reporting a mental health disorder (56.9%, n=148) compared to the prevalence of typical antipsychotics (21.2%, n=55) in this cohort. SSRIs (35.4%, n=92) were the most commonly prescribed antidepressant class in people reporting a mental health disorder, compared to 6.5% (n=17) SNRI, 7.7% (n=20) other type and 2.7% (n=7) TCA. Z-drugs were the most commonly prescribed hypnotic to participants with mental health problems with 8.1%, (n=21) of participants reporting prescription of either zolpidem or zopiclone.

Taking a mood stabilising AED (with no epilepsy diagnosis) was associated with reporting a mental health disorder ($p<0.001$) and reporting a mood disorder ($p<0.001$). Of participants reporting a mental health disorder, 36.9% (n=96) reported taking both an antipsychotic and antidepressant, 21.2% (n=55) reported taking both an antipsychotic and anxiolytic, 14.2% (n=37) reported taking both an antidepressant and anxiolytic and 9.6% (n=25) reported taking both an antipsychotic and hypnotic and sedative medication ($p<0.001$).

Table 7.3-2 Bivariate analysis of psychotropic medication subgroups with regards to participants reporting mental health disorders (n=513)

Prescription of	Total n=513 n (%)	Reported mental health disorder n=260 n (%)	P value	Reported psychotic disorder n=44 n (%)	P value	Reported mood disorder n=180 n (%)	P value	Reported anxiety disorder n=177 n (%)	P value
Take any psychotropic	313 (61.0)	233 (89.6)	**<0.001***	44 (100.0)	**<0.001***	164 (91.1)	**<0.001***	159 (89.8)	**<0.001***
Inter-class psychotropic polypharmacy (Range 2-5)	181 (35.3)	147 (56.5)	**<0.001***	34 (77.3)	**<0.001***	101 (56.1)	**<0.001***	106 (59.9)	**<0.001***
Any antipsychotic	231 (45.0)	185 (71.2)	**<0.001***	43 (97.7)	**<0.001***	126 (70.0)	**<0.001***	133 (75.1)	**<0.001***
Atypical antipsychotics	184 (35.9)	148 (56.9)	**<0.001***	32 (72.7)	**<0.001***	102 (56.6)	**<0.001***	108 (61.0)	**<0.001***
Typical antipsychotics	70 (13.6)	55 (21.2)	**<0.001***	18 (40.9)	**<0.001***	37 (20.5)	**0.001**	40 (22.6)	**<0.001***
Any antidepressant	171 (33.3)	131 (50.4)	**<0.001***	26 (59.1)	**<0.001***	96 (53.3)	**<0.001***	89 (50.3)	**<0.001***
SSRI	119 (23.2)	92 (35.4)	**<0.001***	13 (29.5)	0.297	65 (36.1)	**<0.001***	64 (36.2)	**<0.001***
SNRI	19 (3.7)	17 (6.5)	**0.001***	6 (13.6)	0.003 [a]	15 (8.3)	**<0.001***	11 (6.2)	0.029
TCA	13 (2.5)	7 (2.7)	0.817	3 (6.8)	0.092 [a]	6 (3.3)	0.393 [a]	5 (2.8)	0.773 [a]
Other (trazodone, agomelatine, mirtazapine)	27 (5.3)	20 (7.7)	0.012	5 (11.4)	0.071 [a]	13 (7.2)	0.144	11 (6.2)	0.484
Antipsychotic and antidepressant	115 (22.4)	96 (36.9)	**<0.001***	25 (56.8)	**<0.001***	66 (36.7)	**<0.001***	71 (40.1)	**<0.001***
Diagnosis of epilepsy	188 (36.6)	102 (39.2)	0.218	14 (31.8)	0.487	74 (41.1)	0.123	67 (37.9)	0.681
Mood stabilising AED	198 (38.6)	123 (47.3)	**<0.001***	21 (47.7)	0.193	89 (49.4)	**<0.001***	78 (44.1)	0.065

Table 7.3-2 Bivariate analysis of psychotropic medication subgroups with regards to participants reporting mental health disorders (n=513) (*Continued*)

Prescription of	Total n=513 n (%)	Reported mental health disorder n=260 n (%)	P value	Reported psychotic disorder n=44 n (%)	P value	Reported mood disorder n=180 n (%)	P value	Reported anxiety disorder n=177 n (%)	P value
Mood stabilising AED (no epilepsy diagnosis)	48 (9.4)	38 (14.6)	**<0.001***	8 (18.2)	0.052 [a]	28 (15.6)	**<0.001***	21 (11.9)	0.157
Mood stabilising AED (no epilepsy diagnosis) and antipsychotic	44 (8.6)	35 (13.5)	**<0.001***	8 (18.2)	0.042 [a]	27 (15.0)	**<0.001***	18 (10.2)	0.350
Lithium	14 (2.7)	13 (5.0)	**0.001***	3 (6.8)	0.110[a]	11 (6.1)	**0.001*** [a]	10 (5.6)	0.007 [a]
Antipsychotic and lithium	13 (2.5)	12 (4.6)	0.002	3 (6.8)	0.092 [a]	10 (5.6)	0.002 [a]	9 (5.1)	0.014 [a]
Any anxiolytic	81 (15.8)	63 (24.2)	**<0.001***	11 (25.0)	0.080	40 (22.2)	0.003	46 (26.0)	**<0.001***
Anxiolytic benzodiazepine	78 (15.2)	61 (23.5)	**<0.001***	11 (25.0)	0.058	38 (21.1)	0.006	45 (25.4)	**<0.001***
Antipsychotic and anxiolytic	66 (12.9)	55 (21.2)	**<0.001***	11 (25.0)	0.012	34 (18.9)	0.003	42 (23.7)	**<0.001***
Antidepressant and anxiolytic	42 (8.2)	37 (14.2)	**<0.001***	7 (15.9)	0.076 [a]	25 (13.9)	**0.001**	25 (14.1)	**<0.001***
Diagnosis of dementia	44 (8.6)	24 (9.2)	0.592	4 (9.1)	0.783 [a]	18 (10.0)	0.397	16 (9.0)	0.786
Drugs for dementia	15 (2.9)	7 (2.7)	0.752	<5	-	5 (2.8)	0.885	4 (2.3)	0.517
Anti-cholinergic N04A	68 (13.3)	61 (23.5)	**<0.001***	20 (45.5)	**<0.001***	42 (23.3)	**<0.001***	41 (23.2)	**<0.001***
Any hypnotics & sedatives	51 (9.9)	37 (14.2)	**0.001***	7 (15.9)	0.184 [a]	29 (16.1)	**0.001***	28 (15.8)	**0.001***

Table 7.3-2 Bivariate analysis of psychotropic medication subgroups with regards to participants reporting mental health disorders (n=513) (*Continued*)

Prescription of	Total n=513 n (%)	Reported mental health disorder n=260 n (%)	P value	Reported psychotic disorder n=44 n (%)	P value	Reported mood disorder n=180 n (%)	P value	Reported anxiety disorder n=177 n (%)	P value
Z drugs	30 (5.8)	21 (8.1)	0.029	3 (6.8)	0.735 [a]	16 (8.8)	0.031	15 (8.5)	0.066
Prolonged acting hypnotic benzodiazepine	10 (1.9)	8 (3.1)	0.106[a]	<5	-	5 (2.7)	0.332 [a]	8 (4.5)	**0.004*** [a]
Short acting hypnotic benzodiazepine	5 (1.0)	4 (1.5)	0.373 [a]	<5	-	4 (2.2)	0.054 [a]	4 (2.3)	0.050 [a]
Antipsychotic and hypnotic and sedative	29 (5.7)	25 (9.6)	**<0.001***	7 (15.9)	0.008 [a]	19 (10.6)	**<0.001***	20 (11.3)	**<0.001***
Antidepressant and hypnotic and sedative	23 (4.5)	17 (6.5)	0.023	4 (9.1)	0.125 [a]	15 (8.3)	**0.002***	13 (7.3)	0.023
Anxiolytic and hypnotic and sedative	20 (3.9)	18 (6.9)	**<0.001***	6 (13.6)	0.004 [a]	13 (7.2)	0.004	13 (7.3)	0.003

p=Chi Square test, [a] Fisher Exact test (2 sided). P value: after applying Bonferroni correction α=0.05/31= 0.0016 thus p<0.0016 for significance. <5 denotes fewer than 5 participants. Due to low numbers of participants reporting some psychotropic subclasses (<5), the category 'other anxiolytic' (hydroxyzine/buspirone) was removed from table. **–** denotes unable to calculate p value due to small numbers in subgroups. **Statistically significant results marked in bold and with an asterisk**

7.3.3 Inter-class and Intra-class psychotropic polypharmacy

Inter-class psychotropic polypharmacy (*Table 7.3-3*) was found in 35.3% (n=181) of participants (n=513). Intra-class psychotropic polypharmacy was detected in 8.8% (n=45) of participants reporting antipsychotics, 1.8% (n=9) reporting antidepressants, with <5 participants reporting intra-class hypnotic and sedative polypharmacy. No intra-class polypharmacy was found in participants reporting prescription of regular anxiolytics. Three participants reported being prescribed three antipsychotic drugs simultaneously, and three quarters (66.7%, n=6) of participants exposed to intra-class antidepressant polypharmacy were prescribed mirtazapine with either an SSRI or SNRI. When comparing inter-class and intra-class psychotropic polypharmacy between Wave 1 and Wave 3 of this study, a lower prevalence of intra-class antipsychotic polypharmacy was found in Wave 3.

Table 7.3-3 Inter-class and intra-class psychotropic polypharmacy in Wave 3 (n=513)

Polypharmacy	Wave 3 IDS-TILDA n=513 n (%)	Wave 1 IDS-TILDA O'Dwyer et al. (2017)[176] n=736 n (%)
Inter-class psychotropic polypharmacy (Range 2-5)	181 (35.3)	265 (36.0)
Intra-class polypharmacy - antipsychotics (max=3)	45 (8.8)	82 (11.1)
Intra-class polypharmacy - antidepressants (max=2)	9 (1.8)	9 (1.2)
Intra-class polypharmacy - mood stabilising AEDs (no epilepsy diagnosis)	6 (1.2) (lithium not included in category)	10 (1.4) (includes lithium)
Intra-class polypharmacy - hypnotics and sedatives (max=2)	<5	59 (8.0) (merged in Wave 1) [a]
Intra-class polypharmacy - anxiolytics	0 (0)	

n=513: participants with medication data in Wave 3 and confirmed mental health status. <5 denotes less than 5 participants. Max: maximum number of drugs prescribed intra-class to any participant. Inter-class: between classes of psychotropic medication. Intra-class: same class of psychotropic medication. Interclass psychotropic polypharmacy includes participants taking two or more of: antipsychotics, antidepressants, anxiolytics, hypnotics and sedatives, lithium and mood stabilising AEDs (with no epilepsy diagnosis). [a] n=20 (3.9%) reported both an anxiolytic and hypnotic and sedative in Wave 3 IDS-TILDA.

Of participants reporting a mental health disorder (*Table 7.3-4*), 56.5% (n=147) reported being exposed to inter-class psychotropic polypharmacy, compared to 13.4% (n=34) of participants not reporting a mental health disorder (p<0.001). A third (33.1%, n=86) of participants reporting a mental health disorder reported one psychotropic medication and 10.4% of participants (n=27) reported no psychotropic medication. Both intra-class antipsychotic polypharmacy (p=0.381) and intra-class antidepressant polypharmacy (p=0.706) were not found to be associated with reporting a mental health disorder.

Of participants exhibiting challenging behaviour without reporting a mental health disorder (n=98), 20.4% (n=20) were exposed to inter-class psychotropic polypharmacy compared to 59.7% (n=95) of participants exhibiting challenging behaviour and reporting a mental health disorder (p<0.001). Over half of participants (54.1%, n=53) exhibiting challenging behaviour and not reporting a mental health disorder reported no psychotropic medication, and a quarter (25.5%, n=25) reported one psychotropic medication. In contrast, of those exhibiting challenging behaviour and reporting a mental health disorder, 10.1% (n=16) reported no psychotropic medication. Intra-class antipsychotic polypharmacy (p=0.858) or intra-class antidepressant polypharmacy (p=1.000) was not found to be associated with exhibiting challenging behaviour with or without reporting a mental health disorder.

Table 7.3-4 Bivariate analysis of inter-class and intra-class psychotropic polypharmacy (n=513)

	Total n=513 n (%)	Reported mental health disorder n=260 n (%)	No reported mental health disorder n=253 n (%)	P value	Exhibit challenging Behaviour n=257 n (%)	Exhibit challenging behaviour with mental health disorder n=159 n (%)	Exhibit challenging behaviour without mental health disorder n=98 n (%)	P value
Psychotropic inter-class polypharmacy (Range 2-5)				**<0.001***				**<0.001***
Yes	181 (35.3)	147 (56.5)	34 (13.4)		115 (44.7)	95 (59.7)	20 (20.4)	
No	332 (64.7)	113 (43.5)	219 (86.6)		142 (55.3)	64 (40.3)	78 (79.6)	
Numbers of psychotropic medications				**<0.001***				**<0.001***
0	200 (39.0)	27 (10.4)	173 (68.4)		69 (26.8)	16 (10.1)	53 (54.1)	
1	132 (25.7)	86 (33.1)	46 (18.2)		73 (28.4)	48 (30.2)	25 (25.5)	
2+	181 (35.3)	147 (56.5)	34 (13.4)		115 (44.8)	95 (59.7)	20 (20.4)	
Antipsychotic intra-class polypharmacy				0.381				0.858
Yes	45 (8.8)	20 (7.7)	25 (9.9)		20 (7.8)	12 (7.5)	8 (8.2)	
No	468 (91.2)	240 (92.3)	228 (90.1)		237 (92.2)	147 (92.5)	90 (91.8)	
Antidepressant intra-class polypharmacy				0.706				1.000[a]
Yes	9 (1.8)	4 (1.5)	5 (2.0)		5 (1.9)	3 (1.9)	2 (2.0)	
No	504 (98.2)	256 (98.5)	248 (98.0)		252 (98.1)	156 (98.1)	96 (98.0)	

P value: Chi Square test, [a] Fisher Exact test (2 sided). **Statistically significant results marked in bold and with an asterisk**

7.3.4 Psychotropic pharmacotherapy in those exhibiting challenging behaviour with and without reporting a mental health disorder

Of participants with BPI-S behavioural data (n=422), 60.9% (n=257) were found to exhibit challenging behaviours (*Table 7.3-5*). Of those exhibiting challenging behaviours, 61.9% (n=159) were found to report a co-existing mental health disorder with 38.1% (n=98) not reporting a co-existing mental health disorder. Almost three quarters (74.2%, n=118) of participants exhibiting challenging behaviour who reported a mental health disorder were prescribed antipsychotics. Of participants exhibiting challenging behaviour but not reporting a co-existing mental health disorder, 30.6% (n=30) were prescribed antipsychotics ($p<0.001$). Of participants exhibiting challenging behaviour but not reporting a co-existing mental health disorder, 22.4% (n=22) were prescribed atypical antipsychotics ($p<0.001$) and 12.2% (n=12) typical antipsychotics ($p=0.029$).

With regards to antidepressants, 48.4% (n=77) of participants exhibiting challenging behaviour who reported a mental health disorder were prescribed antidepressants compared to 17.3% (n=17) of participants exhibiting challenging behaviour and not reporting a co-existing mental health disorder ($p<0.001$). Anxiolytics were prescribed to 12.2% (n=12) of participants exhibiting challenging behaviours who did not report a co-existing mental health disorder compared to 27.7% (n=44) of participants exhibiting challenging behaviours who reported a co-existing mental health disorder ($p=0.004$). Taking a mood stabilising AED (with no epilepsy diagnosis) was not associated with exhibiting challenging behaviour with regards to reporting a mental health disorder ($p=0.049$).

Table 7.3-5 Bivariate analysis of psychotropic drug categories with regards to participants exhibiting challenging behaviour (n=257) with (n=159) and without (n=98) reporting a mental health disorder

Prescription of	Exhibit Challenging Behaviour n=257 n (%)	Exhibit challenging behaviour with mental health disorder n=159 n (%)	Exhibit challenging behaviour without mental health disorder n=98 n (%)	P value
Any psychotropic	188 (73.2)	143 (89.9)	45 (45.9)	**<0.001***
Inter-class psychotropic polypharmacy (Range 2-5)	115 (44.7)	95 (59.7)	20 (20.4)	**<0.001***
Any antipsychotic	148 (57.6)	118 (74.2)	30 (30.6)	**<0.001***
Atypical antipsychotics	117 (45.5)	95 (59.7)	22 (22.4)	**<0.001***
Typical antipsychotics	49 (19.1)	37 (23.3)	12 (12.2)	0.029
Any antidepressant	94 (36.6)	77 (48.4)	17 (17.3)	**<0.001***
SSRI	60 (23.3)	50 (31.4)	10 (10.2)	**<0.001***
TCA	10 (3.9)	6 (3.8)	4 (4.1)	1.000[a]
Other (trazodone, agomelatine, mirtazapine)	16 (6.2)	13 (8.2)	3 (3.1)	0.099
Antipsychotic and antidepressant	73 (28.4)	62 (39.0)	11 (11.2)	**<0.001***
Mood stabilising AED	102 (39.7)	74 (46.5)	28 (28.6)	0.004
Mood stabilising AED (no epilepsy diagnosis)	25 (9.7)	20 (12.6)	5 (5.1)	0.049
Mood stabilising AED (no epilepsy diagnosis) and antipsychotic	23 (8.9)	19 (11.9)	4 (4.1)	0.032
Any anxiolytic	56 (21.8)	44 (27.7)	12 (12.2)	0.004
Anxiolytic benzodiazepine	55 (21.4)	43 (27.0)	12 (12.2)	0.005
Antipsychotic and anxiolytic	47 (18.3)	39 (24.5)	8 (8.2)	**0.001***
Antidepressant and anxiolytic	28 (10.9)	25 (15.7)	3 (3.1)	0.002
Drugs for dementia	8 (3.1)	4 (2.5)	4 (4.1)	0.485
Anti-cholinergic N04A	42 (16.3)	37 (23.3)	5 (5.1)	**<0.001***
Any hypnotics & sedatives	30 (11.7)	23 (14.5)	7 (7.1)	0.076
Z drugs	19 (7.4)	15 (9.4)	4 (4.1)	0.111

P value: Chi Square test, [a] Fisher Exact test (2 sided). P value: after applying Bonferroni correction α=0.05/21= 0.002 thus p<0.002 for significance. Due to low numbers of participants reporting some psychotropic subclasses (<5), the categories 'other anxiolytic' (hydroxyzine/buspirone) and short acting hypnotic benzodiazepines were removed from table. The categories SNRI (n=11), lithium (n=9), prolonged acting hypnotic benzodiazepines (n=5), 'antipsychotic and lithium' (n=8), 'antipsychotic and hypnotic and sedative' (n=16), 'antidepressant and hypnotic and sedative' (n=9) and 'anxiolytic and hypnotic and sedative' (n=12) were removed from the table due to low numbers in challenging behaviour without mental health disorder subgroup. **Statistically significant results marked in bold and with an asterisk.**

7.3.5 Association of demographic and clinical factors with exposure to inter-class psychotropic polypharmacy in Wave 3 of IDS-TILDA

The binary logistic regression model (*Table 7.3-6*) showed that participants with a moderate level of intellectual disability [OR 0.477 (95%CI 0.236-0.961), P=0.038] or a severe/profound level of intellectual disability [OR 0.333 (95%CI 0.152-0.733), p=0.006] were significantly less likely to be exposed to inter-class psychotropic polypharmacy after adjusting for confounders. Participants living in a residential/campus setting [OR 3.096 (95%CI 1.138-8.424), p=0.027], reporting a mental health disorder [OR 8.681 (95%CI 5.019-15.014), P<0.001] and exhibiting challenging behaviours [OR 1.915 (95%CI 1.074-3.415), p=0.028] were significantly more likely to be exposed to inter-class psychotropic polypharmacy. Gender and age were not significantly associated with exposure to inter-class psychotropic polypharmacy. A diagnosis of epilepsy [OR 0.591 (95%CI 0.349-1.000)] was also not significantly (p=0.05) associated with exposure to inter-class psychotropic polypharmacy.

Table 7.3-6 Binary logistic regression of exposure to inter-class psychotropic polypharmacy and demographic & clinical factors

	Exposure to inter-class psychotropic polypharmacy (n=386)	
Characteristic	**Odds Ratio (95%CI)**	**P Value**
Gender		0.578
Male	1 (Reference)	
Female	1.153 (0.699-1.902)	
Age		
<50 years	1 (Reference)	
50-64 years	0.548 (0.253-1.187)	0.127
65+ years	0.539 (0.230-1.268)	0.157
Level of intellectual disability		
Mild	1 (Reference)	
Moderate	0.477 (0.236-0.961)	**0.038***
Severe/profound	0.333 (0.152-0.733)	**0.006***
Type of residence		
Family/independent	1 (Reference)	
Community group home	1.859 (0.700-4.936)	0.213
Residential/campus	3.096 (1.138-8.424)	**0.027***
Reporting a mental health disorder		**<0.001***
No	1 (Reference)	
Yes	8.681 (5.019-15.014)	
Exhibit challenging behaviour		**0.028***
No	1 (Reference)	
Yes	1.915 (1.074- 3.415)	
Have epilepsy diagnosis		0.050
No	1 (Reference)	
Yes	0.591 (0.349-1.000)	

Reference groups- male gender, <50 years, mild intellectual disability, independent/family residence, no mental health disorder, no challenging behaviour, no epilepsy diagnosis.

Statistically significant results marked in bold and with an asterisk*

Reference category: Not exposed to inter-class psychotropic polypharmacy

Cox & Snell R^2 0.256 Nagelkerke R^2 0.349

7.4 Discussion

7.4.1 Main findings

This study is an in-depth examination of psychotropic pharmacotherapy and associated factors in older people with intellectual disability reporting mental health disorders. Half of the participants in this study reported a mental health disorder with a greater prevalence found in residential/campus settings. Almost three-quarters of participants who reported a mental health disorder and had behavioural data were found to exhibit challenging behaviours. Antipsychotics were the most commonly reported psychotropic class in participants reporting a mental health disorder (71.2%), with anxiolytics (24.2%) and hypnotics and sedatives (14.2%) prescribed less frequently. Atypical antipsychotics and SSRI antidepressants were the most frequently prescribed antipsychotic and antidepressant subclasses. Six in ten participants in this study reported taking psychotropic medication with 35.3% exposed to inter-class psychotropic polypharmacy. Of participants reporting a mental health disorder, over half were found to be exposed to inter-class psychotropic polypharmacy. In addition, a fifth of participants who exhibited challenging behaviour but who did not report a mental health disorder were exposed to inter-class psychotropic polypharmacy.

Living in a residential/campus setting, reporting a mental health disorder and exhibiting challenging behaviour were found to be significantly associated with exposure to inter-class psychotropic polypharmacy, adjusting for confounders. Participants with a moderate or severe/profound level of intellectual disability were found to be significantly less likely to be exposed to inter-class psychotropic polypharmacy. With regards to treatment, over eight in ten participants in this study reported getting psychiatric treatment since their last interview with most participants who responded (98.6%)

reporting that they received psychiatric treatment from a psychiatrist. In contrast, just over a quarter of participants reported receiving psychological treatment in the form of counselling or behavioural support.

7.4.2 Comparison with other studies

Antipsychotics were the most common psychotropic class among participants in this study (45%). O'Dwyer et al. (2017) found a similar prevalence of antipsychotics (43.1%) in Wave 1 (2009/2010) of IDS-TILDA [176], despite a greater focus in recent years on reducing psychotropic prescribing, especially antipsychotics, with initiatives like STOMP in the United Kingdom, and a new National Clinical Guideline (no.21, 2019) on appropriate prescribing of psychotropic medication for non-cognitive symptoms in people with dementia in Ireland [147, 183, 491, 492]. Overall, a third of participants in this study reported taking antidepressants. Of participants reporting a mental health disorder, this increased to over half. In Wave 1 of IDS-TILDA, O'Dwyer et al. (2017) found a lower prevalence of antidepressant prescribing compared to Wave 3 (26.2% vs 33.3%), suggesting an increasing trend of antidepressant prescribing in this longitudinal study. Nevertheless, among participants reporting a mental health disorder in Wave 3, a decreasing trend of antidepressant prescribing was found with increasing level of intellectual disability (p=0.005) (*Appendix 45*), with 66.7% of participants with mild intellectual disability, 56.0% with moderate intellectual disability and 38.9% with a severe/profound intellectual disability reporting prescription of antidepressants.

High levels of psychotropic inter-class polypharmacy were found (35.3%), increasing to over half (56.5%) in participants reporting a mental health disorder, with the greatest prevalence found in participants reporting a psychotic disorder (77.3%). O'Dwyer

et al. (2017) in Wave 1 of this cohort found a similar but slightly higher prevalence (288/736, 39.1%) of inter-class psychotropic polypharmacy, while McMahon et al. (2020) in a UK cross-sectional total population study of 217 people with intellectual disability aged 18 years and older using the same definition for psychotropic polypharmacy, found a lower psychotropic polypharmacy prevalence of 23%, with 45.7% of participants reporting being exposed to any psychotropic medication. In contrast, low levels of intra-class psychotropic polypharmacy were found in our study, with the greatest prevalence found for antipsychotics (8.8%) and lower for antidepressants (1.8%) and mood stabilising AEDs (with no epilepsy diagnosis) (1.2%). This echoes recommendations for avoidance of intra-class polypharmacy in this population group following concern at high levels of psychotropic prescribing [493].

Similar to O'Dwyer et al. (2017) [176], Lunsky et al. (2018) [493] and McMahon et al. (2020) [494], living in a residential/campus setting was found to be significantly associated with exposure to inter-class psychotropic polypharmacy in this study. A higher prevalence of psychotropic medication is typically found in institutional settings compared with community-based settings [495]. A study by Robertson et al (2000) found people living in residential campus settings (56%) were significantly more likely to receive antipsychotics, compared with people living in either village communities (17%) or dispersed housing (27%) [485]. Of participants reporting a mental health disorder in this study, the greatest proportion of antipsychotics (73.6%) and anxiolytics (28.4%) were found in residential/campus settings compared to other types of community-based residence (*Appendix 43*). Bond et al. (2019) examining the association of life events (for example, change of staff in home or day service; new resident in home; death of a friend) and mental illness in Wave 3 of the IDS-TILDA study found that participants living in

institutional settings had been exposed to significantly ($p<0.001$) more life events than participants living independently or in community group homes [496]. Interestingly, more life events were reported by people who were commenced on mood stabilisers, hypnotics and/or sedatives, or had their existing doses increased between Waves 2 and 3, and in those newly diagnosed with a psychiatric condition, an indication of the emotional instability triggered by life events [496].

Prescribing of atypical antipsychotics has surpassed typical antipsychotics in recent years [497]. In this study, over twice as many participants reported being prescribed the newer atypical antipsychotics compared to the older typical antipsychotics (35.9% vs 13.6%). A similar trend can also be seen in a large US cross-sectional study of adults with intellectual disability (n=4069) living in the community which found that 39% of participants had a prescription for atypical antipsychotics, and only 6% a prescription for typical antipsychotics [498]. In our study, olanzapine (15.4%), risperidone (14.2%) and quetiapine (5.5%) were the most frequently prescribed atypical antipsychotics, with chlorpromazine (6.4%) and haloperidol (4.3%) the most frequently prescribed typical antipsychotics (*Appendix 40*). A UK cross-sectional study of people with intellectual disability (n=2319) from 39 clinical services also found these five antipsychotics to be the most popular in their sample, accounting for 79% of all antipsychotic prescriptions [499]. In addition, Paton et al. (2011) [499] also found comparable daily median oral doses of these medications to Wave 3 of this study *(Appendix 50),* for example, a median oral dose of regular risperidone of 2mg (range 0.125mg -20mg) was found in our IDS-TILDA study compared to regular risperidone median oral dose of 2mg (range 0.5mg-14mg) found by Paton et al. (2011).

Off-label prescribing of psychotropics to treat challenging behaviours is frequently observed in people with intellectual disability, particularly atypical antipsychotics and SSRI antidepressants [500]. In this study, three in ten participants found to exhibit challenging behaviour but who did not report a mental health disorder reported taking antipsychotics, with one in five reporting taking an atypical antipsychotic. Low dose atypical antipsychotics with anxiolytic properties are often used to treat underlying anxiety associated with behavioural problems [501]. A multi-national 4-week randomised, double blind, placebo controlled study (followed by a 48-week open label study) examining the efficacy and safety of the atypical antipsychotic risperidone in adults with disruptive behaviour disorder found it was effective and well tolerated [502]. However, a randomised controlled trial of risperidone, haloperidol, and placebo use in treating aggressive challenging behaviour in people with intellectual disability, found no improvement in behaviour of these drugs over placebo [503]. Furthermore, one in ten participants in this study who exhibited challenging behaviour but who did not report a mental health disorder reported prescription of SSRI antidepressants. A systematic review into the effectiveness of antidepressant medication in the management of behavioural problems found SSRIs improve aggression and SIB in fewer than 50% of cases and the remaining cases show either no improvement or deterioration [504].

7.4.3 Implications for practice

The data outlined in this study reveals that participants with an intellectual disability were closely monitored with regards to psychiatric treatment, with a high proportion of participants receiving psychiatric care from a psychiatrist. However, high levels of exposure to inter-class psychotropic polypharmacy and off-label prescribing are also evident, while

low numbers of participants' report receiving counselling or behavioural support. Indeed, a high prevalence of psychotropic prescribing, often off-label [500], is found in other studies of people with intellectual disability, frequently leading to a significant medication burden. Over half of participants reporting a mental health disorder in this study were exposed to inter-class psychotropic polypharmacy, with one fifth of participants exhibiting challenging behaviour in the absence of a mental health diagnosis reporting same. The antipsychotic burden is particularly significant, especially in those reporting mental health disorders (>70%), although no association was found in this study regarding intra-class antipsychotics and reporting a mental health disorder.

Long durations of treatment and extensive polypharmacy contribute to the risk of over-medication, particularly in institutional settings. It is concerning that following deinstitutionalisation policies in this cohort, reports show levels of psychotropic medication prescriptions remain static both before and after movement to community settings [495], thus highlighting the intense difficulties in reducing psychotropic medication in this cohort. However, it is beyond the scope of this study to examine the influence of residential settings on psychotropic prescribing, as many participants changed place of residence over the course of this study. Between Wave 1 and Wave 3 (10-year period), 32% (241/753) of participants reported a change in living setting with 167 people moving between Wave 2 and Wave 3 [300]. Future research in this cohort should examine this influence more fully. In addition, continued use of low dose antipsychotics, particularly atypical antipsychotics for their anxiolytic properties, necessitates greater evidence of efficacy and patient tolerability, particularly in light of significant adverse effects associated with this class of medication [490].

People with intellectual disability are also exposed to greater risk of drug-drug interactions due to multiple medication use, arising from premature ageing and high levels of comorbidity [147]. Psychotropic medication is also commonly implicated in drug-drug interactions [281]. A UK cross-sectional study by McMahon et al. (2021) examining the prevalence of potential drug-drug interactions in 217 adults with intellectual disability, found that potential drug-drug interactions of clinical significance were frequent, with 519 potential drug-drug interactions of clinical significance identified [281]. McMahon et al. (2021) found that 105 participants were exposed to at least one potential drug-drug interaction of clinical significance, with analysis showing that every prescribed drug led to an 0.87 increase in having a potential drug-drug interaction of clinical significance [281]. Targeted multidisciplinary medication reviews focused on drug-drug interactions, dosages and de-prescribing strategies are essential to combat the challenges of prescribing in this complex environment.

Conversely, difficulties in accurately identifying mood disorders in people with more severe intellectual disability may lead to a deficiency in their care through under-treatment [505] and diagnostic overshadowing [90]. Increased life expectancy of people with intellectual disability [27] compels health professionals to identify and treat appropriately all mental health disorders, including challenging behaviours, to ensure all people with intellectual disability maintain a good quality of life, free from continuous sedative constraint. Greater availability of education resources are needed for healthcare professionals in relation to prescribing for people with complex multimorbidity in intellectual disability, both at undergraduate and postgraduate levels, to ensure sufficient skills and continuity of care are available in line with deinstitutionalisation policies.

In attempting to de-prescribe psychotropic medications, prescribers may be fearful of exacerbating any underlying condition and instigating adverse effects [506]. A systematic review by Sheehan et al. (2017) examining the outcome of reduction or discontinuation of antipsychotic medication used for treating challenging behaviour in people with intellectual disability found that while significant attention has been concentrated on reducing psychotropic medication in people with intellectual disability, this is not without risk of harm, and behavioural deterioration often impedes such action [189]. Communication and cognitive deficits in people with intellectual disability can also lead to difficulties in obtaining informed consent to such treatment and detecting adverse effects [507]. Additionally, drug-drug interactions arising from polypharmacy, together with extensive comorbidity, necessitate minimising where possible, prescribing of these medications unsupported by scientific evidence [506].

7.4.4 Strengths of study

Our study used a large, nationally representative sample of older Irish adults with intellectual disability and representative of the older population of people with intellectual disability in Ireland. Detailed medication data for 90.1% of Wave 3 participants was obtained which was confirmed by interviewers at the time of the interview. The design of the medication record allowed for high quality acquisition of medication data. All participants and/or their proxies received the PIQ which contained the medication record/challenging behaviours section one week prior to the face to face interview giving them an opportunity to consult the participants' medication/health records. Collection of comprehensive data regarding mental health and challenging behaviours allowed

contextual analysis of psychotropic medication. A strict VIF cutoff threshold (<2) was employed to rule out multicollinearity between variables in the regression analysis, contributing to the strength of the study.

7.4.5 Limitations of study

Data was not available for determining mental health status for 36 (6.6%) participants. In addition, the behaviour problems inventory short form (BPI-S) was not completed for 91 (16.6%) participants in this study (n=549). Therefore, these participants were excluded from the analysis. Our sample was under-powered to evaluate small sub-groups in some categories. Data collected regarding medication use, report of mental health disorders and challenging behaviours was based on participants' self-report or proxy report which may result in bias. However, the questions used in the mental health section were utilised in other longitudinal studies in the general population, and the English Longitudinal Study on Ageing (ELSA). The BPI-S has also been validated for use in people with intellectual disability. We did not collect data regarding the severity of the mental health disorder, and if this condition was acute or chronic. With regards polypharmacy, for example with antipsychotics, it is possible that the psychiatrist/prescriber was in the process of substituting one drug for another at the time of interview. Some dosage data was missing for calculating the median dosage (*Appendix 50*). We also did not examine PRN medication in the study, as the study did not collect consumption of PRN medication and thus we do not know how frequently PRN medication was used. Due to the observational cross-sectional study design, we can only describe associations between mental health diagnoses, prescription of psychotropics and demographic and clinical factors. In our

multivariate analysis, any probable bias was removed where possible by adjusting for confounders. Nevertheless, residual confounding factors may remain. It is possible other confounding factors not included in the model contributed to the reporting of inter-class psychotropic polypharmacy. A further limitation of this retrospective study is the possible under-reporting of mental health disorders and challenging behaviours which may under-represent this problem. However, the majority of participants with mental health disorders and challenging behaviours in our study live in residential/campus settings with nursing supervision, thus it is unlikely that this occurred often.

7.5 Conclusion

Our findings highlight the significant psychiatric comorbidity found in people with intellectual disability and the extensive use of psychotropic medication and exposure to inter-class psychotropic polypharmacy. Antipsychotic medication was the predominant psychotropic class, contributing to high medication burdens, despite low numbers of participants reporting a psychotic disorder. Similar to other studies, a high prevalence of antipsychotics, particularly atypical antipsychotics, were found in participants exhibiting challenging behaviours and not reporting a mental health disorder. Inter-class psychotropic polypharmacy was found to be associated with reporting a mental health disorder and with exhibiting challenging behaviour. This study also underlines the significant inter-class psychotropic polypharmacy burden in people exhibiting challenging behaviour in the absence of a psychiatric diagnosis and the importance of regular medication reviews to ensure prescribing is evidence based.

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