Factors associated with the use of gastrointestinal medicines among older people with Intellectual Disabilities in Ireland

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Declaration

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Summary

Background: People with intellectual disabilities (ID) experience multi-morbidity, multiple medication use and have complex health needs. Gastrointestinal (GI) disorders such as constipation and gastroesophageal reflux disorders (GORD) are commonly reported in this population and are among the comorbid conditions that can arise from childhood and have serious consequences.

There are limited studies that investigate the use of GI medication comprehensively in people with ID. This includes medicines that manage constipation (e.g. laxatives) and acid-related disorders (e.g. Proton-Pump Inhibitors (PPIs)).

Objectives: The thesis aimed to investigate use of the most prevalent GI medicines in older people with ID including two GI therapeutic classes; Laxatives and PPIs. This involved exploring their patterns of use, considering population demographic and clinical characteristics, examining the dosage regimen, the relevant reported indications, the length of use (particularly for PPIs), types of drug combinations (particularly for laxatives) and identifying factors that are significantly associated with their use.

Methods: Data for this thesis is drawn from the Intellectual Disability Supplement to The Irish Longitudinal Study on Ageing (IDS-TILDA), a representative study of people with ID aged 40 years and over in Ireland. Data was taken from two waves; Wave 2 (n=677) (conducted in 2013/2014) and Wave 3 (n=549) (conducted in 2016/2017). Furthermore, data from the first wave of IDS-TILDA (conducted in 2009/2010) (n=736) was used to expand analysis of laxative use. Descriptive statistics, bivariate analyses and multiple logistic regression were carried out for this thesis. Furthermore, descriptive comparisons between different waves of the IDS-TILDA study was carried out for both laxatives and PPI use.

Results: *PPI use*: About 28% of the population in Wave 2 reported use of PPIs. Almost 70% of PPIs were used at high doses. Over half reported using PPIs for more than a year and over 4 in 10 reported using PPIs without clear indications. Factors associated with PPI use, after adjusting for confounders, were older ages (≥50 years), severe/profound level of ID and reporting any PPI indications (GORD, peptic ulcers, use of Non-Steroidal Anti-inflammatory Drugs (NSAIDs) and use of antiplatelets). The use of PPIs increased to

35% in Wave 3 (a 7% increase since Wave 2). Over six in ten of participants who reported PPI use in Wave 2 continued to report PPI use in Wave 3. High doses of PPIs were used by a large proportion of participants in Wave 3 (69.9%). PPIs were more likely to be used by older ages (65+), those with severe/profound level of ID or by those who live in residential care at both waves of the IDS-TILDA. There were still some PPIs users who did not report clear indications for their use in Wave 3 IDS-TILDA (37.3%).

Laxative use: Prevalence of laxative use in Wave 2 of IDS-TILDA was 41.5% (n=281). Of these, 74.3% (n=209) reported chronic constipation. About 4 in 10 (n=113) laxative users reported using two or more laxatives, within which, 60% (n=67) were using a combination from the same laxative class. Reporting laxative use increased from Wave 1 to Wave 3 from 37.5% to 44.4%. Although the use of laxatives was prevalent in this population, their use was not ubiquitous among those who had constipation or met Rome III criteria. In addition, some combinations of laxatives were identified and considered illogical (intraclass laxative combination).

Further analysis indicated that the use of laxatives was also linked to substantial exposure to constipation risk factors in this population such as exposure to anticholinergics, medicines and conditions that contributed to constipation.

The factors that significantly associated with laxative use in this population, after adjusting for confounders, were reporting chronic constipation, living in residential care, exposure to anticholinergics and receiving soft food or thickening fluids.

Conclusion: This is the first study to assess the use of PPIs and laxatives comprehensively in an older population with ID. The study identified long-term PPI use with high doses and unclear indications suggesting an inappropriate PPI prescribing practice for this population.

The use of laxatives was very prevalent especially among those in residential care or those exposed to constipation risk factors. The use of laxatives was not sufficient to manage constipation with use of some combinations that were considered inappropriate. Managing constipation in this population should not be restricted to giving laxatives but also to reduce and treat exposure to constipation risk factors.

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Table of Abbreviations

Abbreviation	Term
5-HT3 antagonists	5-hydroxytryptamine type 3 receptor antagonists
AAIDD	American Association on Intellectual and Developmental Disabilities
ACB	Anticholinergic Cognitive Burden
ADL	Activity of Daily Living
ADR	Adverse Drug Reaction
AGA	American Gastroenterological Association
ATC	Anatomical Therapeutic Classification
BI	Barthel Index
BMI	Body Mass Index
BNF	British National Formulary
BPI-S	Behaviour Problem Inventory-Short Form
CAPI	Computer-Assisted Personal Interview
CCAT	Crowe Critical Appraisal Tool
CD	Coeliac disease
CI	Confidence Interval
CIC	Chronic Idiopathic Constipation
CTT	Colonic Transit Time
CVD	Cardiovascular Disorders
DBI-AC	Drug Burden Index (anticholinergic medications)
DSM-V	Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
FDA	Food Drug Administration
GDPR	General Data Protection Regulation

Abbreviation	Term
GI	Gastrointestinal
GIT	Gastrointestinal Tract
GORD	Gastro-Oesophageal Reflux Disease
GP	General Practitioner
H2RAs	Histamine-2 receptor antagonists
HPRA	Health Products Regulatory Authority
HRCDC	Health Research Consent Declaration Committee
HRR	Health Research Regulations
HSE	Health Service Executive
ICD	International Classification of Diseases
ICD-9	International Classification of Diseases-9
ICF	International Classification of Functioning, Disability and Health
ID	Intellectual Disability
IDS-TILDA	Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing
INN	International Non-Proprietary Name
IPAQ	International Physical Activity Questionnaire
IQ	Intelligence Quotient
mg	Milligrams
MHRA	Medicines and Healthcare products Regulatory Agency
MUAC	Mid Upper Arm Circumference
NERD	Non-Erosive Reflux Disease
NIDD	National Intellectual Disability Database
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds Ratio
OTC	Over-The-Counter

Abbreviation	Term
PCRS	Primary Care Reimbursement Service
PCRS	Primary Care Reimbursement Services
PEG+E	Polyethylene Glycol + Electrolyte
PIM	Potentially Inappropriate Medicines
PIN	Personal Identification Number
PIP	Potentially Inappropriate Prescribing
PIQ	Pre-Interview Questionnaire
PPIs	Proton Pump Inhibitors
PRN	Pro Re Nata (As needed)
QoL	Quality of Life
RAPA	Rapid Assessment of Physical Activity
RCTs	Randomised Controlled Trials
RDDA	Regional Disability Database Administrator
SD	Standard Deviation
SPC	Summary of Product Characteristics
SPSS	Statistical Package for Social Sciences
SSRIs	Selective Serotonin Reuptake Inhibitors
START	Screening Tool to Alert to Right Treatment
STOPP	Screening Tool of Older Person's Prescriptions
STRIP	Systematic Tool to Reduce Inappropriate Prescribing
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SWLS	Satisfaction With Life Scale
TILDA	The Irish Longitudinal Study on Ageing
UK	United Kingdom
VIF	Variance Inflation Factor

Abbreviation	Term
WHO	World Health Organisation

Presentations and Publications

Presentations

- Longitudinal evaluation of laxative use among people with intellectual disabilities: Data from a longitudinal study. European Society of Clinical Pharmacy (ESCP) symposium, October 2018, Belfast (Poster)
- Proton pump inhibitors in older adults with intellectual disabilities: tracking the use during a three years duration. International Pharmaceutical Federation FIP Congress, September 2018, Glasgow. (Poster) (Won the prize for the most outstanding poster).
- Laxative Use and Constipation among Intellectually Disabled Older People; Prevalence, Patterns and Association. The 5th International Association for the Scientific Study of Intellectual and Developmental Disabilities (IASSIDD) Europe Congress, July 2018, Athens, Greece. (Oral presentation; nominated Maire O'Dwyer)
- Laxative use by older people with intellectual disabilities, prevalence, pattern and dosage regimen. 39th All Ireland Schools of Pharmacy Research Conference, University College, April 2017, Cork. (Poster)
- The use of proton pump inhibitors among intellectually disabled older people: an observational study. IGS 64th Annual & Scientific Meeting 2016, the Irish Gerontological Society, October 2016, Killarney. (Poster)

Publications

Published abstracts

- Al Mutairi HK, O'Dwyer M, McCarron M, McCallion P, Henman MC., Longitudinal evaluation of laxative use among people with intellectual disabilities: data from three waves of a longitudinal study. International Journal of Clinical Pharmacy. European Society of Clinical Pharmacy Symposium, Belfast, October 2018, edited by Springer International, 41 (1) 2019, pp 370 – 370.
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Published papers

- Al Mutairi, H., O'Dwyer, M., McCarron, M., McCallion, P. and Henman, M.C., 2018. The Use Of Proton Pump Inhibitors Among Older Adults with Intellectual Disability: A Cross-sectional Observational Study. Saudi Pharmaceutical Journal. 2018; 26 (7):1012-1021.
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1. Chapter One: Introduction

1.1. Background

1.1.1. Definition of ID

Intellectual Disability (ID) is defined according to the American Association on Intellectual and Developmental Disability (AAIDD) as "a disability characterised by significant limitations in both intellectual functioning (reasoning, learning, problem solving) and adaptive behaviour (which covers a range of everyday social and practical skills) and originates before the age of 18" (1). Intellectual disability was formerly known as 'mental retardation' which was commonly used in the USA (2), while the term developmental disabilities is a broader term that includes intellectual disabilities or other disabilities that developed during childhood (such as physical disabilities). Developmental disabilities as an alternative term to 'intellectual disabilities' is widely used in Canada (3). The existing terms (learning disability, learning difficulties, cognitive impairment and developmental disability) may include more people than those who meet the definition of 'intellectual disability' which has remained unchanged in recent decades although the International Classification of Diseases refers to 'disorders of intellectual development' as a newly issued term (4).

Diagnosis of ID depends on three main criteria;

1. deficit in intellectual functioning,
2. significant limitation of adaptive behavior
3. and age of onset prior age of 18 (5).

Other than the AAIDD, there are different sources and measures that are used to define and diagnose ID such as the Diagnostic Statistical Manual of Mental Disorders 5th edition (DSM-V) (6), the International Classification of Diseases (ICD) (7) and The International Classification of Functioning, Disability and Health (ICF) (8). Psychological evaluation such as psychological instruments and using clinical judgement are sometimes used to assist in the diagnostic process. Moreover, the Intelligence Quotient (IQ) test is used to measure intellectual functioning (i.e. mental capacity for reasoning, planning, solving problems, abstract thinking, learning quickly etc.). The IQ test defines the groups and

classifies people with ID within these groups. Individuals with IQ scores between 55 to 70 are classified as having a mild level of ID, and those with IQ scores between 40 to 55 are classified in the moderate level of ID. Those with severe and profound level of ID having score of IQ between 25 to 40 and below 25 (9), respectively. Limitations in adaptive behavior can be evaluated by assessing different skills required for everyday living. Examples of these skills are; conceptual (like self-direction, language, literacy and number concepts), social skills (interpersonal skills, self-esteem and gullibility) and practical skills (personal care, health care, occupational skills, schedules/routines and other activities of daily living) (5).

1.1.2. Aetiology of ID

Intellectual disability includes a mixed group of clinical disorders varying from genetic to nutritional, infectious, metabolic or neurotoxic conditions (5, 10). Factors that may cause ID vary depending on their type/nature and the timing of their occurrence. The types of these factors involve (5, 10);

- Biomedical (related to biological process like genetic impairment or malnutrition)
- Neural or brain development impairment
- Social (related to social and family interaction)
- Behavioral (injurious activities or maternal substance abuse)
- Educational (related to availability of educational support to promote adaptive skills and intellectual development)

The time of occurrence of these factors include;

- prenatal like chromosomal disorders and poverty
- perinatal like birth injury and exposure to teratogen
- postnatal like traumatic brain injury, impaired child-caregiver and late diagnosis (5, 10)

Knowing the aetiology of ID is of importance because some aetiologies may be accompanied by other health issues which may influence physical and psychological functioning. In addition, some aetiologies may be treatable, allowing for appropriate treatment to minimise or prevent ID (5).

Examples of syndromes associated with ID are; Down syndrome (Trisomy 21), Edwards syndrome (Trisomy 13), Patau syndrome (Trisomy 18), Fragile X syndrome and Prader-Willi syndrome, some of which are the subject of genetic prenatal screening which is recommended for all women (11, 12).

1.1.3. Prevalence and demographics of ID

Reporting the prevalence of ID is challenging because of the variation in terminology used to define or diagnose ID and the heterogeneity of studies. In a meta-analysis of population-based studies, the overall pooled prevalence of ID amongst all the studies was 10.37/1000 population (13). The highest prevalence of ID was among low income countries where the estimated prevalence per 1000 population was 16.41, while the prevalence from middle and high income countries reported as 15.94 and 9.21 respectively for each 1000 population (13). About half of the reported causal factors were unknown and the other half known causes such as antenatal (genetic factors), perinatal (birth injury or asphyxia) and postnatal (infection or developmental issues) (13). More recent systematic review by McKenzie *et al.* has reported a range prevalence from 0.05 to 1.55 % (14). In the Republic of Ireland, the National Intellectual Disability Database (NIDD) is responsible for collecting information on people with ID who are entitled to, or receive, services related to intellectual disability. According to the NIDD, there are about 28,388 people with an ID enrolled with the NIDD at the end of 2017, representing a prevalence of 5.96 for each 1,000 population (15). The prevalence rate of those with a mild level of ID reported as 1.92 per 1,000 (expected to be underestimated since not all those with a mild level of ID registered in the NIDD). The prevalence of those with a moderate, severe or profound level of ID was 3.49 for each 1,000 population. The reported overall ratio of males to females who registered with ID in all age groups (except those aged ≥55 years) was 1.44 to 1 (15). Another source for reporting the prevalence of ID is the Irish National Census which is conducted every 5 years and records each resident's information including a question related to long lasting difficulties/disabilities which includes intellectual disabilities. Reports from the national census showed that the overall prevalence of children and adults with ID in 2011 was 46,541 (17.7 per 1000 population for children and 9.5 per 1000 population for adults) and this was increased to 56,430 in 2016 (22.2 per 1000 population for children

and 10.5 per1000 population for adults) (4). According to McConkey *et al.*, 1.8 times more children were reported to have ID in the National Census than were reported by the NIDD. Similarly, the prevalence of adults with ID in 2011 identified by the census was 1.8 times the NIDD population with this number rising to 1.9 times more in 2016 (4).

1.1.4. Ageing and intellectual disability

Previously people with ID had considerably lower life expectancy compared to people without ID (16). However, there has been a notable increase in the lifespan of people with ID exceeding the age of 60 (17) and the number of those aged 65 years and over is growing (18, 19). The increased life expectancy occurs mainly in people with mild to moderate level of ID. The improvement in life expectancy among people with ID may be attributed to the better medical interventions, control of infectious disease, improved nutrition, an increase in quality of healthcare provision and in the quality of their living environments (16, 20).

In Ireland, according to the NIDD annual report, of those with a moderate, severe/profound level of ID the prevalence of those aged ≥35 years increased from 37.9% in 1996 to 49.1% in 2017 (15). This has implications for service planning; since there is a high level of need for services specialised to meet the needs of older people with ID. Nonetheless, older people with ID do not have the same chances for healthy ageing as the general population (21).

Figure 1-1 illustrates a general overview of the mean expected life expectancy in years among syndromes specific to the population with ID. Some data suggest that the continued increase in longevity among people with ID may have stalled (22, 23).

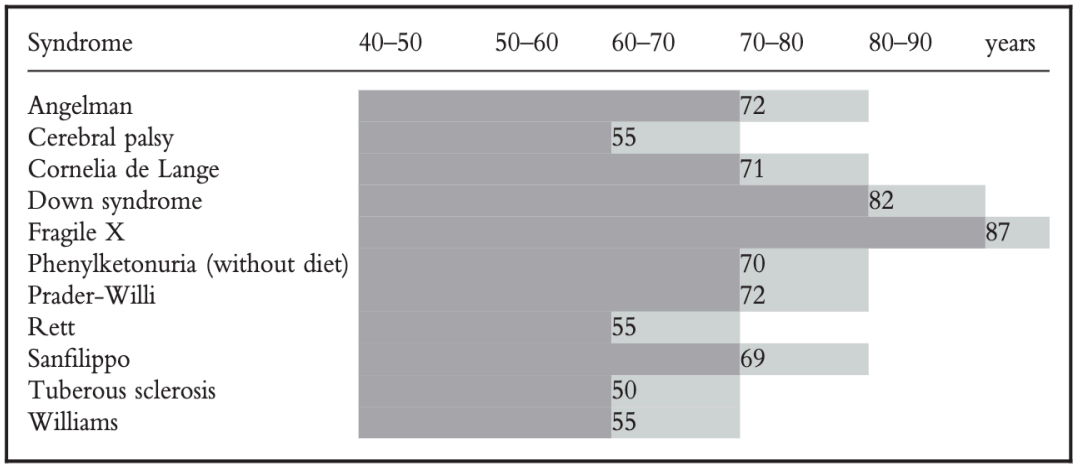

Figure 1-1 Mean expected life expectancy among some syndromes with ID (with maximum age in years) adapted from Coppus *et al.* (16)

Nowadays, people with ID experience a longer life span than previously expected, yet their life expectancies are still typically lower than those from the general population. People with ID experience premature ageing and early signs of functional decline when compared to the general older population (20). The combination of the ageing process and lifelong disability makes people with ID have a unique life experience and perception (24). The cumulative research indicates that there are high rates of common adult and older age-related conditions among older people with ID which are higher than that of the general population (25). They frequently experience aged conditions at a much younger age (at 40-45 years) and on average, the mortality rate is around 19 years earlier than individuals without ID (17, 26, 27). The prevalence of frailty (the increased risk of poor health outcomes and dependency) among people with ID at age 50 to 64 is as high as in the general population aged ≥ 65 years, with an additional increase after the age of 65 (28). Apart from the cause of ID, there are some other modifiable factors that are linked with the premature ageing and mortality among people with ID; such as poverty, access to care and records, difficulties in communication and self-advocacy, dependence on others for mobility and feeding, issues with health and care planning, limitation in recognising their needs and adjusting care as needs change, problems with coordination of care and information sharing (23, 29). The age-related decline in health can lead to more dependency, cognitive function deterioration, which reduces the ability of people with ID to have a good quality of life (30).

1.2. Health conditions among people with ID

Individuals with ID having limitation in the intellectual and adaptive abilities makes them vulnerable to many issues in terms of education, socioeconomic status, employment, housing, health status and so on in their lifelong experience. Furthermore, they are prone to have higher rates of obesity, poor nutrition and frequent hospital admissions for a longer duration compared to people with no ID (5, 31).

People with ID experience several and complex health problems at a rate of 1.7 times more than people without ID (32). The brain dysfunctions that cause deficits in intellectual functioning may be related to other disorders like neurological, psychiatric or sensory and mobility disorders (33) which contributes to the early development of multi-morbidity among this population. In Ireland, multi-morbidity reaches 71% in this population (27).

The health conditions experienced by people with ID are stratified according to van Schrojenstein Lantman and Walsh (34) to primary (associated with ID and syndrome related) and secondary as illustrated in *Table 1-1*.

Table 1-1 Conditions associated with ID, syndrome related and secondary to ID (adapted from van Schrojenstein Lantman and Walsh, and O'Dwyer) (34)

Associated	Syndrome related	Secondary
● Epilepsy ● Visual problems ● Mobility problems, including cerebral palsy ● Mental ill health ● Psychosis ● Alzheimer's disease	● Hypogonadism ● Congenital heart disease (Down syndrome and William syndrome) ● Hypothyroidism (Down syndrome)	● Obesity ● Gastro-oesophageal reflux disease ● Constipation ● Fractures ● Untreated caries ● Edentulous ● Sexually transmitted diseases

Epilepsy is commonly reported in adults with ID, with an average estimate of 22.2% (35) and the prevalence is directly proportional to the severity of ID (19). In Ireland, the reported prevalence of epilepsy is 31% in older adults with ID (36). In

addition, Alzheimer's disease is the commonly reported neurodegenerative condition among people with ID and a significant contributor to dementia.

Mental health/neurological disease represented the most prevalent pattern of multi-morbidity (27) in people with ID in Ireland. Severe mental disorders are well recognised in people with ID and the incidence of newly recorded cases is substantially higher than that in the general population (37, 38). The overall prevalence of mental health diseases among older adults with ID and dementia ranged from 20 % to 48 % increasing with age (19, 27). Depression and anxiety are also prevalent and could be a precipitant of many factors like life events, comorbidity, unaddressed pain, communication barriers or polypharmacy side effects (19).

Although cardiovascular disorders (CVD) are of the most common cause of death among people with ID, they (together with their risk factors like hypertension, hyperlipidemia) are less common among people with ID and present at lower rates when compared with the general population which may play a protective factor for longevity (39). Nevertheless, other CVD risk factors (physical inactivity (40), poor nutrition, obesity, dental issues) are prevalent among this population (39, 41) with females being at greater risks. In a 3-year follow-up study on CVD of Dutch population with ID aged 50+, the incidence of CVD was similar to that in the older general population (42). Myocardial infarction was predicted by atypical antipsychotic use and a history of heart failure in people with ID (42). In Ireland, the commonly reported CVDs among older people with ID are congestive heart disease and abnormal heart rhythm (20).

People with ID suffer from gastrointestinal (GI) disorders with high level of occurrence of constipation, GORD, dysphagia and *H. pylori* infection (19, 39).

Furthermore, musculoskeletal disorders such as osteoarthritis, osteoporosis and fractures are reported to be prevalent among people with ID (39). Osteoporosis and related fractures in people with ID (particularly individuals with Down syndrome) occur at higher rates compared to individuals in the general population (39) with older adults affected more frequently than younger adults (41). In Ireland, bone health assessments among older people with ID show rates of osteoporosis and osteopenia reach 41% and 33% respectively (43, 44).

Other physical conditions reported among people with ID include thyroid disease, hearing problems and vision problems (e.g. conjunctivitis, strabismus, cataracts) (41).

Examples of health conditions that significantly increase with age among people with ID are diabetes, hypertension, osteoporosis and hearing and vision problems (41).

Some people with ID (syndrome-specific) may have some particular health risks than others. For instance; individuals with fragile -X syndrome frequently experience musculoskeletal issues, mitral valve prolapse and early female menopause. Subjects with Prader-Willi syndrome are susceptible to diabetes and cardiovascular conditions secondary from morbid obesity (25).

People with ID often experience oral health issues like gingivitis, dental caries and periodontal diseases. These untreated oral issues are among the top ten secondary causes of limitation in the daily activities in people with ID (39). In a controlled study, periodontal diseases developed earlier and at higher extent and severity in people with Down syndrome when compared to peers from the general population (45). A recent systematic review concluded that people with ID are still experiencing a high burden of poor oral health (poor oral hygiene, gingivitis, periodontitis, untreated dental decay and tooth loss) despite it being preventable (46).

Frailty among older people with ID appears early in their life time and this creates a risk factor for further health deterioration and increased dependency (28, 47). It has been reported that the prevalence of frailty among people with ID at age 50 to 64 years is as high as among those aged ≥65 years in the general population (7-9%) with a further increase after 65 years old (28, 48).

The poor health status of individuals with ID is perceived as a reflection of a combination of many factors such as genetic predispositions to certain disease, less favorable social circumstances and residential circumstances which are increased by inactivity and poor lifestyle (5).

1.3. Multi-morbidity and ID

The occurrence of signs of premature aging among people with ID explained by the frequent older age-related conditions makes it important to further investigate and explore issues related to multi-morbidity among this population. Multi-morbidity – defined by the WHO as the presence of two or more health conditions in an individual- is very frequent in people with ID at all ages at different pattern from that of the general people and is spread across the entire adult lifespan (49). People with ID at age 20–25

have levels of multi-morbidity similar to the general people at age 50–54 year (50). In a recent cross-sectional analysis of a UK cohort (n=920), the prevalence of multi-morbidity among a cohort with ID aged 18 to 74 years old was 61.2% and was independently associated with female gender and severe/profound level of ID (51). Another large population-based study (n= 1023, aged 16+ years) in Scotland found that 98.7% of people with ID had multi-morbidity and the most prevalent illnesses described as painful, disabling and/or life threatening. The reported five most predominant conditions in that study were visual impairment, obesity, epilepsy, constipation and ataxic/gait disorders (49).

Older people with ID have about 2.5 times more chronic conditions than their peers from the general population (27). A study of those aged ≥50 years reported a level of multi-morbidity as 79.8% and was linked to age and severe or profound level of ID (52). In Ireland, multi-morbidity was observed in 71% of older people with ID aged 40 years and over (27) and the level increased from 63% in those aged 40-49, to 72% among those aged 50-64 and further increases to 86% among those aged ≥65 years. The most frequent multimorbid condition combinations was mental/neurological disorder and eye disease was the most prevalent co-occurring chronic issue among population with ID. Chronic mental health conditions among people with ID, particularly challenging behaviour, dementia, depression and anxiety combined have been called psychiatric multi-morbidity and this was also prevalent among this population (53).

Multi-morbidity becomes more complex when considering aging issues that are syndrome-specific. For instance, in people with Down syndrome premature aging shows as a high prevalence of osteoporosis, cataract, sensory impairment, hypothyroidism, epilepsy and dementia (19). In the USA, data from the Longitudinal Health and Intellectual Disability Study (LHIDS) was examined to explore the prevalence and factors linked with multi-morbidity in older adults with ID aged ≥ 41 years. The results of that study showed that older adults with ID and multi-morbidity were more likely to be ≥51 years, live independently or in a group home, unemployed, and have limited mobility compared to those without multi-morbidity (54).

Multi-morbidity can negatively modify the health outcomes and cause more disability and decline in quality of life creating challenges and complexities in regard to providing/planning the care of this population (55, 56).

1.4. Medication use and polypharmacy among people with ID

Multi-morbidity is associated with increased levels of medicine use among older people in the general population (57-59) as well as among people with ID (60). According to Maher *et al.*, about 50% of older people use one or more medicines that are not medically needed (61). The level of medicine use among people with ID is higher than the older general population. In a study in Western Norway of adults with ID, total medication use was 62% compared to adults in the general population (50%) with the most highly used medicines prescribed for the central nervous system (62).

Multiple medication use has been described in several studies using the terms polypharmacy (the use of 5-9 medicines) and excessive polypharmacy (the use of ≥10 medicines) (60).There are several concerns surrounding polypharmacy such as inappropriate prescribing (60), drug related side effects, drug interactions, disease–drug interactions, food–drug interactions, medication administration errors (like phonetic confusion, flip-flopping dosing errors) and hospitalization as consequences (63). Inappropriate polypharmacy may occur also when a person is receiving multiple medications where the benefit of the medication is not being achieved or if there is potential harm that outweighs the benefit of using the medicines (64, 65). It has been reported that people with ID are receiving psychotropic drugs at a rate beyond that of recorded mental disorders (66). Over-prescription of antipsychotics was associated with the presence of challenging behaviour, older age and dementia (66).

Among people with ID, polypharmacy is the focus of many studies and has been identified as a concerning prevalent issue in this population (67-69). This complicates the care of people when people with ID are moved from institutions to the community. Many people with ID may experience, in addition to the intellectual disability, physical disability and chronic somatic or neurological disorders that need long term use of medicines (70).

In Ireland, significant proportions of older people with ID aged 50+ years are exposed to polypharmacy and the reported rates exceeded double that reported in older people without ID (39.0% vs.18.1%) (71). The rates of polypharmacy and excessive polypharmacy were observed in 31.5% and in 20.1%, respectively in older adults with

ID. Intraclass polypharmacy was frequently recorded particularly with antipsychotics, antiepileptics, and laxatives (72, 73).

O'Dwyer *et al.* reported that living in residential care, and reporting a mental health or neurological disorders were strongly linked with polypharmacy and excessive polypharmacy (72). Furthermore, those with GI symptoms were more likely to be exposed to polypharmacy and excessive polypharmacy (68, 72).

1.5. Challenges and disparities among people with ID

Since there is an increase in deinstitutionalisation of people with ID requiring them to use primary healthcare services more frequently than before, a consequence of this is that a person with ID may encounter different health-related challenges considering the multi-morbidity level in this population. The significance of these challenges or barriers differs by countries/regions or healthcare structure (25). Example of these challenges are accessing appropriate and effective health services, affordability, transportation to services, communication difficulties with healthcare personnel, reporting their symptoms or health-related needs, insufficient or lack of medical histories and insufficient healthcare provision (5, 74). These challenges lead to health disparities in the population with ID when compared to the general population (75). Several studies detected health-related disparities among old people with ID especially with respect to number of health conditions which are identified as preventable but were most frequently classed as under-diagnosed or inadequately treated (39, 41). Certain disparities have been identified such as oral health, hearing and vision issues, osteoporosis and GI disorders. A review by Krahn and Fox from the US Center of Disease Control and Prevention summarised the health disparities among people with ID and showed a cascade of disparities *(Figure 1-2)* (75). At the top of the cascade, was the point that people with ID have high prevalence of health disorders like neurological issues (e.g. epilepsy), behavioral/ mental issues and GI disorders with some of these conditions being preventable or amenable to improved care. The remaining factors in the cascade are assumed to be preventable such as undetected vision or hearing loss since people with ID are less likely to have benefitted from preventive health screening and health promotion (5). Living arrangements were also shown to be an important influence

throughout this cascade and the final finding of these disparities was the poor health status of people with ID (75).

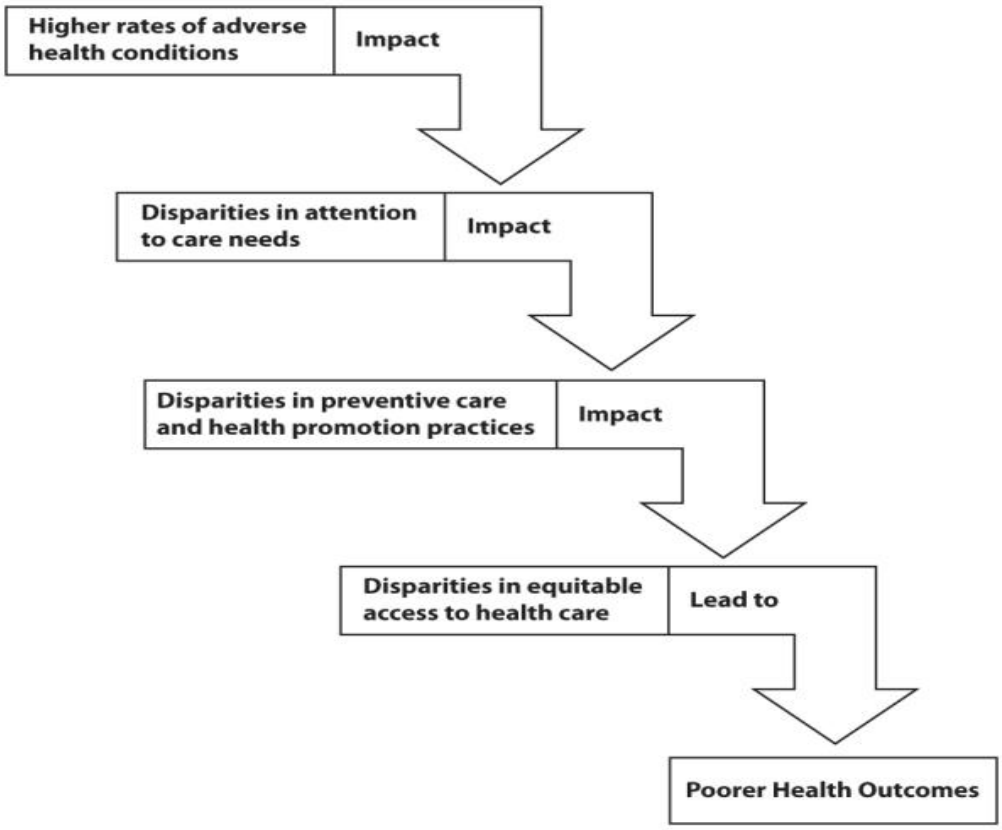

Figure 1-2 Cascade of disparities among people with ID. Adapted from Krahn G *et al.* (75)

The presence of health-related challenges or barriers may create further and potential health consequences among people with ID. For example some individuals with ID may have health conditions or risk factors that are existed from childhood and need an early intervention or management to avoid further disease progression and consequences in their later life (e.g. those with cerebral palsy having GORD/gastritis), or those who receive medicines chronically that are associated with side effects such as anticonvulsants and bone health (76).

Other barriers to people with ID that must be considered are communication difficulties, behavioral issues, insufficient specialised or trained healthcare providers for this population. A general practitioner (GP) or a specialist of a specific disease may need a background knowledge in intellectual disabilities when dealing with a person with ID, so the presence of well-trained specialists can be crucial in enhancing the quality of care for people with ID (25). Moreover, as individuals with ID are frequently excluded from

clinical trials because of limited consent capacity (77), there are few clinical guidelines or standards to manage different health conditions specific for people with ID (5).

1.6. Gastrointestinal health conditions among people with ID

The gastrointestinal tract (GIT) of people with ID is affected by many diseases and disorders. GI conditions among people with ID are very prevalent with GORD and constipation among the contributing conditions to the health disparities among this population as compared to their peers from the general population (19). These are also the health conditions that are not given sufficient importance in health promotion programs for people with ID (19).

Chromosomal disorders that cause ID (e.g. Down syndrome, Edward's syndrome and Patau syndrome) are sometimes associated with GI congenital abnormalities such as duodenal stenosis, oesophageal atresia, hernias and omphalocele (19). Moreover, those with ID and cerebral palsy often experience upper and lower GI motility disorders putting them at risk of developing GORD, dysphagia and constipation as well as their consequences (25). GORD, constipation and dysphagia are functional GI disorders that may arise from childhood (78). In a regional Scottish study, constipation, GORD and dysphagia were the three GI disorders that were in the top 20 physical health conditions for people with ID with prevalence of 33.8%, 14.5% and 12.9%, respectively (49). Findings from a narrative review conducted by Haveman *et al.*, show that GI issues were evident with high occurrence rates of constipation, *Helicobacter pylori (H. pylori)* and GORD (39). In Ireland, constipation and peptic ulcer among older people with ID was more than double of those without ID (17.2% vs. 7.8%) (71).

1.6.1. Constipation

1.6.1.1. Definition

Since constipation is composed of a set of symptoms, its definition or perception by people is influenced by many factors like diet, health situation and social background (79). Some individuals may complain about passing small (reduced faecal volume) and hard stools (faecal consistency) and others may use straining while defecating to define constipation (79). A person may experience fewer than three stools per week and this is

the minimum standard description that has been used to report constipation (79). Nevertheless, the Rome III criteria consider all of the above as contributing to the definition of constipation (80). In order to meet the Rome III criteria for chronic constipation a person should have rare normal or loose stools without laxative use or experience at least 25% of defecations with two or more of the following symptoms over the past 6 months and been active for 3 month; straining, lumpy/hard stool, incomplete evacuation, anorectal obstruction, manual manoeuvre and fewer than three times per week defecation (80).

1.6.1.2. Types of constipation

Constipation can be primary (referred to as chronic idiopathic constipation (CIC) or functional constipation) or secondary due to disease or medicines (81). Primary constipation can be categorised according to the pathophysiology into three types; normal transit constipation - normal anorectal function + normal stool movement along the colon - and this is the most common type of primary constipation. The second type is slow transit constipation - normal anorectal function but slow transit of stool through the colon because of lower or uncoordinated colonic movement. The third type is anorectal dysfunction due to structural abnormalities or defect in contraction/relaxation of the pelvic floor or external anal sphincter and this type is associated with defecation disorders (81, 82).

1.6.1.3. Causes of constipation

There are several underlying causes of constipation including, but not restricted to the following (79, 83-86);

- Dietary: malnutrition or low food intake, poor dentition
- Immobility: due to disease or pain and reduced level of physical activity.
- Geography: difficult access to toilets, lack of privacy, poorly designed toilets.
- Health conditions: metabolic endocrine such as hypercalcemia, hypothyroidism, diabetes mellitus, gut lesion, ischaemia, anal lesion such as fissures and haemorrhoids, neurogenic like multiple sclerosis, Parkinson's

disease, stroke, dementia and depression. *Table 1-2* shows different health conditions that may contribute to constipation with the possible mechanism of causing constipation. In older people, constipation may be because of multiple causes, so finding out one cause should not stop healthcare providers from searching for other possible aetiologies (83).

Table 1-2 Conditions that contribute to constipation

Condition (Possible mechanism in causing constipation)
Neuropathic , myopathy or cardiac
Connective tissue disorders: Scleroderma , rheumatoid arthritis, arthritis
Spina bifida
Autonomic neuropathy
Multiple sclerosis
Amyloidosis
Myotonic dystrophy
Cerebrovascular disease and ischaemia:
Heart attack
Stroke (Causes weakness of the abdominal and pelvic muscles and reduce motility of large bowel and pontine damage may alter behavioural responses to a full rectum(85))
Angina
Congestive cardiac failure
Parkinson's disease (Associated with prolonged transit throughout the entire gut(85))
Paraneoplastic syndrome
Dementia (May be partly by ignoring the urge to defecate)
Psychological diseases
Anxiety
Depression (Predisposes rectal impaction and may be partly caused by ignoring the urge to defecate (85))
Somatisation
Electrolyte imbalance
Hypokalaemia (Causes neuronal dysfunction which decrease acetylcholine stimulation of the gut smooth muscle leading to prolongation of the gut transit time)
Hypercalcaemia (Causes delay in conduction within intrinsic and extrinsic innervation of the gut)
Hypomagnesaemia
Organic intestinal diseases
Obstruction/stenosis: adenoma, colorectal carcinoma, diverticulitis, rectocele, hernia. Faecal impaction, irritable bowel disease.
Anorectal abnormalities: anal stenosis or fissures, proctitis, rectocele, haemorrhoids.
Endocrine-metabolic causes

Condition (Possible mechanism in causing constipation)
Hypothyroidism
Hyperparathyroidism
Diabetes mellitus (Maybe due to the associated autonomic neuropathy)
Hyperglycaemia
Uraemia
Chronic renal insufficiency
Low fibre intake in the diet
Dehydration

- Medications: There are various medicines that cause constipation as a side effect; some of them commonly cause constipation, such as iron or calcium supplements, opioid analgesics, antacids containing aluminium, any medicines with anticholinergic of antimuscarinic properties like antipropulsives, antihistamines, some antipsychotics, antidepressants and antiparknsonian drugs (87). Other therapeutic classes that may cause constipation are (82, 87-91) :
  - Bile acid sequestrants
  - 5-hydroxytryptamine type 3 receptor antagonists (5-HT3 antagonists)
  - Antihypertensives (e.g. clonidine, calcium channel blockers, beta adrenoceptor antagonists)
  - Diuretics
  - Antiarrhythmics
  - Anticonvulsants
  - NSAIDs

The mechanism behind causing constipation varies based on the mechanism of action of the medicines and occurs mostly by either reducing or interrupting the normal rhythm of intestinal muscle contraction (peristalsis) and or by changing the fluid balance in the intestines. Anticholinergics (specifically the antimuscarinics) block the parasympathetic effect of acetylcholine on muscarinic receptors causing suppression of the motility and secretion in the GIT, including the large intestine (92). The resulting reduction in colonic motility permits increased water absorption all along the small intestine creating a drier waste and slower movement of the waste into the large intestine (93). Occasionally the suppression in intestinal motility may cause a paralytic ileus and this has been reported with the use of some antidepressants and atropine (94).

The opioids cause an increase in the segmenting activity and a reduction in propulsive activity of the small and large intestines. This arises from the stimulation of μ and κ-receptors of the gut wall's neuronal plexuses (92). Calcium channel blockers (mostly verapamil) decrease the rate and strength of gut's smooth muscle contraction leading to alteration of gut motility (93). Aluminium (in some antacids) act as a cation that inhibits the motor activity of the stomach and the intestines. Diuretics may cause constipation by depleting the fluid balance in the intestine, apart from those agents with anticholinergic activity.

1.6.1.4. Constipation among people with ID

Constipation is a prevalent complaint in older population and a frequent concern for healthcare professionals in different sectors - hospitals, long term facilities and primary care (85). Generally, normal aging does not cause prolongation of colonic transit time but this may occur in sick individuals such as those who are bed-bound, immobile, with low oral fluid or fibre intake, side effects from constipating medicines or from some diseases (85). Constipation in people with ID has been reported more commonly compared to reports from the general population yet being a treatable condition (39). A systematic review estimated the prevalence of constipation among people with ID and found that the prevalence varies and from 33% to over 50 % (95). The normal ageing process among people with ID itself appears not to be a risk factor for constipation but rather age-related health conditions such as immobility or low level of physical activity, neurological diseases or some medicines (39, 41, 96).

1.6.1.5. Medication associated with constipation among people with ID

Almost any medicine can affect the GI system by different mechanisms. GI side effects from medicines are not uncommon among the older population. GI complications such as GI bleeding, peptic ulcer, erosive gastritis, nausea and vomiting are the most common Adverse Drug Reactions (ADRs) causing hospitalisation in the older adults (97). According to Fernandes and Norman, GI side effects can be predicted as a result of a drug's mechanism of action (98); one example was the anticholinergics, which diminish oesophageal sphincter pressure, causing reflux and heartburn as well reducing colonic transit, causing constipation (98).

Medicine use has been identified as one of the contributing factors of developing constipation in the population with ID. The high burden of exposure to anticholinergic polypharmacy that has been reported among people with ID plays a significant role in developing constipation among this population (72, 99) mainly from antipsychotics, anti-epileptics and antidepressants (99, 100). In Ireland, a study of older people with ID, assessed the cumulative exposure to anticholinergic medicines among people with ID using the validated Anticholinergic Cognitive Burden (ACB) scale. The scores were categorised as no exposure to anticholinergic medications (ACB 0), ACB score of 1–4, and ACB score of 5+. According to O'Dwyer *et al.*, 41.8% of older adult with ID had ACB scores from 1–4 and 29.1% had ACB scores of 5+ reflecting the high exposure to anticholinergics and this was associated with constipation and laxative use (99).

Furthermore the use of PPIs, not as anticholinergics, was significantly associated with constipation among people with ID (101).

The risks and severity of constipation is increased if more than one constipation-causing medication is in use or larger doses of these medicines are taken. People with ID are under a substantial burden of polypharmacy and many of the medications are constipating such as the anticholinergics (72).

1.6.1.6. Other factors that contribute to constipation among people with ID

According to Velde *et al.*, people with ID who have constipation have pathophysiological factors such as prolonged colonic transit time in all segments of the colon, indicating diffuse colonic inertia problems, and those with no constipation have prolonged recto-sigmoidal colonic transit time, suggesting defecation issues (102).

Constipation can be partly the result of other conditions or causes that are frequently present in some genetic or chromosomal disorders. For example, Williams syndrome has been associated with hypercalcemia which may partly contribute to constipation among those individuals (19). Another example is hypothyroidism which is prevalent in people with Down syndrome and is associated with constipation (95). People with Down syndrome may experience Hirschsprung's disease (a congenital gut motility disorder) that is a risk factor for constipation among this group (95). Moreover, neurological disease, cerebral palsy, immobility and intellectual disability (IQ < 30) have

been reported as significant factors that are associated with constipation in the population with ID (101, 103). Moreover, people with ID frequently have sedentary lifestyles (104, 105); physical inactivity has been reported in almost three-quarters of the older population with ID (43, 106).

Furthermore, as edentulism is a frequent issue among people with ID (107), this exposes them to diets with a low fibre intake leading possibly to constipation (19). In line with this, constipation itself has been used as a sign for nutrition-related issues (insufficient fluid and fibre intake) in people with ID (19). In a study of subjects with ID, eating fruit and vegetables was not sufficient to provide a good healthy diet and adequate fibre intake (108). In addition, some people with ID frequently receive thickened fluids because of dysphagia and may be exposed to dehydration if they rely on thickened fluids for oral hydration (109).

Since constipation involves a set of subjective measures, people with ID who have communication difficulties may express their discomfort and pain through behavioral changes and aggression (95, 110).

Constipation if left improperly treated can lead to additional distress and anxiety among people with ID (101). More serious consequences of chronic constipation are bowel obstruction (which may require surgery), encopresis (or faecal incontinence), anorectal disorders (like haemorrhoids and anal fissure), pelvic organ prolapse, rectal distention, idiopathic megacolon, nausea and ischaemic ulcer or perforation of the colon. All these may create distress which is poorly tolerated by older people or older people with ID (111, 112). Among people with ID, constipation is regarded as an ambulatory care sensitive condition and of the common causes for hospitalisation (113).

People with ID may have more serious life threatening consequences from constipation (112) since there are some reports of deaths due to bowel obstruction and intestinal perforation in this population (25, 114).

Generally, constipation has been found to negatively affect the quality of life of adults and of the older general population (115-117) as well among people with ID (118, 119).

1.6.2. GORD and acid-related disorders

GORD occurs when the contents of the gastroduodenal section are retrograded back to the oesophagus or the adjacent GI parts causing a range of symptoms which may be associated with tissue damage (120). Weakness of the lower oesophageal sphincter or oesophageal dysmotility could be the reasons behind the backflow of the gastroduodenal content. GORD can be due to genetic disorders or secondary to some diseases (120).

GORD is a common GI condition in people with ID and is frequently overlooked and underestimated (39). The estimated prevalence of GORD among people with ID was reported from 33%-50% (39). In a Dutch study of patients with ID with IQ < 50 (n=1687), reflux oesophagitis was suspected in 169 patients based on symptoms and then diagnosis confirmed 107 cases mostly with severe grades of oesophagitis (121).

There are many predisposing factors for developing GORD in people with ID. Neurological defects in people with ID may lead them to develop GORD by decreased lower oesophageal pressure resulting in an increased percentage of non-propulsive waves or by delayed gastric emptying time. Another possible factor is the involvement of the 'vomiting centre' of the central nervous system that may cause abnormal gastric motility and vomiting thus instigate GORD (122). One study has suggested that other factors include immobility, cerebral palsy, a severe level of ID (IQ<35), and the use of anticonvulsants or benzodiazepines (39). In addition, people with ID commonly use medicines that have a potential to aggravate GORD, such as calcium channel blockers, anticholinergic agents, benzodiazepines and barbiturates (123).

GORD is associated with some symptoms like abdominal/oesophageal pain, rumination and regurgitation and yet it may also be associated with visceral pain that can be misinterpreted by subjects with ID. Some people with ID may be unable to tolerate GORD-related pain leading to self-injurious behavior (19, 124). Behavioural issues or altered behaviour (e.g. aggression, fear, screaming, restlessness) have been found to be significantly associated with reflux oesophagitis among subjects with ID (124). Furthermore, hand mouthing behaviour was observed more frequently among subjects with a severe level of ID who were diagnosed with GORD (125). Since people with ID may not be able to communicate the symptoms of heartburn (an indication for

GORD), a systematic review concluded that vomiting, haematemesis and rumination (i.e. bringing back up and re-chewing partially digested food that has already been swallowed) are significant symptoms that are associated with the risk of undetected GORD and concluded that there was no clear evidence that GORD is indicated by particular behavioral symptoms (126). Complications of chronic reflux oesophagitis such as Barrett's oesophagus occurs among people with ID at rates of 14% - 26% (127).

1.6.3. Dysphagia

The condition dysphagia refers to difficulty in swallowing while eating or drinking and is not uncommon among people with ID (128). Dysphagia in people with ID often arises because of a combination of behavioural, anatomical and physiological factors. Those with genetic abnormalities that are associated with hypotonia or altered anatomy of the oral cavity (like Down syndrome, Prader-Willi syndrome and Rett syndrome) frequently experience feeding difficulties (19). Behavioural factors like pica (compulsive eating of non-nutritive substances, such as clay, starch, ice and dirt) (129), drinking/eating very quickly and cramming food are triggers for dysphagia in people with ID (130). The severity of ID (severe/profound), comorbid cerebral palsy and motor impairments all are associated with increased likelihood of dysphagia in this population (128). In 40 adults with ID, dysphagia was present at the oral stage for 97.5%, pharyngeal stage 65%, oesophageal 17.5% and 67.5% presented with dysphagia at more than one stage (131). People with ID who experience dysphagia may be able to eat only puréed food/soft food exposing them to dehydration, undernutrition and failure to thrive (131). Dysphagia can be associated with serious complications such as choking, respiratory infection (e.g. aspiration pneumonia) or lung inflammation caused by foreign bodies/liquids and its subsequent morbidity has been reported in people with ID (131).

1.6.4. *H. pylori* infection

People with ID are at risks of many GI infection such as *H. pylori* that colonise the gastric mucosa leading to gastritis, gastrointestinal malignancy and subsequent mortality. Infection from *H. pylori* has been correlated to stomach ulcers and carcinoma as well as primary B-cell lymphoma (132, 133). Among hospitalised adults with ID in

England, about 48% of all deaths from cancer were of a type of stomach cancer which were attributed to *H. pylori* (134).

People with ID are exposed to *H. pylori* infection at nearly twice the rate of the general population and have recurrences after eradication treatment at a rate almost seven times that of the general population (132). *H. pylori* has been observed more in people with ID who were living in residential care and the risk increases with the increased length of residence (39). In a Canadian study of adults with ID, around 80% of participants with a history of institutionalisation presented with *H. pylori* infection and that was 3–4 times more than for adults with no history of residence in an institution (135). The risk factors for *H. pylori* infection in the population with ID are maladaptive behaviors, mental disability of an IQ <50, rumination, hyper-salivation, dysphagia, self-injurious behavior, fecal soiling and fecal ingestion (132). In spite of that, *H. pylori* infection is manageable, Wallace *et al.* emphasised the need for repeat testing for any *H. pylori* infection after management since 40% of people with ID remain infected after treatment and are at risk for diseases related to *H. pylori* (136). *H. pylori* relapse among people with ID has been reported as high and to range from 8%-21% (39).

1.6.5. Coeliac disease

Coeliac disease (CD) is an autoimmune disease that is associated with damage of the surface of the small intestine because of intolerance to the protein “gluten” found in many grains, including wheat, barley, rye and triticale. CD is strongly linked to genetic predisposition (137). People with Down syndrome are more likely to be affected by this disorder with a prevalence of 18% reported in this population (138, 139).

1.7. Proton Pump Inhibitors (PPIs)

1.7.1. Indications for PPI use

PPIs are among the most effective medicines to manage acid-related disorders of the GIT. The major indications of PPI are GORD and gastroduodenal ulcers, and concomitantly with antibiotics to treat *H. pylori* infection. Long term treatment with PPI is used in clinical practice for GORD and concomitantly with any NSAIDs to protect the GI from acidity or ulceration (140). There are few data confirming that the use of low

dose aspirin is associated with GI complications, nonetheless, it is recommend to use PPI prophylaxis especially in older people aged >75 years (141). PPIs may be administered to patients treated with clopidogrel to reduce the upper GI complications but should be individualised depending on the patient's bleeding and cardiovascular risk (98). *Table 1-3* illustrates indications for the use of PPIs reviewed in a Cochrane meta-analysis (140).

Table 1-3 Indications of PPIs adapted from Mössner (140)

Indication	**Results**
Short-term management of reflux oesophagitis	PPIs: most effective medical treatment of reflux oesophagitis. Histamine-2 receptor antagonists (H2RAs) more effective than placebo.
Short-term treatment of non-erosive reflux disease (NERD)	PPIs: more effective improvement of heartburn than H2RAs, both with empiric treatment and in endoscopically confirmed NERD.
Long-term treatment of reflux disease	PPIs: most effective long-term medical treatment to prevent recurrences, with regard to both symptoms and endoscopically confirmed lesions with PPIs more side effects compared with H2RAs, especially headache.
Long-term treatment of reflux disease: PPIs versus laparoscopic fundoplication surgery	Results of the available studies are still inconclusive. Among others, the benefits and risks of surgery must be compared with the risk of long-term PPI treatment.
Interventions for heartburn in pregnancy	Available studies evaluated the use of antacids, sucralfate and acupuncture, but not PPIs. Lack of studies leaves questions unanswered, such as the risk of miscarriage or preterm birth, patient satisfaction, malformation rate, intrauterine growth retardation, low birth weight.
Treatment of heartburn in children	PPIs effectively treat erosive oesophagitis; low level of evidence (insufficient studies)
PPIs for asthma	No improvement of pulmonary function or asthma symptoms
PPIs for non-specific cough	PPIs likely to have no effect

Indication	Results
PPI treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding	Endoscopy may find signs of previous bleeding less frequently if treatment has already been started. Need for endoscopic treatment is reduced. No effect on key clinical parameters, such as rebleeding rates, lethality and indication for surgery.
PPIs for peptic ulcer bleeding	PPIs reduce the re-bleeding rate after endoscopic haemostasis and the need for surgery compared with H2RAs and placebo, but not lethality.
Dose and route of administration of PPIs for peptic ulcer bleeding	The currently available studies do not answer questions about the equivalence, superiority or inferiority of high-dose PPI treatment versus low-dose PPI treatment for the endpoints re-bleeding rate, need for surgery and lethality.
H. pylori eradication	Triple therapy (PPI + amoxicillin + clarithromycin, or PPI + clarithromycin + metronidazole): 2-week treatment regimen achieves higher eradication rates compared with one-week regimen.
Prevention of NSAID-induced gastroduodenal ulcers	PPI, misoprostol and double dose H2RA reduce risk of developing gastric or duodenal ulcers. Misoprostol has more side effects (diarrhoea).

NERD: non-erosive reflux disease; NSAIDs: nonsteroidal anti-inflammatory drugs; HR2A: histamine-2 receptor antagonists.

1.7.2. Long term use of PPIs and associated risks

The use of PPI continues to increase internationally with a concern around side effects and costs from the long-term use (140, 142). In the older population, because of the safety concerns linked with PPIs, PPI use should always be appropriate, with balancing of the benefit and potential harm (143, 144). The most critical postulated risks are represented by vitamin B_{12}, magnesium and iron deficiency, enteric infections, spontaneous bacterial peritonitis, pneumonia, ischaemic heart attacks, chronic kidney disease, dementia, Alzheimer disease and bone fractures (145).

There are some studies that have reported a link between long-term PPI use and the risks of osteoporosis or fractures (146). In 2010 the Drug and Food Administration,

FDA, released a safety warning about the risk of hip, wrist and spine fractures that correlated with PPI use for more than one year (147). The warning was based on reviewing many epidemiological studies, of which, the majority evaluated people aged 50 years and older and showed the higher risks among this age group. Likewise, the European Medicines Agency published a similar warning (148). A meta-analysis of 11 international observational studies indicated that the use of PPIs was associated with a modestly increased risk of hip fractures. Spine fractures were also more frequent among PPI users, and there was a small increase in risk of any-site fractures. Pooling indicated that PPI users for <1 year and >1 year were similarly associated with increased fracture risk (149).

PPI use was identified in some studies as a contributing cause of *Clostridium difficile* infection (150, 151), community-acquired pneumonia (152, 153) vitamin and mineral deficiency (especially B_{12} and magnesium) (154, 155) and dementia (156). In addition, PPI use was linked with increased mortality in settings where residents experienced higher levels of disability and possible susceptibility to adverse drug events (157).

1.7.3. Prevalence of PPI use among older general population

The use of PPI in the general older population is well documented and tracked and ranges from 23% to 79.7% (*Table 1-4)*. A higher reported prevalence of 97.4% and 98% for older people at hospital admission and discharge, respectively has been reported (158). Numerous studies have detected over prescribing of PPIs which were characterised by inappropriate use. In a study of 2,370 nursing home resident in France, most PPI prescriptions were inappropriately related to a general condition of health vulnerability, reflected by polypharmacy and comorbidities (159).

Table 1-4 Studies report the use of PPI among older general population

	Study title/origin	Settings/age	Prevalence/ related information	Additional Comments
	Multi-morbidities and over-prescription of proton pump inhibitors in older patients. France (160).	Hospital (≥75 years).	280 patients treated with PPI. Over prescription of proton pump inhibitors was found in 73.9% (n=207) of the sample. Their mean age was 86.7 ± 7.9 years and 23.2% were nursing homes residents.	Overprescribing considered when the PPI is not prescribed for the following main indications: Treatment of GORD and oesophagitis, prevention and treatment of the gastroduodenal damage due to the NSAIDs in high risk patients, eradication of *H. pylori* and the treatment of gastroduodenal ulcers.
	Prevalence and associations of the use of proton pump inhibitors in nursing homes: a cross-sectional study, France (159).	Nursing homes (Mean age 86±8.2 years).	Sample size n= 6275 residents. PPI use: 37.8% (n=2370).	
	Proton pumps inhibitors utilisation in older people in New Zealand from 2005 to 2013 (161).	Population-based (Older adults).	In 2013 the prevalence of PPI use was 35%.	PPI utilisation increased by 26.7% from 2005 to 2013.
	Marked increase in proton pump inhibitors use in Australia (162).	Population-based (All ages).	Considerable use of PPI was noticed in the elderly with the	

Study title/origin	Settings/age	Prevalence/ related information	Additional Comments
		peak use being among those aged 80 years and over.	
Use of proton pump inhibitors with lack of diagnostic indications in 22 midwestern US skilled nursing facilities. USA (163).	Long term care facilities (Older adult).	Of 1381 total admissions, 79.7% (n=1100) of patients were prescribed PPIs.	There was no appropriate diagnosis for PPI use in 718 patients (65.3%). When long-term use of NSAIDs, including aspirin and/or anticoagulant therapy (warfarin) was considered as appropriate indications for 382 patients, 336 (24%) of all patients were still receiving PPIs with no relevant gastrointestinal ICD-9 diagnostic code.
Prevalence and appropriateness of drug prescriptions for peptic ulcer and gastro-oesophageal reflux disease in a cohort of hospitalised elderly. Italy (158).	Hospital (≥65 years).	Sample size at admission n= 466 and at discharge n=647. PPI use at admission was by 97.4% of patients. PPI use at discharge was by 98% patients.	Lansoprazole and omeprazole were the main agents prescribed.
Proton pump inhibitors and functional decline in older	Hospital (Mean age	Sample size n=401 PPI use = 33% (n=132).	Prescribing PPI without documented indication was observed in 31%.

	Study title/origin	Settings/age	Prevalence/ related information	Additional Comments
	adults discharged from acute care hospitals. Italy (164).	79.2± 5.5 years).		
	Risk of dementia in elderly patients with the use of proton pump Inhibitors. Germany (156).	Community (People aged ≥75 years).	Sample size n= 3076 PPI use: 23% (n=713).	
	Prescribing patterns of proton pump inhibitors in older hospitalised patients in a Scottish health board. Scotland (165).	Geriatric hospital (Mean age 84 ± 7 years).	Sample size n=361 PPIs were prescribed to 41.0% (n=148) of patients. Inappropriate overprescribing was observed in 85.8% (n=127) patients.	Omeprazole was the most commonly prescribed drug (66.9%) followed by lansoprazole (29.1%).
	Prevalence and predictors of non-evidence based proton pump inhibitor use among elderly nursing home residents in the US (166).	Nursing home (≥65 years).	Overall PPI use prevalence was 27%.	Among those who were receiving PPIs, 48.59% of the use was not evidence-based.

ICD-9: International Classification of Diseases-9.

1.7.4. Inappropriate prescribing of PPI in older population

Several studies have investigated the appropriateness of prescribing of medicines in older populations using explicit and comprehensive sets of prescribing indicators (167). Many of these studies, including some that were conducted in Ireland, found that the most potentially inappropriate prescribing was in relation to PPI use *(Table 1-5).* Inappropriate use of a PPI, using the Screening Tool of Older Person's Prescriptions (STOPP) criteria is defined as the use of PPI for uncomplicated peptic ulcers at a full therapeutic dose for more than 8 weeks (168).

The Irish Longitudinal Study on Ageing (TILDA), that included 8,175 subjects (aged ≥ 50 years) highlighted that PPI use was potentially inappropriate in 17.2% with this increasing to 21.9% after follow up at two years (169). This is more than what was reported in Northern Ireland (11%) and the UK (3.7%) (170, 171). In addition, inappropriate prescribing of PPIs in older adults reached a prevalence of 85.8% in hospital settings (160, 165). *Table 1-5* shows some findings from studies conducted to assess the inappropriateness of medicines among the older general population where the use of a PPI featured most frequently.

Table 1-5 Studies to assess the inappropriateness of medicine use in the general older population

Study title, origin	**Settings/age**	**Criteria**	**Results related to PPI**
Potentially inappropriate prescribing in older people with dementia in care homes. a retrospective analysis. England (172).	Nursing homes.	STOPP criteria.	Inappropriate use of PPI was the third most prevalent at the study 1st time point and the second mostly prevalent at the study 2nd time point.
Potentially inappropriate prescribing and cost outcomes for older people: a national population study. Ireland (173).	National population Irish study (age ≥70) in 2007.	STOPP criteria.	Inappropriate use of PPIs was the most prevalent (17%).

Study title, origin	Settings/age	Criteria	Results related to PPI
Potentially inappropriate prescribing in an Irish elderly population in primary care. Ireland (174).	Primary care services Patient aged ≥65years.	STOPP criteria.	The criteria identified a total of 346 potentially inappropriate medicines (PIM) prescribed for 284 patients. The highest prevalence of potential inappropriate prescribing was related to PPI use (n=102).
Inappropriate drug prescription at nursing home admission. Spain (175).	At nursing home admission.	STOPP criteria and the Australian criteria looking for potentially inappropriat e drug treatments.	The most frequent potentially inappropriately used drugs detected were the PPIs.
Longitudinal prevalence of potentially inappropriate medicines and potential prescribing omissions in a cohort of community-dwelling older people. Ireland (169).	Community-based (age ≥50 years). The Irish Longitudinal Study on Ageing (TILDA).	Many tools including STOPP criteria.	Inappropriate use of PPIs was significantly increased from 17.2 to 21.9 % between the baseline and follow-up time (a two years duration) ($p<0.001$).
Potentially inappropriate prescribing and cost outcomes for older people: a cross-sectional study using the Northern Ireland Enhanced Prescribing Database (171).	Participants aged ≥70 years in 2009/2010 who attended primary care.	STOPP criteria.	The overall prevalence of PIM among the study population (n=166,108) was 34 %. The most common was related to PPI use (11 %, n=17,931).
Potentially Inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalised patients. Ireland (176).	Hospital (age ≥65 years).	STOPP and Beers criteria.	The most commonly PIM was inappropriate use of PPIs (n=128).

Study title, origin	Settings/age	Criteria	Results related to PPI
Potentially inappropriate prescribing among older people in the United Kingdom (170).	Participants included those aged ≥ 70 years.	STOPP criteria.	The third most prevalent Potentially Inappropriate Prescribing (PIP) was inappropriate use of PPIs (3.7%). PIP was strongly associated with polypharmacy.
Potentially inappropriate prescribing including under-use amongst older patients with cognitive or psychiatric co-morbidities. Switzerland (177).	Hospital (mean age 80 ± 9 years).	STOPP/ START.	Out of 150 participants, Inappropriate use of PPI represented 14.7% (n=22).

STOPP: Screening Tool of Older Person's Prescriptions, START: Screening Tool to Alert to Right Treatment, TILDA: The Irish Longitudinal Study on Ageing, PIM: Potentially Inappropriate Medicine, PIP: Potentially Inappropriate Prescribing.

2. Chapter Two

2.1. Part I: Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA)

2.1.1. Study design

The data for this research was drawn from the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA), a population-based nationally representative longitudinal study which examines the ageing profile of people with ID (20). IDS-TILDA runs alongside another observational study of community-dwelling older adults aged ≥ 50 years in Ireland, the Irish Longitudinal Study on Ageing (TILDA), which began in 2009, and included a population of over 8,500 participants (178). The unrepresentative number of older people with ID in the TILDA study led to the inception of IDS-TILDA. IDS-TILDA aimed to recruit participants aged 40 years and older in comparison to TILDA who recruited individuals aged 50+ years. This difference was to account for the low life expectancy and presentation of older-age conditions and signs of functional decline and dementia that occurred early in people with ID (28, 179, 180).

There are seven underpinning values of IDS-TILDA including; inclusion, choice, empowerment, person centred, the promotion of people with ID, the promotion of best practice and to make a contribution to the lives of people with ID. This values frame underpins the philosophy of IDS-TILDA to ensure individuals with ID are true participants involved in the development of the study, the review of questions, review of easy read material and support dissemination. Along with a values frame, IDS-TILDA has a comprehensive conceptual framework as shown in *Figure 2-1* which shows the question domains and their subcategories included in the study. Harmonisation between questions of IDS-TILDA and TILDA was designed to allow for comparability between the two studies. This is the justification behind the questions and measures selected for use in IDS-TILDA. Some questions were modified to make them accessible for people with ID. The consent process was adapted specifically for individuals with ID and supported with easy-read and accessible material. The study also employs a system of process consent whereby consent is reaffirmed with the participants between each domain.

The aims of IDS-TILDA are; to understand the health characteristics of people ageing with an intellectual disability; to examine the service needs and health service utilisation of people ageing with an intellectual disability; to identify disparities in the health status of adults with an intellectual disability as compared to TILDA findings for the general population and to support evidence-informed policies, practices and evaluation (20).

People with ID were involved at each stage of the study design, in particular in terms of developing accessible materials and dissemination of findings via easy-to-read materials and short films showing the findings of the study. Data from Wave 1, Wave 2 and Wave 3 were used in this thesis.

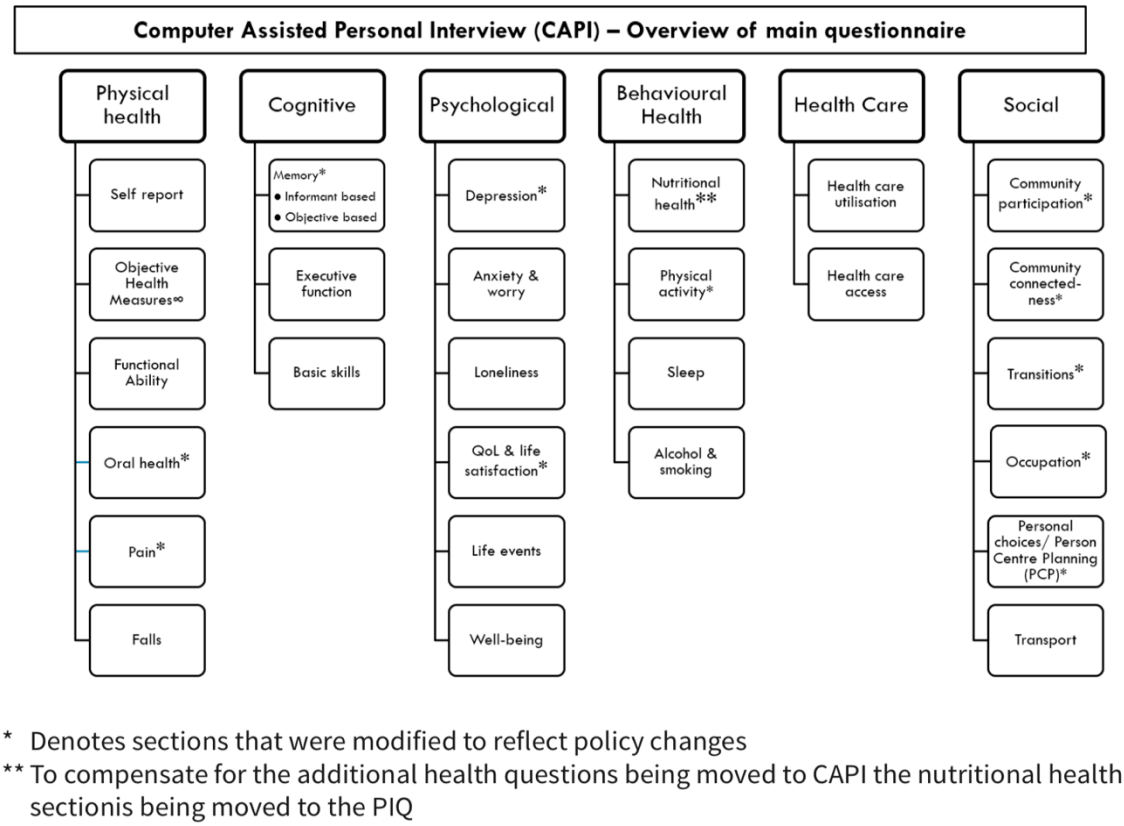

Figure 2-1 IDS-TILDA conceptual framework adapted from Wave 3 IDS TILDA report

2.1.2. Ethical approval

The IDS-TILDA was approved by Faculty of Health Sciences Research Ethics Committee in Trinity College Dublin (*Appendix 1*) and all 138 intellectual disability service providers in Ireland.

2.1.3. Study population and recruitment process

The IDS-TILDA sampling frame was provided from the National Intellectual Disability Database (NIDD), a service tool which gathers data for all people with ID in Ireland eligible for, or receiving services (181). There were 26,066 individuals registered with NIDD at the time of the first Wave IDS-TILDA, which included all individuals of all levels of ID across the full range of residential types, these include living with family, community group homes and residential type services (181). There were 41.1% individuals (n=10,725) aged ≥35 years, among them 29% (n = 3,154) were aged ≥55 years (181). Every individual with ID is assigned a PIN when registered with the NIDD and it was through this PIN system that individuals could be randomly selected.

In total, 1,800 participants PINs were randomly selected from the NIDD by staff at NIDD. The NIDD sent the PIN numbers of potential participants to the Regional Disability Database Administrator (RDDA). The IDS-TILDA study prepared the required number of invitation packs (containing the invitation letter, information booklet, consent form and family agreement form) and sent them to the RDDA who addressed and posted the invitation pack to the person associated with each PIN. This ensured the confidentiality of the individual was preserved and only on return of the consent did the IDS-TILDA study know who was participating, in subsequent waves the same cohort were invited to participate and consent was obtained at the time of their face-to-face interview. It was recognised that some people with an ID would be unable to provide consent independently. Each invitation pack also included a family pack, and in such cases where the support worker/ key worker or the individual themselves perceived the person as unable to independently self-consent, a family member/ guardian was requested to review the materials and to sign a letter of agreement supporting participation in the study of their family member, and to return the letter to the research team in the provided stamped addressed envelope (20). A total of 753 people with ID consented to participate in Wave 1 IDS-TILDA (representing 8.9% of the ID population over the age of 40 years. From Wave 1 (2009-2010), 708 continued participation in Wave 2 (94% retention rate; 2013-2014). Participants in Wave 2 were invited to take part in Wave 3 IDS-TILDA (2016-2017). From Wave 2 (n=708), there were 609 participants who

completed the personal interview in Wave 3 and the most common causes of the attrition since the prior wave were attributed to deaths (70.7%, n=70).

The sample of the three waves were comparable to the NIDD database. This thesis examined data from Wave 2, Wave 3 with some data from Wave 1 to allow for comparison.

2.1.4. Data collection process

Data collection for all waves of IDS-TILDA was performed by field researchers who had extensive experienced working with people with ID. They were all trained with a three days comprehensive training program related to managing their caseload, scheduling interviews, data collection, data protection and adaptive communication skills. Training on collection of medication data was provided by a pharmacist.

Data collection process composed of three sections;

- A pre interview questionnaire (PIQ): which was sent to each participant one week in advance to the scheduled interview. This was designed to increase reliability by giving respondents time to source the information; a follow-up phone call ensured receipt of the questionnaire, addressed any initial queries and confirmed the date and time for the interview. Participants and carers entered data on demographic information, health status, healthcare utilisation and medication usage. The PIQ contained the section for medication data collection (*Appendix 2*) as well as sections related to eye health, heart health, other physical health conditions, chronic lung disease, arthritis, cancer, Parkinson's disease, mental health, epilepsy, constipation, medical tests and screening, female health conditions, male health conditions and healthcare utilisation.
- A Computer Assisted Personal Interview (CAPI): This is a face-to-face interview by a field researcher. Different interview styles were used to support individuals of all levels of ID to participate including self-report, proxy-only or a combination of both. A proxy is a person (family member, carer or keyworker) familiar with the person with ID for a period of at least six months. The CAPI included sections related to demographics (like place of residence and religion), cognitive health, social participation (general activities, social activities and transport), social

connectedness, personal choices, ageing perceptions, occupation (employment, sheltered work, day services, unemployment and retirement), sources of income, voluntary work, life-long learning (reading, writing, numeracy, money and technology), physical health (overall health, eyesight, hearing, general communication, oral health, nutritional health, foot health, falls, fear of falling, steadiness and fractures, pain, bladder incontinence, bowel incontinence), mental health, behavioural health, activity of daily living (ADL), functional limitations, dressing, walking, getting about the home, bathing and showering, oral hygiene, eating, getting in and out of bed, using the toilet, support with activities of daily living, preparing a hot meal, shopping for groceries, making telephone calls, managing money and doing household chores.

- A comprehensive health assessment was carried out at Wave 2, the objective measures included height, weight, waist to hip ratio, grip strength, timed up and go test, blood pressure (4 measures, 2 sitting and 2 standing), and quantitative heel ultrasound. These were conducted by a trained research nurse. In Wave 3 a mini home health assessment was conducted and this involved collecting objective measures including weight, waist size, and mid upper arm circumference (MUAC) for all participants. Each field researcher received specific training on administering these assessments and each was assessed for technique and competency by an experienced health assessor (182).

In Wave 3, additional scales were added to collect further information on issues arising from Waves 1 and 2. These include the Rapid Assessment of Physical Activity (RAPA), validated measures of life satisfaction (Satisfaction with Life Scale - SWLS), purpose in life (Ryff Psychological Wellbeing Scale), quality of life using Personal Wellbeing Index- ID (PWI-ID). Furthermore, Behaviour that Challenges was assessed in Wave 3 using a validated measure called The Behaviour Problem Inventory-Short Form (BPI-S). Carers were asked to rate the frequency and severity of thirty different behaviours which included items of aggression, self-injury and stereotyped behaviours (182).

The author played an active role in medication data cleaning for Wave 2 and medicine data entry, coding, quality assurance and health conditions crosschecking for Wave 3. The medicines data entry and cleaning involved checking Anatomical Therapeutic Classification (ATC) codes, verifying doses for relevant medications, re-examining hard copies of PIQs to solve queries related to medication name, ATC codes, doses and identifying errors. Template copies of the PIQ and CAPI are available online at:

https://idstilda.tcd.ie/about/resultsw2.php

2.1.5. General Data Protection Regulation (GDPR)

IDS-TILDA complies with the requirements of the General Data Protection Regulation (GDPR). Data is kept secure, ensuring that researchers do not remove data from the research office and that any identifiable personal data is only accessible to the PI, the project manager and the Senior Executive Officer. The Assisted Decision- Making (Capacity) Act, 2015 presumes in law that someone can provide consent unless it is proven that they cannot. However, it is not always possible to get informed consent in intellectual disability so proxy respondents have been invited to participate on the person's behalf. Under GDPR and the Health Research Regulations, 2018 (HRR), this is not allowed. The implication being that any data collected in the past where there was no consent given or sought would have to be destroyed. The only exception to seeking re-consent (or gathering data from those who cannot consent) is to get a waiver from the Health Research Consent Declaration Committee (HRCDC). The application from IDS TILDA is pending a decision from this Committee in Autumn 2019.

The author completed the online GDPR learning module provided by Trinity College Dublin Blackboard Learning before implementation of GDPR on 25th May 2018, and attended 4 hours GDPR lecture after that date. The author also completed the masterclass on data protection regulations within the IDS-TILDA study and signed the studies agreement protocol see *Appendix 3*. The protocol includes agreement that no data will be copied or saved on any external form, the author could only access data on the secure IDS-TILDA drive and data was pseudonymised by giving every participant a Personal Identification Number (PIN). The author was not involved in this

pseudonymisation process and did not have access to the identification keys for the study.

2.1.6. Access to IDS-TILDA dataset

In order to avoid any risk of identifying individuals when combining variables, no researcher has full access to the complete dataset of variables. Therefore, no public dataset of IDS-TILDA data is available. Access to data was approved by IDS-TILDA Data Controller.

In order to access variables, a request was made to the Data Controller upon providing an explanation of the purpose of requesting these variables. After the requests were assessed by the Data controller, access to the requested data was provided. *Table 2-1* provides a list of variables that were requested and accessed for use for the four studies in this thesis. Access to data was only possible by accessing specific IDS-TILDA "hot desks" and datasets could not be removed from these access points or transferred to personal computers.

Table 2-1 Variables accessed for the four studies in this thesis

Study (Chapter)	Involved wave	Carried from Wave 1	PIQ	CAPI	Health assessments
Study 1 (Chapter 3)	Wave 2	**Demographic Data** Level of ID	**Demographic Data** Gender Age range **Medication Data** Medication Name ATC Code Strength Frequency Route of Administration Date Prescribed **Health conditions** Have you ever had a doctor's diagnosis of…? Gastroesophageal reflux disease Stomach ulcers	**Demographic Data** Type of residence	
Study 2 (Chapter 4)	Wave 2 Wave 3	**Demographic Data** Level of ID	**Demographic Data** Gender Age range **Medication Data** Medication Name ATC Code Strength Frequency Route of Administration Date Prescribed	**Demographic Data** Type of residence	

Study (Chapter)	Involved wave	Carried from Wave 1	PIQ	CAPI	Health assessments
			Health conditions Have you ever had a doctor's diagnosis of…? Gastroesophageal reflux disease		
Study 3 (Chapter 5)	Wave 2	**Demographic Data** Level of ID	**Demographic Data** Gender Age range **Medication Data** Medication Name ATC Code Strength Frequency Route of Administration Date Prescribed **Health conditions** Have you ever had a doctor's diagnosis of…? Arthritis (including osteoarthritis or rheumatism) Angina Congestive heart failure A heart murmur An abnormal heart rhythm Other heart trouble Heart attack Parkinson's disease Multiple sclerosis	**Demographic Data** Type of residence **Barthel Index** Please indicate the level of difficulty, if any, you have with walking 100 yards. Please indicate the level of difficulty, if any, you have with climbing one flight of stairs without resting. Please indicate the level of difficulty, if any, you have with dressing, including putting on shoe and socks. Please indicate the level of difficulty, if any, you have with bathing or showering. Please indicate the level of difficulty, if any, you have with cleaning your teeth/taking care of your dentures. Please indicate the level of difficulty, if any, you have with eating such as cutting up your food, use of utensils, drinking from a cup/glass etc? Please	Body Mass Index (calculated from height and weight user)

Study (Chapter)	Involved wave	Carried from Wave 1	PIQ	CAPI	Health assessments
			Alzheimer's disease Spina bifida Dementia Epilepsy Cerebral palsy Muscular dystrophy Stroke Ministroke/transient ischaemic Attack Diabetes Chronic constipation Irritable bowel syndrome Depression Manic depression Anxiety condition **Rome III symptoms** During the last 6 months have experienced the following and been active for 3 months…? Straining lumpy/Hard stool Incomplete evacuation Anorectal obstruction Defecation fewer than 3 times per week Manual manoeuvre Normal stool without laxative use	indicate the level of difficulty, if any, you have with getting in or out of bed. International Physical Activity Questionnaire (IPAQ) Category	

Study (Chapter)	Involved wave	Carried from Wave 1	PIQ	CAPI	Health assessments
			Diet What type of diet are you following…? Soft liquidised Thickening fluids		
Study 4 (Chapter 6)	Wave 1 Wave 2 Wave 3	**Demographic Data** Level of ID	**Demographic Data** Gender Age range **Medication Data** Medication Name ATC Code Strength Frequency Route of Administration Date Prescribed **Health conditions** Have you ever had a doctor's diagnosis of...? Arthritis (including osteoarthritis or rheumatism) Angina Congestive heart failure A heart murmur An abnormal heart rhythm Other heart trouble Heart attack Parkinson's disease	**Demographic Data** Type of residence Cause of ID The Behaviour Problem Inventory-Short Form (BPI-S) Personal Wellbeing Index-Intellectual Disability (PWI-ID)	

Study (Chapter)	Involved wave	Carried from Wave 1	PIQ	CAPI	Health assessments
			Multiple sclerosis Alzheimer's disease Spina bifida Dementia, organic brain syndrome or senility Epilepsy Cerebral palsy Muscular dystrophy Stroke Ministroke/transient ischaemic Attack Diabetes Chronic constipation Irritable bowel syndrome Depression Manic depression Anxiety condition **Rome III symptoms** During the last 6 months have experienced the following and been active for 3 months…? Straining lumpy/Hard stool Incomplete evacuation Anorectal obstruction Defecation fewer than 3 times per week		

Study (Chapter)	Involved wave	Carried from Wave 1	PIQ	CAPI	Health assessments
			Manual manoeuvre Normal stool without laxative use **Diet** What type of diet are you following…? Soft liquidised Thickening fluids		

2.2. Part II: Gastrointestinal medication use among adults and older adults with intellectual disability: A literature review

2.2.1. Introduction

People with ID experience earlier health-related issues compared to their peers from the general population (50). Multi-morbidity – the presence of two or more health conditions – is very frequent in the population with ID with an estimated prevalence of 71% (27, 50). People with ID experience many mental, neurological, gastrointestinal conditions and sensory impairments, which may present since childhood or adolescence. Gastrointestinal conditions among people with ID are one of the morbidities that are frequently reported (39, 183, 184) with chronic constipation (185, 186), GORD, *H. pylori* infection (187-189) and dysphagia (190, 191) being the commonest. The prevalence of multi-morbidity among people with ID creates many challenges in prescribing practice with high burden of medication use, exposing people with ID to the risks of side effects, drug-drug or drug-disease interactions (192, 193). It has been reported that people with ID were receiving four times as many repeat prescriptions as the non-ID individuals (32). Polypharmacy and excessive polypharmacy have increased to a concerning level among people with ID (67). Several studies investigated medication use by people with ID and the main body of research was around scoping the use of psychotropic medications (194-201). Knowing that people with ID receive multiple medicines and considering that GI conditions are prevalent, this review aimed to explore the prevalence of GI medicine use in the population of ID. The focus of this review was based on the following questions: How frequent is the use of gastrointestinal medications in people with ID? Are there any studies that assess or report the effectiveness or side effects of GI medicines in people with ID?

2.2.2. Methods

Electronic databases were searched including PubMed, Science Direct, EMBASE, CINAHL, Scopus and Web of Science.

A preliminary search suggested that there were no randomised controlled trials (RCTs) conducted among adults with ID but only published case studies so the search was limited to dates from 1990 to Aug 2015 (the start of the author's PhD). The inclusion criterion were; adult and older adult with ID, English language and reports on GI medicine use (even if the main aim of the study is not relevant), analysis of effectiveness or side effects of GI medicines among people with ID. The exclusion criteria were conference abstracts or if the study has mainly paediatric participants. The search terms that used were 'intellectual disability', 'mental retardation', 'learning disabilities', 'developmental disabilities' 'gastrointestinal medications', 'laxatives', 'proton pump inhibitors', 'antacid', 'medication use', 'prescribing', 'side effects' 'constipation', 'anti-ulcers' 'gastroesophageal reflux disease', '*H. pylori* infection'. The search was applied repeatedly with each time a combination of three or more key words was used. For example;

-'intellectual disability' OR 'developmental disabilities' OR 'mental retardation' AND 'medication use' AND 'constipation'

-'intellectual disability' OR 'developmental disabilities' AND 'gastrointestinal medications'

All titles and abstracts were used to exclude studies which were clearly not relevant. The full text of papers was screened for all those potentially relevant studies or for studies where the decision on study relevance cannot be achieved from the abstract.

The bibliography of studies that meet the inclusion criteria was searched. The relevant studies were discussed with a second author to decide on whether or not they met the inclusion criteria. *Figure 2-2* shows the search method.

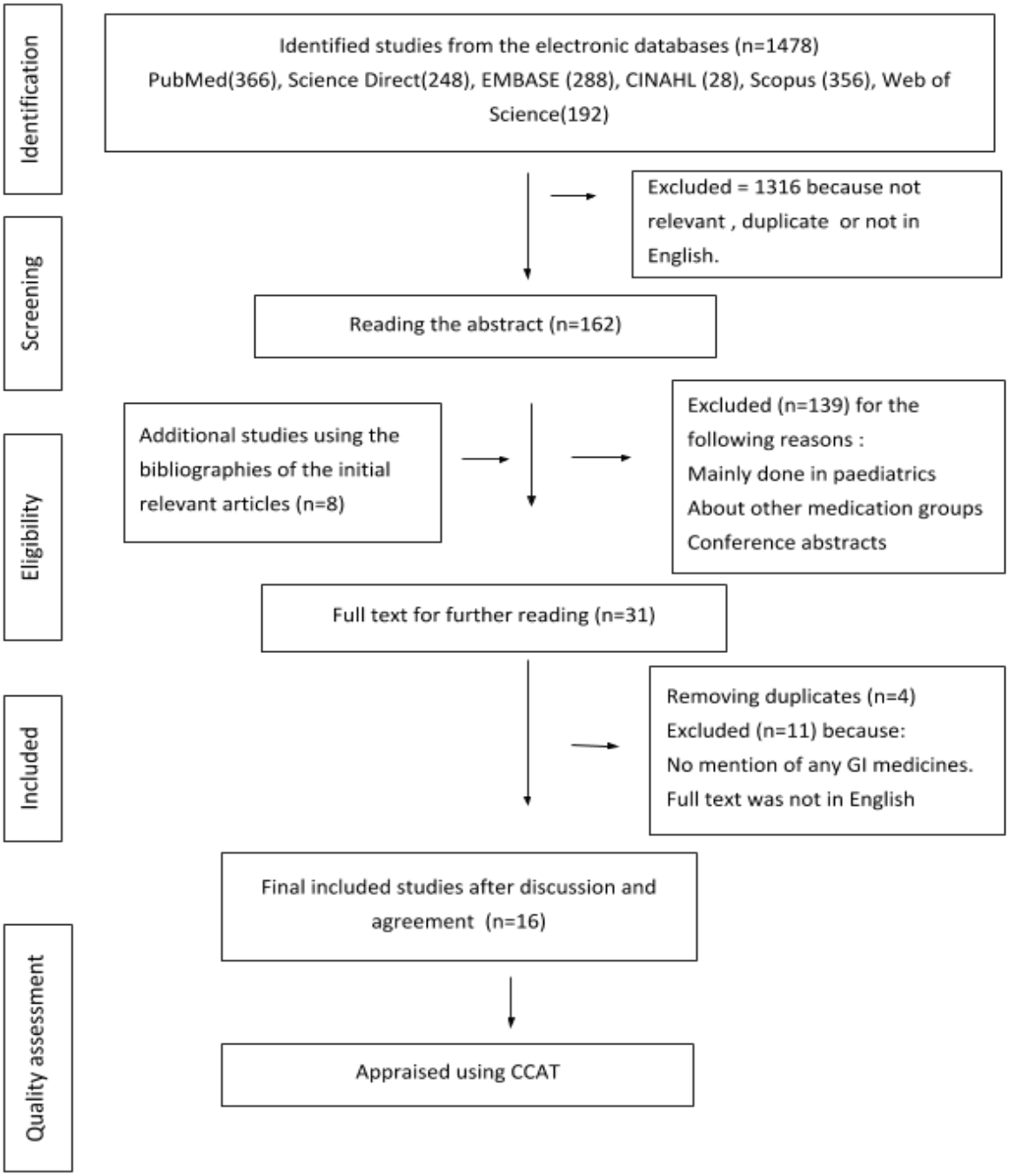

Figure 2-2 Flow chart of the search method

2.2.3. Quality assessment of the relevant studies

The quality of the included studies had been assessed using the Crowe Critical Appraisal Tool (CCAT) (version 1.4) *(Appendix 4)* (202, 203). CCAT tool was developed at the James Cook University, Australia. It was developed to help reviewers to appraise most common types of study methodology and design. It consists of eight categories that comprised of a total of 54 items. These categories are preliminary (evaluate the title, abstract and text overall), evaluate the introduction (background and objectives),

assess the design (research design, intervention, exposure, outcomes and measure, bias such as confounder variables or group allocation), sampling (such as sampling method, protocol or sample size), data collection (assessing items such as collection method and its suitability and the protocol followed), ethical matters (such as informed consent, privacy, anonymity), results and discussion. The items are graded on a nominal scale (present/absent/not applicable). The items of the tool can be applied to both quantitative and qualitative studies. Research designs should be appraised on their own merits, not to a 'gold standard'.

The CCAT appraisal tool was used in conjunction with the CCAT User Guide that includes a comprehensive guidance on scoring each part of a paper. Item descriptors are marked as present (✓), absent (✗), or not applicable (■). The tick marks are a guide to scoring a category. All categories must be scored and each category receives its own score on a 6 point scale from 0–5. The lowest score a category can achieve is 0 and the highest score is 5. The total score (out of 40 or as a percentage) is reported in addition to each category score. The CCAT User Guide was used also to obtain the corresponding percentage for each total score (204).

2.2.4. Data extraction

After consensus, the included studies were analysed and summarised in *Table 2-2*. Data on GI or GI related medicines were extracted. The studies have been tabulated according to study aim and objectives, design/data collection, sample/age, relevant findings and CCAT score.

2.2.5. Results

As shown in *Table 2-2*, sixteen studies were found relevant or relatively relevant (because of some paediatric participants). Three studies were published before the year 2000. The range of score given to the included studies varied from 63% to 95% with the lowest scores given to those missing some items of the CCAT.

The included studies were from various countries; 37% from Netherlands (n=5) (52, 101, 127, 205, 206), 1 from Netherlands and Belgium (121), 2 from Australia (73, 207), 3 from USA (208-210), 2 from Belgium (102, 211), 1 from France (212), 1 from UK

(213) and one used data from 7 European countries (which assessed polypharmacy in nursing home residents with severe cognitive impairment) (68).

Overall, there were different study designs among the included studies with 5 being cross-sectional (observational, descriptive or exploratory studies) (52, 68, 73, 206, 211), one study was a pilot study (prospective randomised crossover design) (213), two were longitudinal studies (one case-control and another a cohort study) (101, 207). There were no Randomised Controlled Trials.

The aims of these studies varied notably. The primary aim of seven studies out of the 16 was GI related treatments (121, 127, 205, 207, 211-213), with an additional 3 studies with the aim to assess GI related conditions (101, 102, 209). The aim of the remaining studies varied from investigating general medication use with a cross-sectional design or focused on investigating the total medical conditions, comorbidities or polypharmacy. Among the studies which aim to investigate GI related medicines (n=7); there were 5 studies that aimed to assess the effectiveness of therapy as follows;

- Assess the effectiveness of laxatives compared to massage (pilot study) using prospective randomised crossover design (213), where the participants were allocated randomly to both interventions.

- Assess efficacy and tolerability of Polyethylene Glycol + electrolytes (PEG+E) using a retrospective study design (212).

- Assess effectiveness *H. pylori* eradication therapy which included the use of a PPI (Not RCTs; Longitudinal exploratory study (included observation of participnats)) (207).

- Report the prevalence of GORD and assess the effectiveness of PPIs (mainly omeprazole) in relieving the symptoms (conducted prospectively) (127).

- Report the prevalence of GORD and assess the effectiveness of PPIs (mainly omeprazole) in relieving the symptoms (conducted retrospectively included a primary data audit) (121).

There were 12 studies that reported a prevalence of GI medication using general term 'GI medication' 'bowel medication' or precisely as laxatives, proton pump inhibitor 'omeprazole', antiulcer, H2 receptor antagonist and drugs for peptic ulcer /gastroesophageal reflux. Only 3 of these studies reported a representative sample population (52, 73, 101).

The target population in this review was adult and older adult with ID aged 18 years and older. Five of the studies included paediatric participants (101, 121, 127, 205, 211). Nevertheless the number was minor; one study (total sample n=254) contained 7% who aged less than 18 years (205), two studies consisted of 11% (127) (total sample n=435) and 22% (101) (total sample n=215) who aged less than 20 years, of whom 21 and 8 participants aged less than 10 years, respectively. Another two studies described the sample age range as 2-72 years (median age was 29 year) and 2-92 years (121, 211).

The place of residence of the included studies varied with 50 % (n=8) based on institution/ residential care samples (68, 101, 102, 121, 127, 205, 211, 213), one additional study include sample of institutionalised participants or with a history of living in an institution (207). The other studies were from community, ID service providers (which constitute either institutionalised or community group homes), specialised inpatient clinics, healthcare institutions or developmental centres. Only one who used a sample from different places of residence but the sample was syndrome-specific participants (102 subjects with Prader- Willi syndrome aged 18-66 years).

There were 31.2% (n=5) of studies with samples characterised by moderate to profound level of ID (IQ <50) and a further 25% (n=4) with samples of severe-profound level of ID. Furthermore, 31.2% (n=5) of studies had samples with all levels of ID (borderline/mild to profound). Only two studies had samples with level of ID not clearly stated (207, 210).

Table 2-2 Summary of studies that reported GI medicine use among people with ID

Reference (Origin)	Study Aims & Objectives	Research Design/ Data collection	Sample/age	Findings relevant to the review.	Total score % of CCAT
1-Van der Heide C. *et al.* (2009) (205). (The Netherlands)	To investigate the frequently used medication of four therapeutic areas (anticonvulsants, laxatives, drugs for peptic ulcer and gastro-oesophageal reflux (GORD) and psycholeptics) and investigate the documented indications for these four classes.	Descriptive survey. Health problem data taken from medical notes and prescribing data (obtained from pharmacies) as well as informal interview whenever needed.	254 participants with profound intellectual and multiple disabilities from eight residential facilities. Median age was 49 ranging from 6 to 82 years old. Only 7% were below 18 years.	89% of participants (n=226) were prescribed medication over the course of 1 year. 65% of participants (n=165) were on laxatives, the indication was documented for 68% (n=112). Constipation was reported by 60%. 52% participants (n=132) were on drugs for peptic ulcer and GORD. Of these, 44% (n=58) had an indication documented. The worst case of documenting the indication was among drugs treating peptic ulcer and GORD.	63%
2-Doan T. *et al.* (2013) (73). (Australia)	To examine the extent of medication use in Australian community dwelling adults with ID who accessed generic	Cross-sectional study. Data collected form medical records, health screening tool and telephone	117 participants aged 19–71 years who live in the community (with a mild to profound level of ID).	Gastrointestinal medication prescribed for a 25% (n=29). Of them, laxatives were the most frequent medication used.	95%

Reference (Origin)	Study Aims & Objectives	Research Design/ Data collection	Sample/age	Findings relevant to the review.	Total score % of CCAT
	primary healthcare.	interviews.	The sample was comparable to those with ID who lived in a community in Australia.		
3-Charlot L. *et al.* (2011) (208). (USA)	To investigate the total number of medical conditions and medication listed in medical files. To investigate if any correlation between medical diagnosis and length of hospital stay and to assess if the number of psychoactive medications correlated with the number of medical diagnoses.	Retrospective review of discharge summaries.	198 participants with ID who had been admitted to a specialised inpatient psychiatric unit. Included people aged 16 years and older (mean age 39 with mild-severe ID).	Bowel medications were used by 39%. Medicines for acid related disorders (PPI, Histamine-2 receptor antagonists (H2RAs)) were used by 31%. The most prevalent medical condition was constipation accounting for 60 % followed by GORD in 38% of the sample. Dysphagia occurred in 10% of the sample.	80%
4-Van Winckel M. *et al.* (1999) (211). (Belgium)	To investigate the frequency of laxative use and identify its correlates.	Descriptive cross-sectional study used a primary medical chart review and structured interview with the	420 institutionalised participants with moderate to profound ID (IQ<50).	26.4% of residents were using laxative regularly with a further 2% using laxatives occasionally. 13% were using oral laxatives only. Oral laxatives and enemas were	83%

Reference (Origin)	Study Aims & Objectives	Research Design/ Data collection	Sample/age	Findings relevant to the review.	Total score % of CCAT
		participant's carers.	Median age was 29 years (range 2-72 years).	used by 9.3%. Enemas only were used by 2.7%. 78% of the oral laxative users used them for long term (> 1 year). 71% of the sample used one laxative agent. Two laxatives were used by 23% and 6% used combination of three laxatives. Osmotically-acting laxatives were used by 67% followed by stimulant laxatives (30%) and bulk-forming laxatives (19%). The most commonly used enema was phosphate enemas (58%, n= 28). The use of laxatives was positively and independently associated with non-ambulatory, female gender, medicines use (other than laxatives) and oral motor dysfunction (on pureed or tube feeding). Of the laxative users, defecation frequency remained low in 41% and stools remained hard in 20%.	

Reference (Origin)	Study Aims & Objectives	Research Design/ Data collection	Sample/age	Findings relevant to the review.	Total score % of CCAT
5-Velde. S. *et al.* (2010) (102). (Belgium)	To identify total and segmental Colonic Transit Time (CTT) in patients with ID and compare results to healthy controls.	Prospective case-control. It involved observation of the patients' clinical parameter, primary data review and questionnaire.	58 participants older than 16 years. The control group consisted of 32 healthy volunteers of comparable age. Median age is 35.5 years with moderate to profound ID (IQ<50).	before the study, laxatives were used by 41% (n=24) and only 36% had constipation. 54% (n=13) of laxative users used only oral laxatives and 45% (n=11) used both oral and rectal. Those with ID and constipation had a significant prolonged CTT in all segments. Those with ID and no constipation had prolongation of the rectosigmoid CTT, suggesting defecation problem or retentive constipation.	83%

Reference (Origin)	Study Aims & Objectives	Research Design/ Data collection	Sample/age	Findings relevant to the review.	Total score % of CCAT
6-Emly M. *et al.* (1998) (213). (UK)	To compare a non-pharmacological therapy for constipation (abdominal massage) with the pharmacological treatment (laxatives).	Prospective randomised crossover design pilot study. Included a primary data review and structured interview.	32 profoundly disabled institutionalised adults aged 24-74 years. The sample inclusion criteria was: people with cerebral palsy or any conditions with an abnormal muscle tone symptoms and people who used laxatives or enema.	90% (n=29) of the sample was on laxatives for more than 5 years. Enema was required always for 47% (n= 15) of the sample, and often used by 19 % (n= 6). There was not difference between laxative and massage therapy. There was a grossly abnormal colonic transit time of the study population at all times.	88%
7-Migeon-Duballet I *et al.* (2006) (212). (France)	To assess the efficacy and tolerability of polyethylene glycol + electrolytes (PEG+E) in intellectually disabled inpatients.	A retrospective study included a primary audit of the medical data.	54 individuals with severe intellectual and physical disabilities in mental healthcare institution. The mean age was 36.1 ± 11.9 years.	The mean number of stools per patient per month was significantly higher after the addition of PEG+E (24.9 ± 6.3) compared to before its use (12.4 ± 3.4) ($p < 0.00$), indicating that PEG+E was effective in the clinical management of constipation in an institutional setting. The mean monthly number of	83%

Reference (Origin)	Study Aims & Objectives	Research Design/ Data collection	Sample/age	Findings relevant to the review.	Total score % of CCAT
				episodes of diarrhoea per patient before and after the PEG+E use was 0.1 ± 0.1 and 6.3 ± 2.9, respectively ($p < 0.001$). Long-term treatment with PEG+E showed less adverse effects on body weight or blood biochemistry.	
8-Hermans H. *et al.* (2014) (52). (The Netherlands)	To identify multi-morbidity among older adults with intellectual disability by evaluating the chronic health conditions.	Exploratory cross-sectional study included a primary data review and observation of participants.	1047 older adults (50 years and over) with ID. Level of ID (borderline to profound). The sample was representative to those who know the ID service provider in Netherlands.	The study reported three of the GI conditions as comorbid and prevalent conditions. They were dysphagia, constipation and GORD. Laxative use (was used to predict chronic constipation) which accounted for 43.3%.	83%
9-Böhmer C. *et al.* (2001) (101). (The	To identify the prevalence of constipation and associated factors.	Case-control longitudinal observation.	215 institutionalised participants included 48 children (age < 20 years; eight	About 69.3% (n=149) of participants had constipation. Constipation was significantly correlated with non-ambulance,	95%

Reference (Origin)	Study Aims & Objectives	Research Design/ Data collection	Sample/age	Findings relevant to the review.	Total score % of CCAT
Netherlands)			participants aged < 10 years). Level of ID was from moderate to profound (IQ < 50). The sample was comparable to those who live in institutions in Netherlands.	cerebral palsy, the use of anticonvulsive, benzodiazepines, H2RAs or proton pump inhibitors, food refusal, and an IQ < 35. 58% used bisacodyl or magnesium oxide. Lactulose was used by 39%. Sodium phosphate enemas were given alone to 9.7%. Two combinations of laxatives were used by 34% (n=51) of laxative users and three combinations were used by 9.4% (n=14) of users. The most common combination used either alone or with the addition of a third was bisacodyl/ magnesium oxide plus lactulose representing 15.4% (n=23). Manual evacuation was performed in 7% of cases.	
10- Matson J. *et al.* (2011) (209).	To assess the prevalence of toileting problems.	Exploratory survey using a screening tool and primary data	153 adults with ID from two large developmental	Fibre or laxative use was recorded by a 72.5 % of participants. By using the tool, one of the most	78%

Reference (Origin)	Study Aims & Objectives	Research Design/ Data collection	Sample/age	Findings relevant to the review.	Total score % of CCAT
(USA)		review.	centres. Mean age was 49.81 years (SD = 12.66) with mild to profound level of ID.	frequently endorsed problems was 'requires the use of fibre supplements /laxatives to defecate'.	
11- Kerins G. *et al.* (2008) (210). (USA)	To investigate medical conditions and medication use in adults with Down syndrome.	Retrospective descriptive study involved a chart review.	141 inpatients with Down syndrome aged 30-65 years.	GORD found in 14 % (n=20) of the sample and GORD-related medicines were used by 20% (n=28).	68%
12-Sinnema M. *et al.* (2013) (206). (The Netherlands)	To investigate the consequences of high morbidity rates including medication.	Exploratory cross-sectional. Data collected using a semi-structured interview and primary data review.	102 adults with Prader-Willi syndrome. Age range was 18-66 years with mild to severe ID. About 79% of participants lived in institutional residential or community residential facilities while 20% lived at home.	The second most frequently used medicines were laxatives (n=23) after psychotropics.	85%

Reference (Origin)	Study Aims & Objectives	Research Design/ Data collection	Sample/age	Findings relevant to the review.	Total score % of CCAT
13-Vetrano D. *et al.* (2013) (68). (7 European countries)	To evaluate the frequency and factors linked to polypharmacy in nursing home residents with ID.	Observational cross-sectional included a primary data review, questionnaire and direct observation of participants.	1449 participants with a mean age 84.2 ± 9 years with severe cognitive impairment. (The sample was not selected randomly and was not intended to be representative of all nursing homes in each country).	Excessive polypharmacy was directly linked to gastrointestinal symptoms (OR 1.20; 95% CI 1.43–3.39). GI symptoms were observed in 46% of participants. Among all medication used, laxatives were the most commonly used drugs (49.4%) followed by antiulcer drugs (37.2%).	95%
14-Wallace R. *et al.* (2004) (207). (Australia)	To evaluate a standard *H. pylori* eradication protocol. To assess adverse effects and influence of eradication on functional ability and maladaptive behaviour level.	Longitudinal exploratory study included observation of participants.	168 adults aged 17 years and older from a single institution and from a specialised medical outpatient clinic.	Treatment protocol was as follows; omeprazole 20 mg twice daily, amoxicillin 1 g every 12 hours, clarithromycin 500 mg every 12 hours for 7 days. About 70 % (n=117) of subjects were infected with *H. pylori* at baseline. After 1 year: eradication rate was observed in 60% of those who had infection, which was less than that seen in the general population. Side effects were noticed in 31% of those who received treatment and	95%

Reference (Origin)	Study Aims & Objectives	Research Design/ Data collection	Sample/age	Findings relevant to the review.	Total score % of CCAT
				the most commonly reported were anorexia, vomiting or diarrhoea. Maladaptive behaviour and disability level did not improve with eradication. With the low eradication rate resulted, the author recommended an evaluation for eradication after treatment to avoid the consequences of *H. pylori*.	
15-Böhemer C. *et al.* (2002) (127). (The Netherlands)	To investigate the prevalence of GORD and reflux oesophagitis among persons with ID. To evaluate if any relation between disease risk factors and testing results (twenty-four hour oesophageal pH testing and endoscopy). To investigate the effectiveness of omeprazole.	A representative prospective study. The study included a primary review and testing methods.	435 institutionalised participants with IQ<50. mean age 34.1 years (range 4–77 years). There were only 48 children (age less than 20 years with 21 aged less than 10 years). Omeprazole efficacy experiment included 186 participants who underwent endoscopy (42.7% of the total	GORD was prevalent and usually overlooked or underestimated. Confirmed cases of oesophagitis were received omeprazole for 3 months. Omeprazole was effective in all grades oesophagitis with minimum side effects.	85%

Reference (Origin)	Study Aims & Objectives	Research Design/ Data collection	Sample/age	Findings relevant to the review.	Total score % of CCAT
			population). Treatment success was defined as endoscopically verified healing (grade 0)		
16- Böhmer C. *et al.* (1997) (121). (The Netherlands and Belgium)	To examine the presence of Reflux Oesophagitis (RO). Analyse the reflux symptoms and the possible associated factors. To evaluate treatment effect on symptoms after at least one year of therapy.	An exploratory retrospective study includes a primary data audit.	1687 participants with IQ< 50 from 5 different institutes in Netherland. Age range was 2-92 years. 169 participants were suspected for RO (based on symptoms) and 107 confirmed cases of RO after endoscopy (6.3% of the total population). Treatment was assessed for the 107 participants.	Omeprazole was given to a 43% of participants and was seen effective in 96% of them. H2RAs were found effective in 60% and surgery in 39%. Possible associated factors for RO were cerebral palsy, constipation, anticonvulsant drugs, an IQ < 35, underweight and gastrostomy feeding.	80%

CCAT: Crowe Critical Appraisal Tool, GORD: Gastroesophageal Reflux Disease, CTT: Colonic Transit Time, H2RAs: Histamine-2 receptor antagonists, IQ: Intelligence Quotient, PEG+E: Polyethylene Glycol + Electrolytes, RO: Reflux Oesophagitis.

2.2.6. Discussion

a. Laxatives

Reporting a valid prevalence of GI medicines among adult or older adult people with ID, in general, or a GI class (e.g. laxative use), in specific, was not possible in this review since there were variations between studies in the sample sizes, sample characteristics, study aims and designs. There were 12 studies that reported frequency of GI medicine (sample sizes ranged from 32 to 1449) with the lowest sample was from a pilot study (213). The design of the other studies were as follows; 5 cross-sectional (descriptive, observational or exploratory), 3 retrospective studies (2 exploratory and 1 descriptive), 2 survey studies (descriptive or exploratory) one prospective case-control and one observational case-control. Among these studies, 4 studies aim to assess GI medicine use (2 assess the effectiveness, one of them pilot study) and further 2 primarily aim to assess GI related conditions (constipation, toileting problems). Among studies that described the frequency of GI medicine use (n=12), medicines to manage constipation (laxatives) were the most commonly reported (9 studies). The reported frequency of laxative use ranged from 22.5% (among 102 participants with Prader-Willi syndrome with age range from 18 to 66 years) (206) to 73% in a US study of 153 adults aged 16–89 years from two large developmental centres.

Laxatives were reported as the most frequent medicines used in two studies (73, 206). Five out of the nine studies that reported laxative prevalence were of population with severe/profound level or with IQ<50 (moderate to severe) (68, 101, 102, 205, 211) and the remaining 4 studies reported a range of level of ID among their population (mild-profound) but none have their primary aim was to investigate laxative prevalence (52, 206, 208, 209).

Two studies reported details about laxative regimen and combinations. According to Böhmer *et al*., 2+ laxatives had been used by 43.6% of the laxative users (101). In another study, the use of 2+ laxatives was reported by 29% of those who used laxatives on a daily basis (211). In these two studies, oral laxatives were used on a regular basis or occasionally with or without the use of enema as adjunctive therapy with stimulant

or osmotic laxatives were the most common types used. In some circumstances, manual interventions had been applied to give additional relief. Two studies found a use of laxatives for more than a year or 5 years, indicating a long term use of laxatives among people with ID (211, 213).

According to Van Winkle *et al.*, the factors that were independently associated with laxative use in institutionalised people with ID were female gender, non-ambulatory, oral motor dysfunction and medicine use (other than laxatives) (211). These factors differ slightly from the correlates of constipation among people with ID which were immobility, cerebral palsy, some kind of medications (anticonvulsants, benzodiazepines, H2 receptor antagonists or PPIs), food refusal, and an IQ < 35 and this was consistent with some results from another study conducted by Morad *et al.* (103).

b. Drugs for gastro-oesophageal reflux disease

Drugs for peptic ulcer or GORD (such as PPIs and H2 receptor antagonist) were reported in 4 studies with a prevalence of 20% in retrospective descriptive study on 141 inpatients with Down syndrome (210), 31% in exploratory retrospective study of 198 inpatients with ID (208), 37.2% in a cross-sectional study of 1449 of nursing home resident with severe cognitive impairment (68) and 52% in a descriptive survey of 254 subject with profound intellectual and multiple disabilities from residential facilities in Netherlands (205). In addition, there was further study (retrospective study of 1687) which reported the use of PPIs at a prevalence of 43% (121). Among these five studies, only two had a primary aim to report the prevalence of drugs for GORD (205) or assess the effectiveness of a PPI (omeprazole) (121) and both were of population either with profound or moderate to severe level of ID (IQ<50).

c. Effectiveness and reporting side effects of GI treatment in people with ID

There were 5 studies that assessed the effectiveness of GI treatments; two related to constipation management, 2 related to GORD management and one related *H. pylori* infection management. Apart from a pilot study, none of these studies were an RCT.

One of these related to constipation, was a prospective randomised crossover design pilot study (n= 32) assessed the efficacy of laxatives compared to bowel massage among subjects with profound level of ID with cerebral palsy or any conditions with

abnormal muscle tone symptoms (213). The study consisted of 3 phases; an initial 16-day baseline measurement phase without any treatment, followed by two seven-week treatment phases separated by a one-week washout period. Every participant received seven weeks of massage and seven weeks on his/her previous laxative regimen. The main outcome measures were gastro-intestinal and segmental transit times, assessed at the end of the baseline phase and of each treatment phase. Secondary measures included stool frequency, size and consistency, the requirement for enemas and an assessment of patient well-being. The pilot study did not detect differences between laxatives and abdominal massage on the outcome measures and the authors attributed this to the small sample size used (n=32). This pilot study revealed that there were abnormal colonic transit times of the study population at all times and suggested that the laxatives may be ineffective for a large proportion of the population with ID (213).

The second study included a primary audit of the medical data and conducted retrospectively to assessed the efficacy and safety of PEG+E in 54 residents in ID specialised health institution (212). The study treatment period was 24 months. Participants were treated with PEG+E (1–3 sachets a day) for 24 months. The number of stools, episodes of diarrhoea (defined as frequent stools), body weight and blood biochemistry were recorded. Data were compared with those recorded during the 21 months prior to the introduction of PEG+E for 16/54 residents who had been treated with other therapy for constipation. The study reported that stool frequency improved with the use of PEG+E with the mean (± SD) number of stools per patient per month was significantly greater after the introduction of PEG+E (24.9 ± 6.3) compared to before its use (12.4 ± 3.4) ($p < 0.001$). The same study reported that the use of PEG+E was safe in the long-term with minimal side effects as the mean (± SD) monthly number of episodes of diarrhoea / patient before and after the introduction of PEG+E was 0.1 ± 0.1 and 6.3 ± 2.9, respectively ($p < 0.001$). In addition, the study reported that PEG+E use was not associated with side effect on body weight or blood biochemistry values. Although findings of this study indicated that laxative PEG+E was effective, there are some other studies highlighted that the use of laxatives among people with ID (especially those in residential places) was not sufficient to relieve symptoms of constipation and probably ineffective (101, 213).

Among the general older population, effectiveness of laxatives has been evaluated

(214-217) with some reports concluding that there were unsatisfactory outcomes especially among those living in residential care. Laxatives show superiority in treating idiopathic constipation compared to placebo (218). However, older people or those with ID may require a comprehensive constipation treatment protocol rather than relying on laxatives alone to relieve the symptoms. This may include combining non-pharmacological and dietary measures with pharmacological agents as well as managing the underlying causes of constipation. A constipation management protocol was used in older people which included thorough assessments, diagnosis, management (combination of pharmacological and non-pharmacological therapy) and follow up assessments. The findings after applying the protocol described a reduction in the "average number of incidences of constipation per patient" but no change in the rate of constipation (219).

In this review; there were two studies that evaluated the effectiveness of PPI (omeprazole) in people with ID. In both studies, omeprazole was the only PPI reported and was considered effective (121, 127) using different study designs (retrospective and prospective). In the retrospective study, there were 1687 participants with IQ < 50 from 5 different institutes in the Netherlands and Belgium (age; 2-92 years), 169 participants were suspected for reflux oesophagitis (based on symptoms) and 107 were confirmed cases after performing endoscopy. Assessment of treatment (omeprazole and H2 receptor antagonists) was performed to the confirmed cases with omeprazole was given to 43% of the 107 cases and was effective for 96% of them (based on symptoms relief) with minimal side effects (121). In that study, the author reported that H2 receptor antagonists were found effective in 60% of the cases (121).

In the prospective study of 435 institutionalised participants with IQ<50, patients underwent 24-hour oesophageal pH testing and endoscopy and those diagnosed with oesophagitis (n=126) were treated with omeprazole for 3 months (127). In a second visit (after 3 months treatment, second endoscopy was performed to assess treatment success (defined as endoscopically verified healing of oesophagitis), doses was adjusted then depending on the results of endoscopy, in the third visit (after 9 months), endoscopy was performed only to those with a relapse at prior visit). The study reported that only one patient developed a skin rash which was possibly related to the

omeprazole. A conclusion of this study was that omeprazole is highly effective with only a few minor side-effects (127).

A study in paediatric population with ID reported similar results (220). Nonetheless, these studies investigated one PPI (omeprazole) while there are other PPIs that were approved by FDA and are broadly used nowadays which need to be evaluated in the population with ID. Investigating PPI use is important since there are growing concerns about their side effects like vitamins mal-absorption, increased risks of fractures or pneumonia (149, 221-225).

Furthermore, one longitudinal exploratory study aim to evaluate a standard *H. pylori* eradication protocol (which included a PPI) which originated from Australia and involved participants observation (n=168 adults aged ≥ 17 years) (207). The study reported that the eradication rate of *H. pylori* was 60% among people with ID which was less than that seen in the general population (70-95%) (207). However one-year after successful eradiation, a follow up investigation may show re-infection (207). The study conclusion was supported by Aheesh *et al.* who stated that the rate of treatment failure and *H. pylori* relapse is high among people with ID (226). PPI-based regimens are very effective and well tolerated among general older people (227, 228) and could be effective in people with ID, and the low rate of *H. pylori* eradication in people with ID could be attributed to other factors, such as living in residential care, which need further investigation.

d. Reported GI conditions among people with ID from this review

GI symptoms among people with ID reached 46% according to one study (68). This review shows that constipation was reported as the most common condition ranged between 60-70% (101, 205, 208). Hermans *et al.* considered both constipation and GORD as comorbid conditions among people with ID (52). One study aimed to assess the prevalence of toileting problems using a screening tool and reported that 'require the use of fibre supplement /laxatives to defecate' was of the most frequently endorsed issue (209). Two studies in this review reported a long and abnormal colonic transit time among ID population (102, 213). This is also reported in a paediatric group with ID (229), suggesting that constipation could be a long term condition that may arise from childhood.

There were four studies in this review who reported GORD (121, 127, 208, 210) at a range from 6.3 % (in a sample of 1687 participants with IQ< 50 from 5 different institutes in Netherlands and Belgium) (121) to 42.7% (among institutionalised participants in Netherlands) (127).

Early prediction of GORD will help in early intervention and preventing any consequences linked to this conditions (230). According to Böhmer *et al.*, the factors that associated with GORD were cerebral palsy, constipation anticonvulsant, IQ <35, low weight and gastrostomy feeding. In addition, hand mouthing as a behaviour is one of the risk factors that is related to GORD (125).

Serious concerns may arise when the GI diseases are not properly treated. An example is *H. pylori* infections that may lead to stomach cancer (231). It has been reported that digestive disorders cause mortality in people with ID at rate 2.5 times more than that of the general population, and the causes were bowel obstruction and perforated ulcers (232). Van der Heide *et al.* reported that the worst level of documenting the indications was seen with medication that treat peptic ulcer and GORD (205). In addition, another study reported that 34% of non-constipated participants were using laxatives (102). It is either they had constipation but no indication documented or they were at high risk and that laxatives were given as prophylaxis.

Two recent systematic reviews were published on constipation and constipation management among people with ID (95, 233) in 2008. These systematic reviews followed a controlled list of inclusion/exclusion criteria, focused on one condition and its treatment (constipation and its management), included the paediatric population (except neonates), and searched for published studies from 1990-2016 (for constipation) or 1990-2017 (for constipation management). While this review was conducted in mid-2015, searched for any GI medications and restricted to adult and older adult with ID over age of 18 years. Nonetheless, findings from these two systematic reviews were consistent with results in this review that related to constipation and laxative use where constipation was very prevalent in this population and that laxative use, despite limited effectiveness, was the main approach used in this population.

Finally; the CCAT that used to appraise the included studies is more reliable than

an informal appraisal of the research paper. Unlike formal appraisal tools (234), the CCAT uses a variety of research designs (qualitative and quantitative) and is associated with scoring systems that sufficiently reflect the content of research papers. The CCAT was built upon a review of the design of 44 critical appraisal tools across all research designs (235).

2.2.7. Conclusion

This review shows that people with ID frequently used medicines for digestive disorders. The limited studies available together with the variation in study designs and aims limit us from reporting a valid prevalence of GI medicine use. From this review, two classes of GI medicines were frequently reported; laxatives and medicines to manage GORD or acid related disorders. In addition, the review highlighted some issues associated with GI medication use such as low levels of documenting indications or insufficient treatment to overcome GI symptoms thus emphasising a need for further investigation to improve the quality and optimise GI medication use in people with ID.

2.3. Part III

2.3.1. Limitations of previous research

Upon appraisal of the studies that reported GI medicines in the ID population to date;

- The use of laxatives and acid related medicines (PPIs, antacid or histamine antagonists) in the population of ID always have been reported more frequently than other GI classes.
- There are very limited studies that aim mainly to explore the use of laxatives or PPIs but rather aim to investigate the burden of medicines use, polypharmacy, multi-morbidity or a GI medical condition.
- The majority of research to date has tended to focus on therapeutic classes in the psychotropics, such as antipsychotics although reports indicated that the level of laxative use was close to (or may be more than) that of the psychotropic medicines (68, 206).
- The few available studies that reported any GI medicine have recruited convenience samples or were pilot studies creating either a small or non-representative sample which may lead to insufficient power to carry out statistical analysis.
- In addition, most of the studies which reported GI medicines (e.g. laxatives or PPIs) applied to those who were institutionalised or those who have profound level of ID (together with physical disability) resulting in underestimation of the prevalence use of these classes among other people with ID who live in community/with family or those with mild level of ID.
- Most studies included a sample of different ages (children and adults) and were not specific to older people with ID.
- Some studies investigated constipation, the related risks or the pathophysiology behind it but there are limited information about the related treatment and whether it is sufficient or not. In addition, laxative use may be reported just to predict chronic constipation without looking for details related to their use.

- Since there are concerns that have been raised regarding long-term PPI use, there are a lack of studies assessing the use duration of PPI (or even assessing the prescribed doses) in the population with ID.
- Furthermore, there are no large scale studies that employed a multivariate analysis to assess the factors associated with either laxatives or PPIs among people with ID.

2.3.2. Aims and objectives

The overall aim of the dissertation is to describe the most frequently used GI medicines (mainly laxatives and PPIs) in a representative population with ID aged 40 and over in Ireland. This is to provide a better understanding of their use and give a provision of their current prescribing practice in the population with ID which may aid in any intervention related to appropriate and effective medication use. The aims and objectives are displayed and mapped to the relevant thesis chapter in *Figure 2-3* and described as follows;

- Explore prevalence and patterns of PPI use among older people with ID in Wave 2 IDS- TILDA and to more specifically; (1) Examine the dosage regimen, length of use and the recorded indications; (2) Explore the patterns of use with respect to clinical and demographic factors; (3) Determine the clinical and demographic factors associated with PPI use.
- Investigating the use of PPIs in Wave 3 IDS-TILDA (2016/2017) and conduct a descriptive comparison of the Wave 3 findings with findings from prior wave (Wave 2). The objectives were to a) Investigate the prevalence and patterns of PPI use by demographics and clinical characteristics at Wave 3 IDS-TILDA (2016-2017), b) Investigate the reported doses and length of use of PPIs at Wave 3, c) Compare the results with findings from Wave 2 IDS-TILDA, d) Track the use of PPIs from Wave 2 to Wave 3 IDS-TILDA to identify those who continue using PPIs at both waves, those who stopped or those who initiated PPIs at Wave 3 and e) Investigate the characteristics, demographics and PPI dosage of those who used PPIs at Wave 2 and Wave 3 continuously, those who stopped or initiated PPIs at Wave 3.

- Explore prevalence and patterns of laxative use among older people with ID in Wave 2 IDS- TILDA. The secondary aim was to compare the characteristics of those using laxatives and those reporting chronic constipation using two indicators for chronic constipation. The objectives were to a) Determine the prevalence of use, patterns, dosage, the related indication(s) and combination of laxatives and b) Identify the factors significantly associated with laxative use.
- Investigate, compare and track the use of laxatives over a 3-year time period, from Wave 2 (2013/2014) to Wave 3 (2016/2017) of IDS-TILDA. The second aim was to expand the investigation of the clinical and demographic characteristics of laxative users by including data from the first wave IDS-TILDA (2009/2010). More specifically the objectives were, a) Investigate the use of laxatives in Wave 3 of IDS-TILDA in terms of prevalence, patterns, dosage and indications, b) Include data from the first wave IDS-TILDA to examine laxative users over a 10-year period (from Wave 1 to Wave 3) in terms of their demographics, clinical characteristics, exposure to constipation risk factors, c) Compare these characteristics with those participants who reported doctor's diagnosis of constipation over the three waves IDS-TILDA, d) Compare detailed laxative use in Wave 3 with the findings of previous wave (Wave 2) (Chapter 5), e) Track laxative users from Wave 2 to Wave 3 to identify those who used laxatives at both waves, those who stopped laxatives at Wave 3, or those who started laxatives at Wave 3-IDS-TILDA, f) Investigate the characteristics, demographics and laxative dosage among those who used laxatives at both Wave 2 and Wave 3, those who stopped or started using laxatives at Wave 3, g) Explore laxative use among participants with Down syndrome in Wave 1-Wave 3 IDS-TILDA, h) Evaluate the use of laxatives and reporting constipation in relation to behaviours that challenge in people with ID in Wave 3 IDS-TILDA, i) Investigate impact of constipation on quality of life in people with ID at Wave 3 IDS-TILDA.

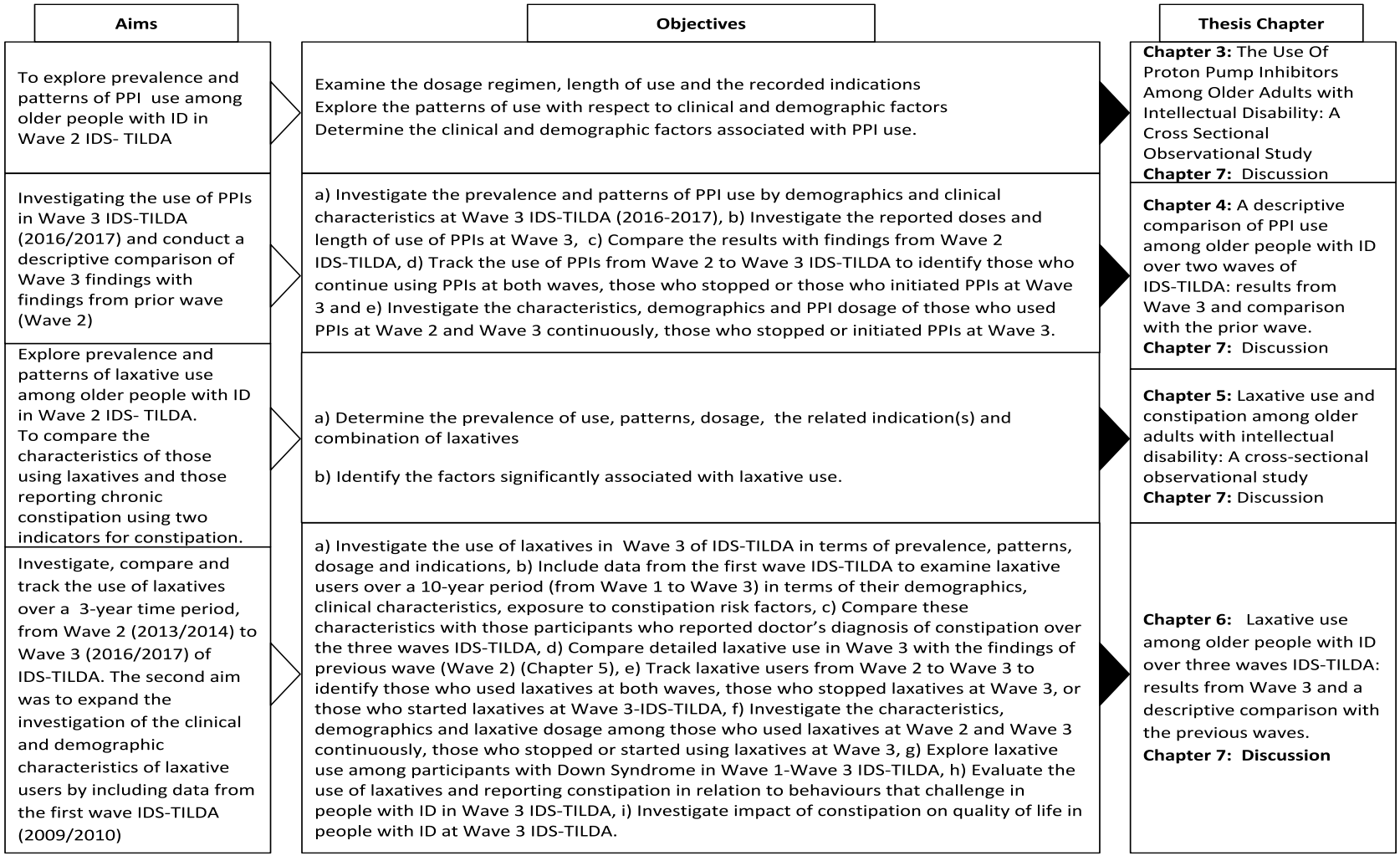

Figure 2-3 Mapping of aims and objectives of the thesis

2.3.3. Thesis structure

Chapter 3 includes a published paper investigating the prevalence and patterns of PPI use in Wave 2 IDS-TILDA. It includes a comprehensive assessment of dosage information, patterns of using high doses or long term of use per demographics such as level of ID, age and place of residence. Furthermore, the use of PPIs was investigated in relation to the reported indications. This chapter includes analysis of factors that significantly associated with PPI use in this population using a multiple logistic regression.

Chapter 4 presents a descriptive comparison of the use of PPIs and the trend in use per demographics over two waves of IDS-TILDA. In this chapter, an investigation of the use of PPI in Wave 3 IDS-TILDA was conducted and then the use was compared to findings from the prior wave. In addition, PPI users were followed from Wave 2 to Wave 3 to identify three groups; those who use PPIs at both waves, those who stopped or those who initiated PPIs at Wave 3. Further investigation of the demographics, characteristics and dosage information of those three groups was carried out.

Chapter 5 examines the use of laxatives among people with ID in Wave 2 IDS-TILDA. This involves investigating laxative use in relation to two constipation indicators; doctor's diagnosis of constipation and Rome III criteria, identifying the factors that associated with laxative use using multiple logistic regression, and investigating laxative combination by class. The patterns of laxative use and laxative combinations was also assessed considering the demographic of participants. This chapter is a published paper.

Chapter 6 includes investigation of laxative use, dosage and combination in Wave 3 IDS-TILDA and data were compared to findings in the prior wave. The chapter begins with creating a list of drugs that commonly contribute to constipation which was used together with other constipation risk factors in the analysis. In this chapter, the characteristics of laxative users were assessed in Wave 1, Wave 2 and Wave 3 IDS-TILDA which were compared to the characteristics of those who reported constipation in the three waves. Furthermore, participants who used laxatives in Wave 2 were followed and

tracked in Wave 3 to identify and investigate the characteristics of those who used laxatives at both waves, those who stopped or those who initiated laxatives in Wave 3. In this chapter, the use of laxatives was investigated among people with Down syndrome. In addition, laxative use and constipation were assessed in relation to behaviours that challenge and the effect of constipation on quality of life was also investigated.

Chapter 7 summarises the main thesis findings and highlights recommendations and implications for future research. It is wished that findings from this thesis will contribute to future interventions that relate to appropriate and effective use of laxatives and PPIs and aid in changing policies and creating guidelines for best health related quality of life among older people with ID.

3. Chapter Three: The use of proton pump inhibitors among older adults with Intellectual Disability: A cross-sectional observational study

3.1. Abstract

Background: Older people with Intellectual Disability (ID) have a high prevalence of gastrointestinal conditions such as GORD. However, despite this, information about treatment, in particular the use of PPIs, in this population is sparse and limited.

Objective: To investigate the prevalence and pattern of PPI use among older people with ID.

Method: Data on PPI use and key demographics was analysed from Wave 2 (2013/2014) of IDS-TILDA, a nationally representative longitudinal study of 677 participants aged 40 years and above in Ireland. Descriptive statistics, bivariate analyses and binary logistic regression were carried out.

Results: Just over a quarter, 27.9% (n=189), of participants reported use of PPIs, and 53.4% (n=101) were female. The largest proportion of PPI users (53.4%) were aged between 50-64 yrs. Most of the PPIs were used in maximum doses (66.7%). However only 43.9% of PPI users had an indication for PPI use (GORD, stomach ulcer or/and an NSAID use), and further 13.2% were also taking an antiplatelet agent. Use among those in residential care homes (54.3%) was much higher than for those living independently or with family (7%). PPI use among those who have severe/ profound ID was 25% higher than those with mild ID. Information about the length of PPI use was missing for 31.2%, but of those with data, just over half recorded using the PPIs for more than a year. Apart from an indication, the factors associated with PPI use were older ages (≥50years), severe/profound level of ID.

Conclusion: PPI use among older people with intellectual disability is prevalent and frequently long term, often without a clear indication. PPI use especially among those with severe/profound ID and those who live in residential care homes, could predispose these individuals to additional comorbidities and in order to avoid inappropriate long term of use regular review is required.

3.2. Introduction

Older people are at increased risk of many GI diseases such as GORD (236). Unlike younger adults, older people may experience non-specific symptoms and more severe oesophagitis which may be associated with complications such as erosive oesophagitis, Barrett's oesophagus, or extra-oesophageal complications such as pulmonary aspiration (237, 238). Treatment of GORD in older people is challenging as they are often have multiple comorbidities and polypharmacy. The mainstay and mostly effective treatment are the PPIs (239). The major indications for PPI use are GORD, oesophagitis, stomach ulceration, and treatment of *H. pylori* infection and concomitantly with NSAIDs to protect the GI from damage or ulceration. In addition, PPIs are prescribed off-label for patients taking antiplatelet drugs who are considered to be at risk of GI damage (240).

Intellectual disability is "a disability which originates before the age 18 and characterised by significant limitations in both intellectual functioning and in adaptive behaviour, which covers many everyday social and practical skills" (1). 'Intellectual Disability' was formerly described as 'Mental Retardation' in the United States (2), while the term Learning Disability is preferred in the United Kingdom (241) and Developmental Disabilities in Canada (3). The causes behind ID varies and include genetic (X-linked, other chromosomal), metabolic, teratogenic, central nervous system defects, birth defects, neonatal, perinatal, causes that are multifactorial, and causes of no known aetiology (242, 243). Level of ID is classified based on Intelligence Quotient (IQ) scores as follows; mild (50 – 55 to approx. 70), moderate (35 – 40 to 50 – 55) and severe/profound (below 35 - 40) (244).

Although life expectancy for older people with ID has risen (16, 245, 246), they still experience a higher mortality rate compared to the general population (26, 29, 247). People with ID, have been estimated to have twice as many health problems as among those without ID and to receive four times as many repeat prescriptions (32, 248, 249). They commonly have epilepsy, sensory impairments, osteoporosis, schizophrenia, dementia, musculoskeletal problems, and nutritional problems (250). GORD, *H. pylori* infection, dysphagia and constipation are most frequently GI health issues among adults and older adults with ID (39, 52, 126, 127, 135, 136, 251).

The use of PPIs in the general older population is well documented, with an overall prevalence ranging from 23% to 79% (156, 161, 163, 165, 252). Prevalence of PPI use is also reported to range from 27% to 79.7% among older people who are admitted to long-term facilities or nursing homes (159, 163, 166). In clinical settings such as geriatric units, PPI uses range from 33-41% (164, 165). One study reported a PPI prevalence of 97.4% and 98% for older people at hospital admission and discharge, respectively (158). As the use of PPIs, particularly their long-term use has increased, there has been growing concern about side effects and associated costs (142, 173).

Two studies of adult and older adults with ID, reported use of drugs for stomach ulcer or GORD as 31% and 52% respectively (205, 208), and one study reported that omeprazole, the only PPI then available, was used by 43% of institutionalised people with ID (121). In Wave 1 data from the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA) (2011), the reported prevalence of PPI use was 21.7%, and 44% of those who had excessive polypharmacy (10+medicines) were exposed to PPIs (72).

Inappropriate prescribing or a non-evidenced based use of PPIs is considered in the absence of the following indication: treatment of GORD, erosive oesophagitis, peptic ulcer disease, long term NSAIDs use for patients with history or at high risk of GI complications and for eradication of *H. pylori* (253) . Furthermore, in the absence of risk factors, full therapeutic doses for more than eight weeks are considered inappropriate (254). Studies, including some that have been conducted in Ireland, have reported that the highest prevalence of potentially inappropriate prescribing was among PPIs (173, 174, 176). This was confirmed in The Irish Longitudinal Study of Ageing (TILDA), that included 8,175 subjects (aged ≥ 50 years, without ID) where PPI use was found as potentially inappropriate in 17.2% and this significantly increased to 21.9% ($p<0.001$) after follow-up at two years (169).

In this study, the primary aim was to explore prevalence and patterns of PPI use among older people with ID in Wave 2 IDS- TILDA and to more specifically; (1) Examine the dosage regimen, length of use and the recorded indications; (2) Explore the patterns of use with respect to clinical and demographic factors; (3) Determine the clinical and demographic factors associated with PPI use.

3.3. Methods

Data for this study was drawn from Wave 2 (2013/2014) of the nationally representative longitudinal study (IDS-TILDA) (20). The study includes older people with ID aged 40 and above who have registered in the national intellectual disability database. It is exploring the ageing profile, physical and behavioural health (including medication use), health service needs, psychological health, social networks, living situations, community participation and employment. This study has been previously described in detail elsewhere (20, 43). In this study, we have used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting in observational cross-sectional studies (255).

3.3.1. Participants

From Wave 1 (n=753), 6% (n=45) of subjects did not participate in Wave 2, and of these 75.5% (n=34) had died *(Figure 3-1)* for a 94 %(n=708) response rate. Those with missing medicines data were excluded and the final number of participants was 677 (95%).

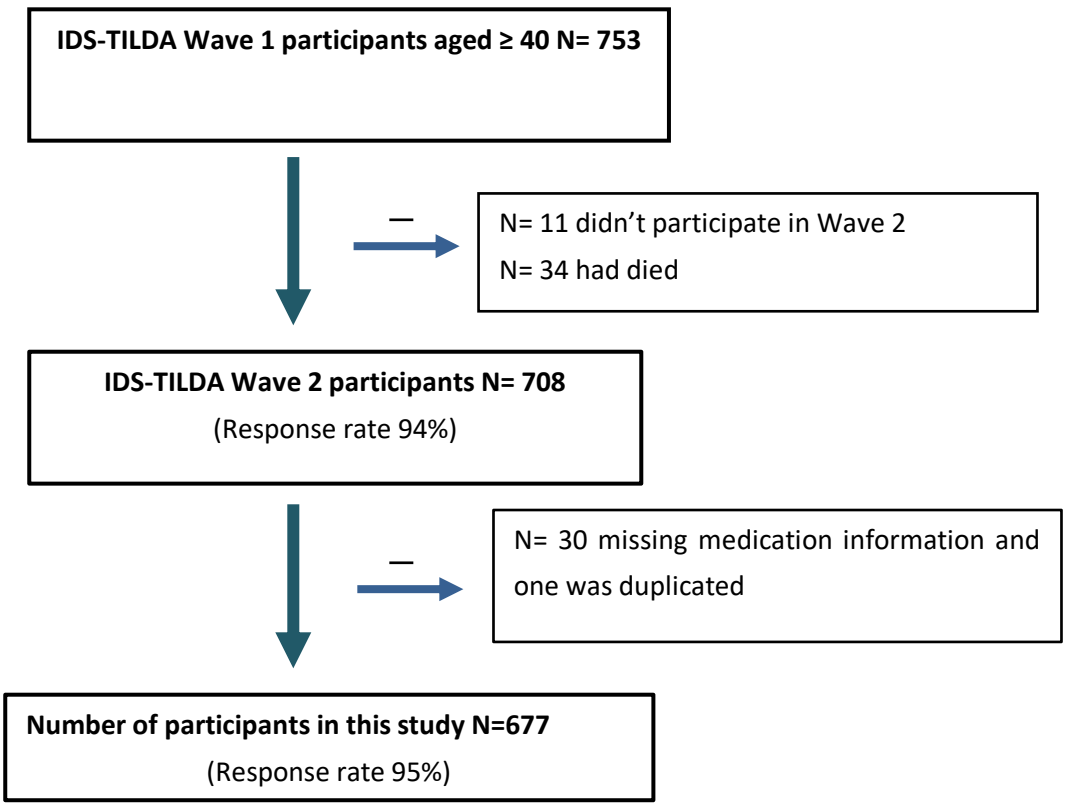

Figure 3-1 Flow of participants from Wave 1 to Wave 2 IDS-TILDA

3.3.2. Data collection and categorisation

The data collection process has been described comprehensively elsewhere (43). In brief, data collection in Wave 2 comprised a Pre-Interview Questionnaire (PIQ), an extensive face to face Computer Assisted Personal Interview (CAPI) and health assessments. The PIQ was sent to each participant at least a one week before the interview and gathered data on demographics, health status, healthcare utilisation and medication use. Data collected by the PIQ were then confirmed during the interview. The vast majority of subjects completed PIQ and CAPI of Wave 2 (98.7%, n=699). PIQ only was completed by 0.28% (n=2). Different interviewing styles were used during the CAPI, depending on the participant's communication ability and ID level. A respondent-only interview was undertaken directly with the subjects, a proxy interview was completed with a family member or carer most familiar with the subject, or an interview conducted with participant was supported by a proxy.

3.3.2.1. Medicine information

In the PIQ, participants and/or proxy were asked to record all medicines taken on a regular basis (e.g. 'daily or weekly'). This included any kind of medicine being used: prescribed, over-the-counter, and any supplements. The information reported involved medicine name (generic or brand), full dosage regimen and date of first prescription. Medicine data was then confirmed by the interviewers at the time of the in-person interview and was further checked independently by two pharmacists (H. Alm. and A.B.). Medicines were classified according to the WHO Anatomical Therapeutic Chemical (ATC) system using a seven digit code (256). Exposure to PPIs was the primary outcome of interest. Five PPIs were authorised in Ireland for adults at the time of the study; omeprazole, lansoprazole, esomeprazole, pantoprazole and rabeprazole. Doses were stratified as low to medium and high dose based on guidance in the Summary of Product Characteristics (SPC) approved by the national Irish medicines regulator, the Health Products Regulatory Authority (257), the British National Formulary (BNF) (258), and cross-checked with the published criteria for medicines use in older people - STOPP/ START which are extensively used in clinical practice in Ireland and the UK (172, 173, 259, 260). For older people, PPI doses considered as low to medium were 15 mg for

lansoprazole, 10-20mg for omeprazole, 20mg esomeprazole, and 20 mg for pantoprazole and 10 mg for rabeprazole. Doses considered as maximum were 30 mg for lansoprazole, 40 mg for omeprazole, 40mg for esomeprazole, 40 mg for pantoprazole or 20 mg for rabeprazole. Any dose beyond the maximum was categorised as a dose that exceeded the maximum.

The length of PPI exposure was stratified into a 'less than a year' and 'more than a year'. Data collection of Wave 2 was between May 2013 and February 2014. Based on this range, all documented prescription dates for each PPI agent was checked along with the participants' data collection time individually and any date before May 2012, was considered as ≥ year length of use.

The number of medicines (excluding supplements) that were used concurrently by each participant was assessed to reflect the polypharmacy status. The number of medicines used were stratified into three categories: zero to four - no polypharmacy, from five to nine medicines - polypharmacy, and ten medicines or more - excessive polypharmacy (261, 262).

3.3.2.2. GI conditions and PPI indications

Participants were asked if they had ever been diagnosed by a doctor with any GI conditions. GORD and stomach ulcers that are treated mainly using PPIs were of particular interest. In addition, the use of NSAIDs, another licensed indication for PPIs (257) was also collected, along with data on those using antiplatelets since they may be at a high risk of GI bleeding and may be prescribed PPIs concurrently (240).

3.3.2.3. Other covariates

Demographic co-variates included level of ID, classified into mild, moderate and severe/profound; place of residence, classed as those who live independently or with family, those who live in a community group home and those who resided in residential nursing homes.

3.3.3. Statistical analysis

Data were analysed using the statistics package SPSS version 22. Demographic characteristics of the cohort were expressed as frequencies and percentages (with

Wilson 95% confidence intervals for proportions). A p-value of <0.05 was considered statistically significant.

A binary logistic regression was applied to the dependent variable, PPI users or PPI non-users to determine factors associated with PPI utilisation. Cross tabulation and chi-squared statistics were used to compare potential independent variables with the dependent variable (PPI use). In the regression, six variables were included. Four of these variables were demographic characteristics: gender, age, level of ID and place of residence. Two of the variables were associated with PPI indication: any of licensed indications for PPI use in Ireland (included as one variable) and antiplatelet use (included as separate variable). Variable categories that had small numbers in subgroups were collapsed; for example, PPI users who lived independently or with family (n=13) were collapsed with PPI users who live in community groups (n=71) into one group. Finally, only those with a verified level of ID (n=623) were included in the regression.

Before applying the regression, multicollinearity between the independent variables was tested, by examining the Spearman's correlation coefficient and Variance Inflation Factor (VIF). According to Dancey and Reidy's categorisation of Spearman's correlation coefficient, a value of coefficient ≤ 0.39, suggests the relevant variables will be weakly correlated (263) and thus we considered them to be of no concern. In addition, the VIF was investigated for all the variables, with a cut-off value ≥2 considered as correlated (264, 265). All the variables were entered in the regression model simultaneously.

Results were expressed as odds ratio (OR) with the corresponding 95% confidence interval and significance level of <0.05. The minimum sample size needed for the regression model according to Peduzzi (266) was calculated using the equation: $N=10k/p$, where p is the smallest of the proportions of negative or positive cases in the population, k is the number of independent variables. For the regression model, there were 6 covariates and the proportion of positive cases (as PPI use) was 0.27, therefore a minimum sample size (N) of 222 was needed. Given there were data from 623 individuals available for regression analyses, sample size was adequate.

3.4. Results

3.4.1. Demographic characteristics of the cohort

As illustrated in *Table 3-1*, more than the half of the cohort (56.3%, n= 381) were female. Half of the sample were aged between 50-65 years (51%, n=346) and those aged 65 years and over represented 21% (n=142). Most participants (46%; n=287) had a moderate level of ID. About 44% (n=298) lived in community group homes, almost as many 40.8% (n=276) in residential care.

Table 3-1 Baseline demographic characteristics of the eligible subjects (n= 677)

Characteristic	Total 677 n (%) (95%CI)
Gender	
Male	296 (43.7) (40.0-47.4)
Female	381 (56.3) (52.5-59.9)
Age, years (n=677)	
44-49	189 (28) (24.6-31.4)
50-64	346 (51) (47.3-54.8)
65+	142 (21) (18.0-24.2)
Level of ID (Missing=53)	
Mild	150 (24) (20.8-27.5)
Moderate	287 (46) (42.1-49.9)
Severe / Profound	187 (30) (29.9-33.6)
Type of residence (Missing=1)	
Independent/Family	102 (15) (12.5-17.9)
Community group home	298 (44) (40.3-47.8)
Residential care	276 (40.8) (37.1-44.5)

3.4.2. PPI users and their demographics

Among the total population, 28 % (n=189) reported the use of PPIs. There were significant differences between PPI users and non-users (except for gender and NSAID use) as illustrated in *Table 3-2*; among PPI users over half were aged between 50 to 64 years old (n=101), and 30.2% (n=57) were aged over 65 ($p<0.001$); and there were significantly more people with a severe to profound ID level ($p<0.001$). There was a significant association between place of residence and exposure to PPIs; half of the PPI

users resided in a residential care settings (n=102), 38.8% (n=73) lived in community group homes ($p<0.001$).

Table 3-2 Bivariate analysis for PPI and non- PPI users

Category	PPI users (n=189) n (%) (95%CI)	PPI non-users (n=488) n (%) (95%CI)	p-value
Gender			.354
Male	88 (46.6) (39.6-53.7)	208 (42.6) (38.3-47.1)	
Female	101 (53.4) (46.3-60.4)	280 (57.4) (52.9-61.7)	
Age, years			
40-49	31(16.4) (11.8-22.3)	158 (32.4) (28.4-36.7)	**<0.001**
50-64	101 (53.4) (46.3-60.4)	245 (50.2) (45.8-54.6)	
65+	57 (30.2) (24.1-37)	85 (17.4) (14.3-21)	
Level of ID	(Missing=13)	(Missing=40)	
Mild	28 (15.9) (11.2-22)	122 (27.2) (23.3-31.5)	**<0.001**
Moderate	76 (43.2) (36.1-50.6)	211 (47.1) (42.5-51.7)	
Severe/Profound	72 (40.9) (33.9-48.3)	115 (25.7) (21.8-29.9)	
Place of residence	(Missing=1)		
Independent/family/Community group homes	86 (45.7) (38.8-52.9)	314 (64.3) (60.0-68.5)	**<0.001**
Residential settings	102 (54.3) (47.1-61.2)	174 (35.7) (31.5-40.0)	
Number of Medicines			**<0.001**
≤ 4 (n=256)	28 (14.8) (10.5-20.6)	228 (46.7) (42.3-51.2)	
Polypharmacy (5-9) (n=258)	75 (39.7) (33.0-46.8)	183 (37.5) (33.3-41.9)	
Excessive polypharmacy (10+) (n=163)	86 (45.5) (38.6-52.6)	77 (15.8) (12.8-19.3)	
PPI-licensed indications			

Category	PPI users (n=189) n (%) (95%CI)	PPI non-users (n=488) n (%) (95%CI)	p-value
Reported diagnosis of GORD		(Missing=8)	**<0.001**
Yes (n=69)	58 (30.7) (24.6-37.6)	11 (2.3) (1.3-4.1)	
No (n=600)	131 (69.3) (62.4-75.4)	469 (97.7) (95.9-98.7)	
Reported diagnosis of stomach ulcer.		(Missing=8)	<**0.001**
Yes (n=35)	28 (14.8) (10.5-20.6)	7 (1.5) (0.7-3.0)	
No (n=634)	161 (85.2) (79.4-89.5)	473 (98.5) (97.0-99.3)	
NSAIDs use			0.174
Yes (n=56)	20 (10.6) (7.0-15.8)	36 (7.4) (5.4-1.0)	
No (n=621)	169 (89.4) (84.2-93.0)	452 (92.6) (90.0-94.6)	
Any of the licensed indications	83 (43.9) (37.0-51.0)	50 (10.2) (7.9-13.3)	**<0.001**
Antiplatelet medicine use	36 (19) (14.1-25.2)	47 (9.6) (7.3-12.6)	**0.001**

3.4.3. PPI dosage information and reported indications

Three PPIs accounted for over 80% of reported PPIs; lansoprazole (30.7%, n=58), esomeprazole (27%, n=51) and omeprazole (25.4%, n=48). As may be seen in *Table 3-3*, the majority of PPIs were used at the maximum licensed dose (66.7%, n=124). Eight participants (4.3%) were on PPI doses beyond the maximum licensed dose in Ireland. All users received a PPI daily and this use was for more than a year by over half of the cohort (52.3%, n=68). Among those who used a PPI at the maximum dose, a majority, 61.8% (n=42) were using it for more than a year. There was no significant difference between the dose and duration of use (p>0.05). There were no instances of PPIs being used in conjunction with the antibiotics that form part of the recommended *H. pylori* eradication regimens in Ireland.

Table 3-3 PPI dose versus length of use (n=189) using a bivariate analysis

	PPI Length of use [a] n (%) (95%CI)			
Category	< 1 year	≥ 1year	Missing information	Total
PPI Dose [a] Low to Medium	15 (24.2) (15.2-36.2)	22 (32.4) (22.4-44.2)	17 (30.4) (19.9-43.3)	54 (29) (23-35.9)
Maximum	45 (72.6) (60.4-82.1)	42 (61.8) (49.9-72.4)	37 (66.1) (53.0-77.1)	124 (66.7) (59.6-73.0)
Exceed the maximum	2 (3.2) (0.9-11.0)	4 (5.9) (2.3-14.2)	2 (3.6) (1-12.1)	8 (4.3) (2.2-8.3)
Missing information	-	-	3 (5.1) (1.7-13.9)	3 (1.6) (0.5-4.6)
Total	62 (47.7) (39.3-56.2)	68 (52.3) (43.8-60.7)	59 (31.2) (25-38.1)	189 (27.9) (24.7-31.4)

[a] p-value of the two categories = 0.736

A comparison of PPI users with and without the licensed indications did not show any significant differences between the two groups in their characteristics or in the dose /duration of PPI use *(Table 3-4).*

Table 3-4 Differences in demographics between PPI users with or without licensed indications (GORD, stomach ulcer and NSAID use)

Category	PPI users (n=189)		
	With licensed indication n = 83 n (%) (95%CI)	Without licensed indication n = 106 n (%) (95%CI)	p-value
Gender			0.91
Male	39 (47) (36.6-57.6)	49 (46.2) (37.0-55.7)	
Female	44 (53) (42.4-63.4)	57 (53.8) (44.3-63.0)	
Age, years			0.31
40-49	17 (20.5) (13.2-30.4)	14 (13.2) (8.0-21.0)	
50-64	40 (48.2) (37.8-58.8)	61 (57.5) (48.0-66.5)	
65+	26 (31.3) (22.4-41.9)	31 (29.2) (21.4-38.5)	
Level of ID	(Missing=5)	(Missing=8)	
Mild	13 (16.7) (10.0-26.5)	15 (15.3) (9.5-23.7)	0.96
Moderate	33 (42.3) (32.0-53.4)	43 (43.9) (34.5-53.7)	
Severe/Profound	32 (41) (30.8-52.1)	40 (40.8) (31.6-50.7)	
Place of residence	(Missing=1)		0.88
Independent/ Community group home	37 (45) (34.8-55.9)	49 (46.2) (37.0-55.7)	
Residential settings	45 (55) (44.1-65.2)	57 (53.8) (44.3-63.0)	
PPI dose	(Missing=2)	(Missing = 1)	0.075
Low – Medium	17 (21) (13.5-31.1)	37 (35.2) (26.8-44.7)	
Maximum	59 (72.8) (62.3-81.3)	65 (62) (52.4-70.6)	
Exceed the maximum	5 (6.2) (2.7-13.6)	3 (2.9) (1.0-8.1)	

Category	PPI users (n=189)		
	With licensed indication n = 83 n (%) (95%CI)	Without licensed indication n = 106 n (%) (95%CI)	p-value
Length of use	(Missing =23)	(Missing=36)	0.058
<year	34 (56.7) (44.1-68.4)	28 (40) (29.3-51.7)	
≥year	26 (43.3) (31.6-55.9)	42 (60) (48.3-70.7)	

Figure 3-2 presents the frequency of use given reported indications and/or antiplatelet use. Those with GORD (with/without stomach ulcers) reported PPI use most frequently. In total, 81 (42.8%) participants were using a PPI without a reported indication. Antiplatelets, primarily aspirin (n=78), and clopidogrel (n=6) were reported. There were 46 and 34 participants on antiplatelets and NSAIDs respectively, who did not report the use of a PPI. Those groups were also assessed for any other acid supressing agents and negligible numbers were using an antacid (n=3) or a H2 receptor antagonist (n=3).

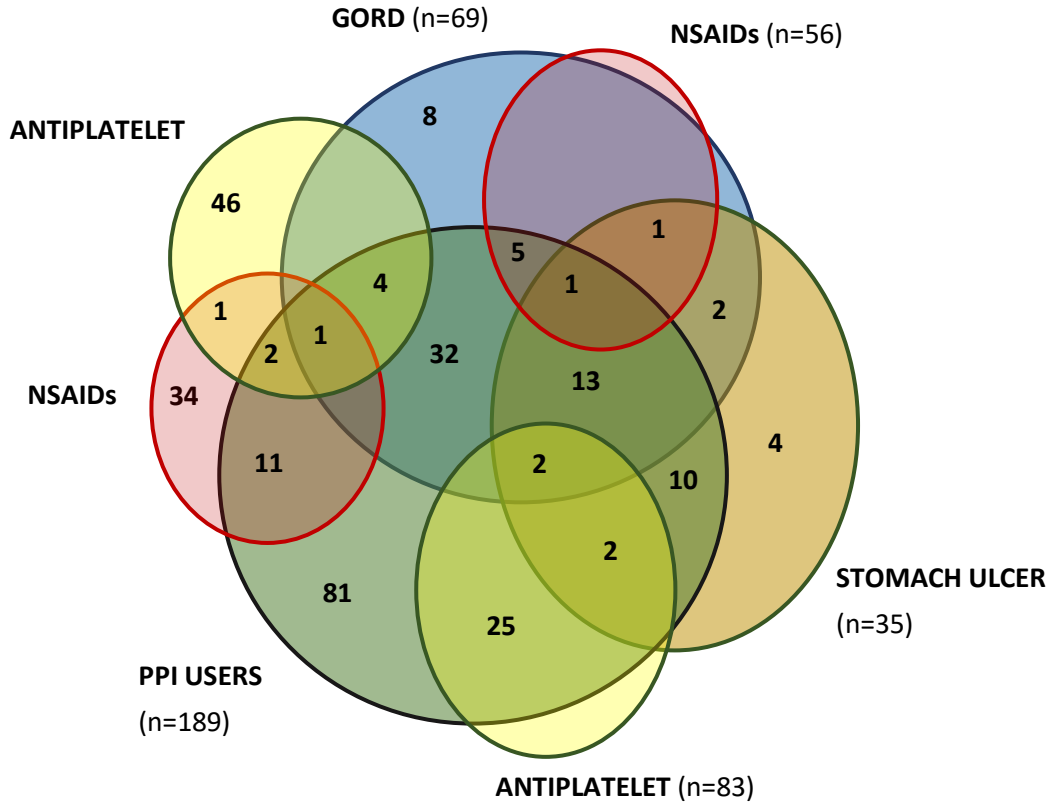

Figure 3-2 Reported indications, antiplatelet use and PPI use expressed by number of participants

3.4.4. Demographic patterns in PPI use and dosage

The relationship between PPI use/dosage information and place of residence was examined *(Table 3-5).* Differences in PPI use duration across the place of residence were not statistically significant, although the proportions of those who lived in either community group homes (51%) or residential settings (57.3%) using a PPI for more than

a year was higher than for those who lived independently or with family (12.5%). The relationship between gender/age group/ level of ID and PPI dosage information was also analysed *(Table 3-6).* There were no significant differences between gender/ age group and ID level in terms of PPI length of use, although those with severe/profound ID level were using PPI for more than a year at a rate double that for those with mild ID (60.8% vs. 31%, respectively). There were significant differences between age/ ID level (but not gender) and PPI doses. Subjects aged over 65 years were using doses beyond the maximum at a higher rate than younger age groups (10.5% vs. 2% and 0%, p=0.003) and among those with severe/profound ID level (7%) as compared with moderate ID level (2.7%) (p=0.014).

Table 3-5 Pattern of PPI use and dosage information categorised based on place of residence (n=188)[a]

Category	Independent /family n (%)	Community group home n (%)	Residential care n (%)
PPI use	13 (7)	73(38.8)	102 (54.3)
Age, years			
40-49 (n=31)	2 (15.4)	12(15.4)	17 (16.7)
50-59 (n=100)	9 (69.2)	39 (53.4)	52 (51)
60+ (n=57)	2 (15.4)	22 (30.1)	33(32.4)
PPI dose [b]	(Missing =1)	(Missing 2)	
Low- Medium	3 (25)	22 (31)	29 (28.4)
Maximum	8 (66.7)	48 (67.6)	67 (65.7)
Exceed the maximum	1 (8.3)	1 (1.4)	6 (6)
PPI length of use [c]	(Missing =5)	(Missing=26)	(Missing= 27)
<Year	7 (87.5)	23 (48.9)	32(42.6)
≥Year	1(12.5)	24 (51)	43(57.3)

[a] One PPI user did not report the place of residence, [b] P-value =0.625, [c] P-value =0.053.

Table 3-6 Pattern of PPI use and dosage information by gender, age and level of ID

	Gender		Age, years			Level of ID		
	Male n (%)	Female n (%)	40-49 n (%)	50-59 n (%)	65+ n (%)	Mild n (%)	Moderate n (%)	Severe/profound n (%)
PPI use	88 (46.6)	101(53.4)	31 (16.4)	101(53.4)	57(30.2)	28 (15.9)	76 (43.2)	72 (40.9)
PPI dose	(Missing =3)		(Missing=2)	(Missing=1)		(Missing=1)	(Missing=2)	
Low-Medium	26 (30.6)	28 (27.7)	11 (38)	21 (21)	22 (38.6)	9 (33.3)	13 (17.6)	28 (39)
Maximum	56 (65.9)	68(67.3)	18 (62)	77 (77)	29 (50.9)	18(66.7)	59 (79.7)	39 (54.2)
Exceed the maximum	3 (3.5)	5 (5%)	0 (0)	2 (2)	6 (10.5)	0(0)	2 (2.7)	5 (7)
PPI length of use	(Missing=31)	(Missing =28)	(Missing=14)	(Missing=28)	(Missing=17)	(Missing=8)	(Missing=26)	(Missing=21)
<year	26 (45.6)	36 (49.3)	9 (52.9)	35 (47.9)	18 (45)	13 (65)	27 (54)	20 (39.2)
>year	31 (54.4)	37 (50.7)	8 (47.1)	38 (52.1)	22 (55)	7 (35)	23 (46)	31 (60.8)

3.4.5. Factors associated with PPI use

Results from the binary logistic regression (*Table 3-7*) show that neither gender nor living in a residential institution were significantly associated with PPI use after adjusting for confounders. The strongest predictor of PPI use was reporting any one of the licensed indications (GORD, stomach ulcer, NSAID use; OR=7.18 CI 4.55-11.33; p<0.001) while receiving an antiplatelet (OR=2.55 CI 1.47-4.40; p = 0.001), being aged 50-64 years (OR=2.04 95%CI 1.22-3.39; p =0.006), being aged ≥65 years (OR=2.59 95%CI 1.43- 4.71; p =0.002) or having with severe to profound ID (OR=2.86 95%CI 1.57- 5.20; p =0.001) were significant correlates with PPI use.

Table 3-7 Factors associated with PPI use among older people with ID, Logistic regression (n=623)

Characteristics	OR (95% CI)	p-value
Gender		
Male	1.00	
Female	0.70 (0.47- 1.04)	0.08
Age, years		
44-49	1.00	
50-64	**2.04 (1.22-3.39)**	**0.006**
65+	**2.59 (1.43- 4.71)**	**0.002**
Level of ID		
Mild	1.00	
Moderate	1.69 (0.97- 2.95)	0.06
Severe/profound	**2.86 (1.57– 5.20)**	**0.001**
Place of residence		
Independent/Family/Community groups	1.00	
Residential care settings	1.41(0.93– 2.14)	0.09
Any PPI indication (NSAIDs use, GORD, Stomach Ulcer)	**7.18 (4.55-11.33)**	**<0.001**
Antiplatelet use	**2.55 (1.47-4.40)**	**0.001**

Reference categories= no PPI use, male, 44-49 years, mild ID level, Independent/Family/ Community groups, no any PPI indication, no antiplatelet use. Cox & Snell R Square = 0.188, Nagelkerke R Square = 0.27. All significant factors in bold.

3.5. Discussion

3.5.1. Statement of principal results

This study examined use of PPIs among a representative sample of older Irish people with ID. The use of PPIs was reported by just over a quarter (27.9%) of the participants, however less than six in ten of those exposed to PPIs reported any indication for PPI use (GORD, stomach ulcer, NSAID use or antiplatelet use). Over half of those exposed to PPIs were aged between 50-64 years of age, lived in a residential care home (54.3%). Comparing the prevalence with what has been reported from Wave 1 of this cohort (21.7%) (72), our study shows that there is 6.2% increase in PPI use in 3 years. Two-thirds of PPIs were used at maximum doses and of those who had a documented date of prescribing, just over half recorded use for more than a year. PPI users with an indication did not differ from those without an indication. After adjusting for confounders, factors that were strongly associated with PPI use were older age (≥50 years), severe/profound level of intellectual disability, reporting of any of the three authorised PPI indications and antiplatelet use, while place of residence and gender were not significant.

3.5.2. Comparison with other studies

To our knowledge there are no previous studies of PPI use in older people with ID so direct comparison was not possible. Studies in the Irish older general population (169, 267) have reported high rates of inappropriate PPI use as have international studies (159, 163, 165, 166, 268) but these populations and study characteristics differ substantially from our cohort so that comparisons have limited validity.

Unlike reports for the general older population (156, 161, 166), there were no differences between males and females in PPI use. Among those who lived in residential care, 37% received a PPI and the proportion of people with severe-profound level of ID taking a PPI was significantly higher than non-users. Furthermore, PPI users with these two characteristics tend to use a PPI for longer duration. Although it might be expected that those with severe and profound ID would live in a residential setting, in Ireland, people with moderate and even mild ID might also live there and so, despite initial

indications, after adjusting for covariates, our binary regression did not find that residential care was a predictor for PPI use.

Omeprazole was the most frequently reported agent among those who lived in residential care and although effective it has more potential drug interactions than the other PPIs (269). PPI use was also strongly associated with polypharmacy and excessive polypharmacy. In addition, living in residential care facilities was associated with polypharmacy and excessive polypharmacy (72) and this may expose individuals to potentially serious drug-drug interactions (71, 270).

3.5.3. Doses and reported indications of PPIs

Our study illustrates that two-thirds of the reported PPI doses would be considered as maximum in older people. There were also 4.3% of PPI users who reported doses exceeding the maximum recommended dose for older people (257). Nevertheless, these high doses predispose this small group of vulnerable people to higher risks and more side effects over time (143).

In this study, PPI use was associated with one of the three licensed indications in 44% of participants, and even with the addition of the pragmatic indication of antiplatelet use, for almost half of those reporting PPI use, there was no recorded indication. The indications in this study are self-reported by participants, or by a proxy in some situations. Therefore, it is possible that some of the subjects/proxies were unaware of why the medicine was being taken and/or the related medical reason. Nevertheless, a previous study of people with ID, found poor documentation of indications for drugs to treat stomach ulcer and GORD (205). The absence of this information and/or the lack of awareness, suggests that the care processes for GI disorders are of poor quality and that evaluating PPI use is not a high priority. This may account for the lack of differences between PPI users with and without a recorded indication.

In contrast to those PPI users without a recorded indication, there were 5% (n=34) of participants receiving NSAIDs who were not receiving a PPI (nor any other agent for gastro-protection), this is classed as a potential prescribing omission according to Assessing Care of Vulnerable Elders (ACOVE) indicators (271). Furthermore, among the cohort, 6.8% (n=46) of participants were taking antiplatelets without also taking a PPI.

Individuals who are on antiplatelet are at higher risk for GI bleeding (272) and old age renders them more vulnerable (273). However, further assessment is required to determine the need for a PPI, the balance of benefit and risk associated with use of both groups of drugs, and the potential drug-drug and drug-supplement interactions since almost half of PPI users are exposed to excessive polypharmacy (71, 240, 274).

3.5.4. Long term use and associated risks

This study highlights that the use of PPIs for over one year among old people with ID is common (52.8%). It was not possible in our cohort to estimate what proportion of the remaining 62 participants who had taken a PPI for less than one year had nevertheless been taking them for longer than the recommended 8-12 week period. An Irish retrospective population-based cohort study used the pharmacy claims database and reported that older people were the majority of those who used a PPI for >3 months (275). Additionally, a repeated cross-sectional study, used the same data source and showed that long term PPI use (> 8weeks) at high dose increased from 0.8% in 1997 to 23.8% in 2012 (276).

The long term or inappropriate use of PPI has raised concerns regarding their side effects. A number of studies of the general older population have reported a link between long term PPI use and risks of osteoporosis or fractures (146, 150, 277, 278). A meta-analysis of general population studies (149) and a specific examination of people ageing with ID (279) concur that there is a significant relationship between PPI use and the risk of fracture. Other risks from PPI use must also be considered including *Clostridium difficile* infection (151, 152), community-acquired pneumonia (153) vitamin and mineral deficiency - especially vitamin B_{12} and magnesium (154) and dementia (156).

3.5.5. Clinical relevance of study findings

PPI use should be periodically evaluated every three months for their continued need among older people with ID, especially those with severe or profound ID (3). Assessment of need in older people is based on the recording of symptoms and invasive investigations. However, people with ID may not be able to communicate their symptoms or to tolerate investigations especially those with a severe or profound level

of ID (126, 127). Trained and experienced healthcare professionals are required to assess and monitor people with ID effectively and consistently, particularly as they age (135, 280). For the safe use of a PPI the lowest effective dose, for the shortest possible duration is recommended. Continued PPI use is indicated for severe esophagitis, chronic use of NSAID or documented evidence of bleeding ulcers (281) but nevertheless periodic re-evaluation is needed to titrate to the lowest effective PPI dose (282). Alternatives to long term use include intermittent use and de-prescribing strategies like step-down dosing or symptom-driven (i.e. on demand) dosing in the general elderly population (281, 283-285) should be investigated in people with ID to reduce their long-term exposure to PPIs. Comprehensive guidelines for treatment of acid-related health conditions need to be created specifically for people with ID to address their needs. These guidelines should not only include treatment approaches but also the criteria for diagnosis and review to ensure that PPI prescribing occurs once the long term of use and associated risks of these medicines has been assessed.

3.5.6. Strengths and limitations

This study has a number of key strengths: First, to the best of our knowledge, it is the first investigation of the prevalence, pattern, dose regimen, and predictors associated with PPI use among older people with ID. The study used a rigorously drawn representative sample, which means the results may be generalised to the ID population in Ireland. The large sample size also provided power to the statistical analysis. Next, the accuracy of the subject's medical information was strengthened by cross- checking, and accuracy in the medicine use information was improved using two pharmacists to independently inspect and code the information. Finally, comprehensive information was available in relation to medicine doses, frequency, length of exposure and a wide range of covariates, facilitating both a thorough dosage regimen analysis and the investigation of PPI use-associated factors.

Among the study limitations, there were instances of missing PPI duration of use data and information about self-reported /or diagnosis of *H. pylori* infection/or oesophagitis was not captured, meaning it was not possible to verify if some PPI use was to manage this health issue. Similarly, no measures of PPI side effects were available.

3.6. Conclusion

PPI use among older people with ID is prevalent and frequently at a maximum dose, over a long term, and often without a clear indication. The pattern of long term PPI use without an indication, of no distinguishing features between those with and without an indication and the substantial group of participants taking an NSAID or an antiplatelet and so potentially needing, but not receiving a PPI, suggests that the regular review of GI disorders and their management is not routine, or is inadequate. This is a major concern as people with ID are particularly susceptible to GI disorders that may be chronic and in many cases progressive (127, 280). Therefore, under-diagnosis and under-treatment, as well as unnecessary treatment have a significant potential to harm and to reduce the quality of life of this vulnerable and dependent population. The quality of care that people with ID who have GI disorders needs to be assessed and measures taken to review the care needs of the most vulnerable and of those exposed to the greatest risk of harm. Building upon these findings, tailored de-prescribing approaches for people with ID should be developed and evaluated.

4. Chapter Four: A descriptive comparison of PPI use among older people with ID over two waves of IDS-TILDA: Results from Wave 3 and comparison with the prior wave.

4.1. Introduction

PPIs are among the most effective medicines to manage acid related disorders (286). Due to their evidenced superiority in relieving symptoms and healing of mucosal lesions, PPIs have quickly substituted the histamine receptor antagonists in the treatment of any clinical acid-related disorder (287). However, the long-term use of PPIs has been connected to some potential adverse consequences. For example, analysis of data from two observational cohort studies show that chronic use of PPIs has been associated with increased risk for dementia, with similar risk increases for Alzheimer's and non-Alzheimer's dementia (156, 288). The possible mechanism was assessed by invitro studies which proposed that PPIs may block the enzyme responsible for metabolising the amyloid-b (Ab) protein causing its accumulation and predisposes Alzheimer's disease (289). In addition, some studies found a link between chronic use of PPIs and some types of enteric infections. For example, PPI use may result in intestinal bacterial overgrowth by reducing the bactericidal effect of gastric acid in the stomach and the proximal small bowel (282). It may also cause a "downstream" effect on colonic bacteria predisposing the development of *Clostridium difficile* infection (282). The link between these infections and the use of PPIs has been identified by many studies (152, 290). Other risks that are associated with chronic use of PPIs are deficiencies of some micronutrients (magnesium and B_{12}) (291, 292) and detrimental effects on bone health particularly when used in high doses and for long term (>1year) (158-160). Some meta-analyses proposed that the risk of fracture is raised by 10-40% above baseline with chronic use of PPIs (150, 277, 293, 294). Among older people with ID, PPIs have been identified as contributing factors to osteoporosis and osteopenia (279). The use of PPIs is also connected to the risk of developing pneumonia (153, 295), yet this was related to the short term of use as concluded by a meta-analysis (222). More seriously, there are inconclusive debate surrounding the excess burden of death due to cardiovascular disease, chronic kidney disease, and upper gastrointestinal cancer that was attributable to use of PPIs with the risk increased with the increase in duration of exposure (296).

Despite the safety concerns, the use of PPIs continues to expand nationally and internationally and this creates growing concerns in terms of quality of prescribing and

appropriateness of their use (297). Many studies investigated the over-prescribing or inappropriate use of PPIs and high rates have been detected in both hospitalised and primary care settings with an average over 50-57% (287, 297). In addition, the continuous increase in long-term PPI utilisation has established a significant issue for many regulators not only because of increased in reporting potential adverse events, but also due to the increased expenses (275, 298).

The use of PPIs was identified frequently among older population and the use tends to increase with age (297). In a population-based study in Ireland using the Health Services Executive (HSE) Primary Care Reimbursement Services (PCRS) pharmacy claims database, PPI prescribing was the most frequent in the older age groups (≥65 years) (275). Moreover, PPIs represented 20% of all prescriptions issued in Ireland in 2017, of which 80% were on long-term therapy (297). Moreover, their use has been established commonly without clear indications especially among older people (299).

There are few studies investigating PPI usage prevalence in people with ID although acid-related disorders (for which the PPIs are indicated) is double that in the general older population (71). Furthermore, studies assessing the patterns of use of PPIs in relation to indications, use duration or doses are almost lacking in this population. The few studies available that described PPI use in people with ID, were not recent and mainly focused on the original PPI omeprazole (300), while there are other PPIs that are widely used nowadays but have not been investigated in this population (286). In the population with ID, PPIs were associated with poor level of documenting indications (205) and findings from Chapter 3 indicate that the use was frequently for long-term and at high doses.

Since there has been some national and international discussion regarding discontinuing long-term PPI use by applying deprescribing approaches (281, 301), it is expected that the prescribing pattern of PPIs may change over time. The trend in using PPIs have been assessed and tracked by many studies in adult and older population (161, 165, 302, 303). However, none investigating the use at different periods among people with ID.

On the view of complexity of PPI use in this cohort identified from findings of Chapter 3, investigation for their use in this population over two IDS-TILDA waves may provide a better understanding of this complexity.

The main aim in this chapter was to investigate the use of PPIs in Wave 3 IDS-TILDA (2016/2017) and conduct a descriptive comparison of the Wave 3 findings with findings from prior wave (Wave 2).

The objectives were to;

a) Investigate the prevalence and patterns of PPI use by demographics and clinical characteristics at Wave 3 IDS-TILDA (2016-2017)
b) Investigate the reported doses and length of use of PPIs at Wave 3
c) Compare the results with findings from Wave 2 IDS-TILDA
d) Track the use of PPIs from Wave 2 to Wave 3 IDS-TILDA to identify those who continue using PPIs at both waves, those who stopped or those who initiated PPIs at Wave 3
e) Investigate the characteristics, demographics and PPI dosage of those who used PPIs at Wave 2 and Wave 3 continuously, those who stopped or initiated PPIs at Wave 3

4.2. Methods

4.2.1. Wave 3 IDS-TILDA population

Wave 3 is the third and most recent wave completed as part of the nationally representative longitudinal study of older adults with ID in Ireland, the IDS-TILDA. The methodology, sampling and data collection of the IDS-TILDA are described thoroughly elsewhere (20, 182). The IDS-TILDA study is composed of waves, one every three years. Wave 1 to 3 were completed. Details of the methodology of Wave 3 is presented elsewhere (182). In brief, information on Wave 3 IDS-TILDA study design and data collection is similar to what was reported in Wave 2 (Chapter 2). At Wave 3, data collection process continued to be gathered using a Pre-Interview Questionnaire (PIQ), an extensive face to face Computer Assisted Personal Interview (CAPI) and health

assessments. The PIQ was sent to each participant and/or proxy/carer at least one week before the interview. This enabled carers/proxies time to gain assistance and support to complete the PIQ and consult their medical files. The PIQ covered topics such as medications, health service use, dietary information, and reported challenging behaviour. The CAPI, completed in person, questions like health, social and family circumstances, quality of life, and inter-personal relationships and was given by a trained interviewer in the location of the respondent's choice. Interviews continued to be a combination of self-report and/or by proxy (which were completed by family or staff) (refer to Chapter 2 and Chapter 3). Data for this study was obtained from Wave 3 IDS-TILDA and was conducted in 2016/2017. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for cross-sectional studies was used in reporting the findings. Ethical approval for the IDS-TILDA was granted by the Faculty of Health Sciences Research Ethics Committee in Trinity College Dublin and local and/or regional ethical committee approval was granted from 138 service providers.

4.2.2. Participants in Wave 3

All participants in Wave 2 were invited to take part in Wave 3 IDS-TILDA. From Wave 2 (n=708), there were 609 participants who completed the personal interview in Wave 3 with the most common causes of the attrition since the prior wave were attributed to deaths (70.7%, n=70). Of the 609 participants in Wave 3, there were 15 participants who did not complete the questionnaire, 41 participants had missing medicines data and 4 participants refused to answer medicine section. For the purpose of this study, participants with no medicine data were excluded (n=60) leaving 549 participants with medicines data available for analysis (retention rate 90%) and this representing the total population of this study. The flow of participants from Wave 2 to Wave 3 is presented in *Figure 4-1*.

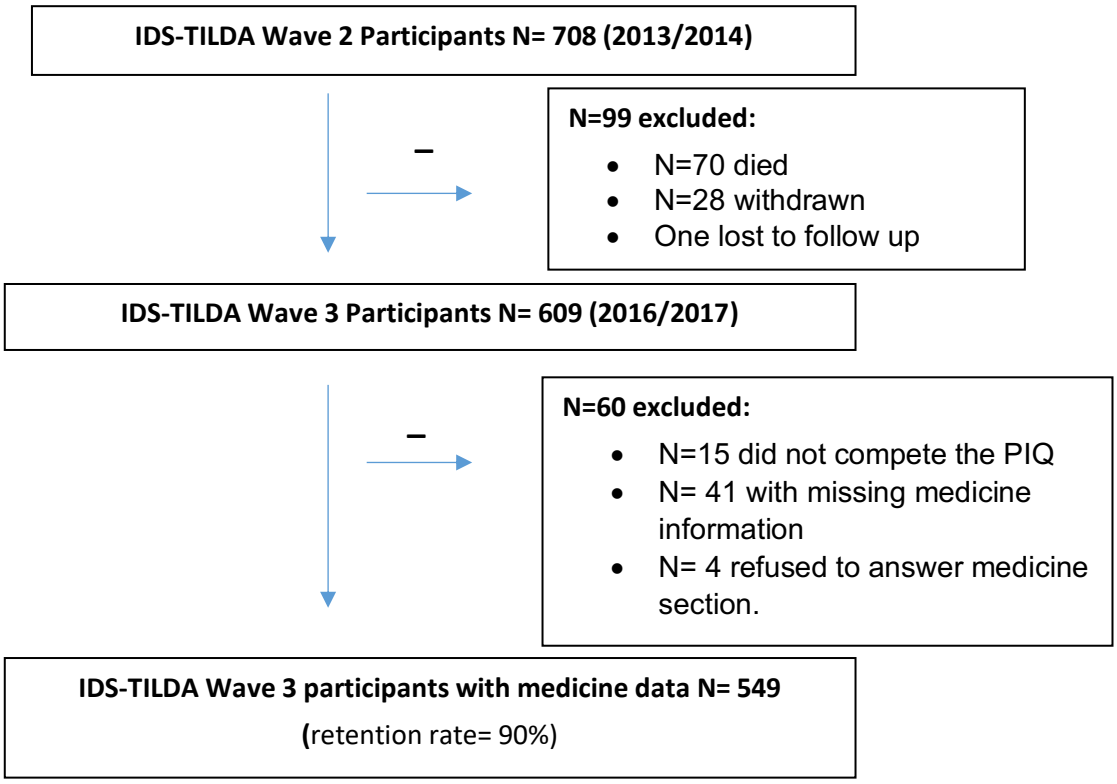

Figure 4-1 Flow of participants from Wave 2 - to Wave 3 IDS-TILDA

4.2.3. Medicines information

In the PIQ, participants/proxies were asked to fill out questions related to medications. The question was "Can you tell me what medications (including prescribed or over the counter (OTC) and supplements you take on a regular basis (like every day or every week)?". Medication data was recorded by brand name/International Non-Proprietary Name (INN), dose, frequency, route of administration and date on which medicine was prescribed. Medicines were inspected and coded using the Anatomical Therapeutic Chemical Classification System (ATC) (256) by two pharmacists independently and this was verified by one additional pharmacist independently. Exposure to PPIs (ATC code A02BC) was the primary outcome of interest. Five PPIs were authorised in Ireland at the time of the study; omeprazole, lansoprazole, esomeprazole, pantoprazole and rabeprazole. Doses were stratified as low to medium and high dose based on guidance in the SPC approved by the Health Products Regulatory Authority in Ireland (257), BNF (258) and cross-checked with the published criteria for medicines use in older people - STOPP/ START which are extensively used in clinical practice in Ireland and the UK (172, 173, 259, 260). For older people, PPI doses considered as low to medium were 15 mg for lansoprazole, 10-20mg for omeprazole, 20mg esomeprazole,

and 20 mg for pantoprazole and 10 mg for rabeprazole. Doses considered as maximum were 30 mg for lansoprazole, 40 mg for omeprazole, 40mg for esomeprazole, 40 mg for pantoprazole and 20 mg for rabeprazole. Any dose beyond the maximum was categorised as a dose that exceeded the maximum. The use duration of PPIs for Wave 3 was assessed based on the time of data collection of Wave 3 which was conducted between September 2016 to March 2017. Based on this range, all documented prescription dates for each PPI was checked along with the participants' data collection time individually to stratify the length of use to "<1 year "or "> 1 year".

4.2.4. Indications of PPIs

At Wave 3, interviews were sought from all respondents who participated in any previous wave and who agreed to be contacted again. Any previous answers in the physical health part in Waves 1 and 2 were "fed forward" and confirmed, or updated in Wave 3. Of the reported GI conditions, GORD and stomach ulcers that are treated with PPIs were of particular interest. In addition, the use of NSAIDs, another licensed indication for PPI use was also reported, along with data on those using antiplatelets since they may be at a high risk of GI bleeding and may be prescribed PPIs concurrently (240).

4.2.5. Other covariates

Demographic co-variates examined included level of ID, classified into mild, moderate and severe/profound; place of residence, classed as those who live independently or with family, those who live in a community group home and those who resided in residential settings (where ten or more people living together on campus-based accommodation). Level of ID of participants was verified from case notes at Wave 1 and Wave 2 of the IDS-TILDA study.

4.2.6. Comparison with Wave 2 IDS-TILDA

The findings of this study was compared to findings of Wave 2 (Chapter 3). In addition, participants who used PPIs on Wave 2 were followed at Wave 3 using the participant's identification number. Variables for those reporting PPI use at both waves, those who stopped or those initiated PPIs at Wave 3 were then created in Wave 2 and

Wave 3 dataset. This was to further investigate the trend in demographics and the characteristics of these groups.

4.2.7. Statistical analysis

Descriptive statistics and bivariate analyses were carried out in this study using SPSS version 24 (IBM corporation) and a p-value of <0.05 was considered statistically significant.

4.3. Results

4.3.1. Baseline characteristics of Wave 3 IDS-TIDA cohort.

Among Wave 3 participants in this study (n=549), over half were female (57%, n=313) and just over 63% were aged between 50 to 64 years (n=346) with a quarter (25.3%, n=139) aged 65 years and over. There were 45.6% (n=231) of participants with a moderate level of ID and 30% (n=154) with a severe/profound level of ID. The proportions of those living in community group homes or residential care were 40.6% (n=223) and 45.2% (n=248) respectively but only 14% (n=78) of participants lived independently or with family. The prevalence of a doctor's diagnosis of GORD was 16.6% (n=91) and stomach ulcer 5.6% (n=31). *Table 4-1* provides details for the Wave 3 cohort demographics in this study.

Table 4-1 Characteristics of the study population in Wave 3 IDS-TILDA (n=549)

Characteristics	Total n (%)	Male (n=236, 43%) n (%)	Female (n=313, 57%) n (%)
Age, years			
<50	64 (11.7)	34 (14.4)	30 (9.6)
50-64	346 (63)	150 (63.6)	196 (62.6)
65+	139 (25.3)	52 (22)	87 (27.8)
Level of ID	(Missing= 42)	(Missing= 21)	(Missing=21)
Mild	122 (24)	46 (21.4)	76 (26)
Moderate	231(45.6)	94 (43.7)	137 (47)
Severe /Profound	154 (30.4)	75 (35)	79 (27)

Characteristics	Total n (%)	Male (n=236, 43%) n (%)	Female (n=313, 57%) n (%)
Place of residence			
Independent/Family	78 (14.2)	38 (16)	40 (12.8)
Community group home	223 (40.6)	92 (39)	131 (42)
Residential care	248 (45.2)	106 (45)	142 (45.4)
Reported GORD	91 (16.6)	38 (16)	53 (17)
Reported ulcer	31 (5.6)	16 (6.8)	15 (4.8)

4.3.2. Changes in demographics since Wave 2

Details of the difference in demographics at both waves are illustrated in *Figure 4-2.* As people grow older, there is shift in relation of the age groups from Wave 2 to Wave 3, with less people aged <50 years in Wave 3 (n=64, 11.7%) compared to Wave 2 (n=189, 28%). The proportions in the categories of gender or level of ID in the two waves were quite consistent. There was a decline in proportion of those living in community group homes from 44% (n=298) to 40.6% (n=223) and an increase in proportions of those who live in residential care from 40.8% in Wave 2 to 45.2% in Wave 3.

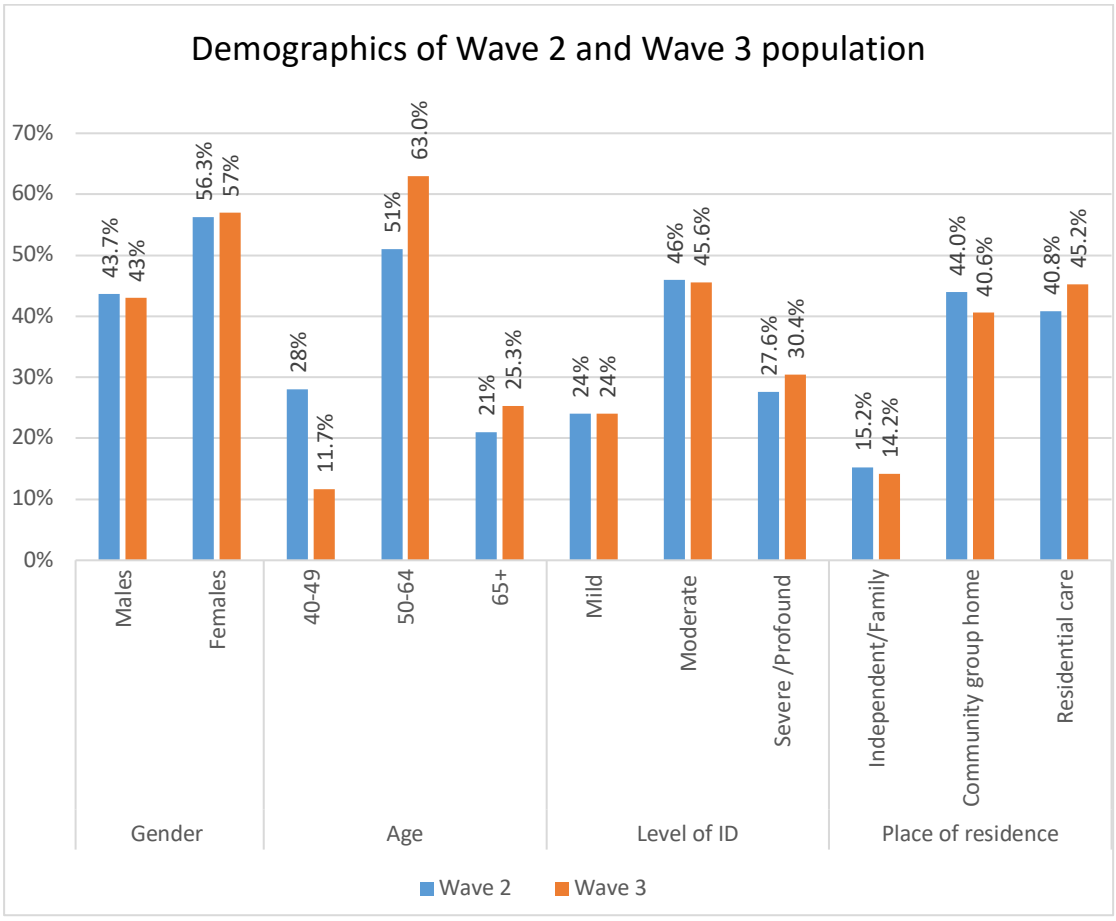

Figure 4-2 Trend in demographics in Wave 2 (n=677) and Wave 3 (n=549) IDS-TILDA

4.3.3. The use of PPIs in Wave 3

Table 4-2 shows the prevalence of PPI use in Wave 3 and presents a comparison between PPI users and PPI non-users using a bivariate analysis. Among the overall participants, there were 35 % (n=193) reported using a PPI in Wave 3. PPI users did differ in terms age, level of ID and place of residence but not gender (p=0.47) than PPI non-users. There were more PPI users aged 65+ years (33.7% vs 20.8%, p= 0.001); more PPI users with a severe/profound level of ID (37%, n=70) and more living in residential care (57.5%, n=111) than the non-users (26%, n=84) and (38.5%, n=137) respectively. PPI users were more likely to report GORD (41.5% vs 3.1%), stomach ulcer (15.5% vs 0.3%) or antiplatelet use (16.6% vs 9.8%) but not NSAID use when compared to PPI non-users.

Table 4-2 Bivariate analysis between PPI users (n=193) and PPI non-users for Wave 3 IDS-TILDA

Category	PPI users (n=193) n (%)	PPI non users (n=356) n (%)	p-value
Gender			0.47
Male (n=236)	79 (41)	157 (44)	
Female (n=313)	114 (59)	199 (56)	
Age, years			0.001
<50 (n=64)	14 (7.3)	50 (14)	
50-64 (n=346)	114 (59)	232 (65.2)	
65+ (n=139)	65(33.7)	74 (20.8)	
Level of ID (Missing= 42)	(Missing =8)	(Missing=34)	0.004
Mild (n=122)	32(17.3)	90 (28)	
Moderate (n=231)	83 (45)	148 (46)	
Severe/Profound (n=154)	70(37.8)	84 (26)	
Place of residence			<0.001
Independent/family (n=78)	14 (7.3)	64 (18)	
Community group homes (n=223)	68 (35.2)	155 (43.5)	
Residential settings (n=248)	111 (57.5)	137 (38.5)	
Reported diagnosis of GORD			<0.001
Yes (n=91)	80 (41.5)	11 (3.1)	
Reported diagnosis of stomach ulcer			<0.001
Yes (n=31)	30 (15.5)	1(0.3)	
NSAIDs use (n=36)	18 (9.3)	18 (5)	0.054
Any of the above three indication (n=133)	103 (53.4)	30 (8.4)	<0.001
Antiplatelet use (n=67)	32 (16.6)	35 (9.8)	0.02

4.3.4. Reported PPIs dosage and use duration in Wave 3

Table 4-3 provides details on the doses and duration of use of PPIs. Almost two thirds of the reported PPIs were used at maximum doses (63.2%, n=122) and a further 6.7% (n=13) of doses exceeded the maximum in older people. Among those who reported a date of PPI prescription, there were 57.7% (n=71) reported using PPIs for less than a year and 42% (n=52) reported PPI use for more than a year. Among those who reported PPIs for more than a year, over the half reported using maximum doses (57.7%, n=30). The relation between the use duration and doses of PPIs was analysed using a bivariate analysis and the results did not show statistical significant difference between the two categories ($p>0.05$).

Table 4-3 PPI dose versus length of use (n=193) using a bivariate analysis for Wave 3 IDS-TILDA

		PPI Length of use [a]			
	Category	< 1 year n (%)	≥ 1year n (%)	Missing information n (%)	Total n (%)
PPI Dose [a]	Low - Medium	17 (23.9)	16(30.8)	21 (30)	54 (28)
	Maximum	49(69)	30 (57.7)	43 (61.4)	122 (63.2)
	Exceed the maximum	5 (7)	4 (7.7)	4 (5.7)	13 (6.7)
	Missing information	-	2 (3.8)	2 (2.9)	4 (2.1)
	Total	71(57.7)	52(42.3)	70 (36.3)	193 (35)

[a] P-value of the two categories = 0.679

4.3.5. PPIs use and relevant indications in Wave 3

The relationships between the use of a PPI and their indication - GORD, stomach ulcer and the use of NSAIDs and of antiplatelets is shown in *Table 4-2* and illustrated in the Venn diagram (*Figure 4-3*). Over one-quarter of PPI users reported the condition GORD alone (25.4%, n=49) and further 16% (n=31) reported GORD with other indications mainly stomach ulcer (n=13) or antiplatelet use (n=10). There were also those who used NSAIDs (n=8), antiplatelets (n=18) or both (n=3) and reported the use of PPIs.

However, there were 8 participants who reported GORD, 30 reported antiplatelet use and 16 reported NSAID use who did not report using a PPI. In addition, there were 37.3% of those who reported PPI use but without reporting any of the indications (n=72).

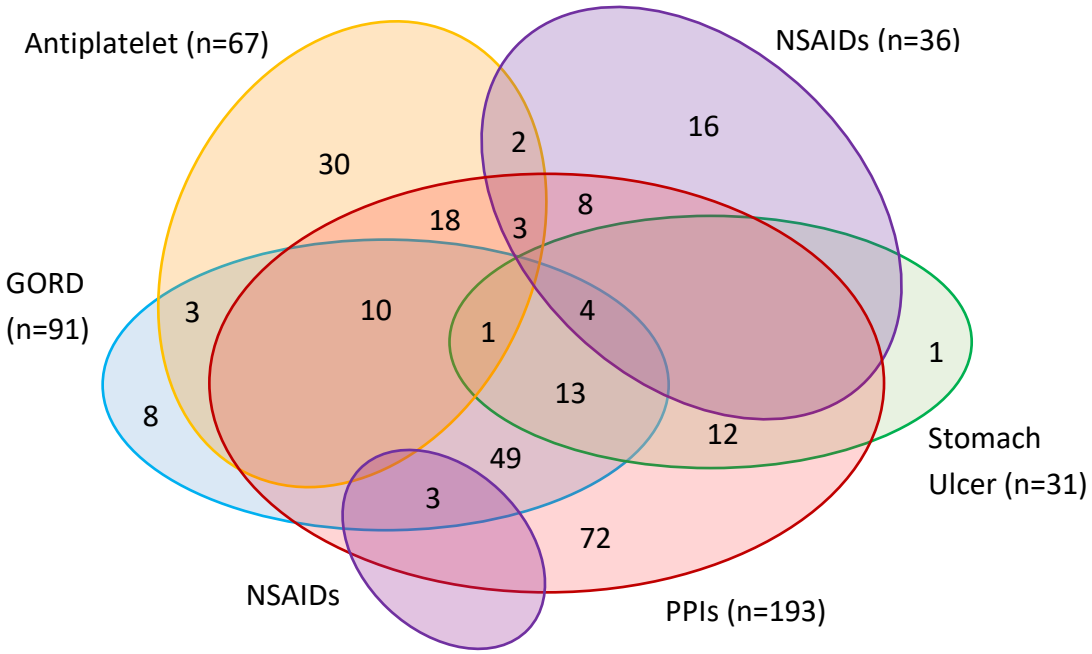

Figure 4-3 Reported indications among PPI users in Wave 3 IDS-TILDA expressed by numbers

4.3.6. Overall changes in the prevalence, pattern of the reported PPI doses, use duration and indications

There was an increase in the proportion of those using PPIs in Wave 3 by 7% compared to Wave 2 (Wave 2: 28% n=189; Wave 3: 35%, n=193).

Figures 4-4 and *Figure 4-5* illustrate proportion of reported doses and length of use at Wave 2 and Wave 3. There was large proportion of PPIs being used at maximum doses in the two waves of IDS-TILDA as shown in *Figure 4-4* which representing 63.2%-65.6% of the PPI users and those who used PPIs at doses beyond the maximum increased in Wave 3 to 6.7%. Among those who reported the date of prescription of the PPIs, the use of PPIs for more than one year represented a large proportion in both waves although the percentage decreased by 10 in Wave 3 (Wave 2: 52.8% vs Wave 3: 42.3%) *(Figure 4-5*).

The percentage of those who did not report any authorised indication nor antiplatelet use but using of a PPI decreased by 5.5% in Wave 3 compared to Wave 2 (Wave 2= 42.8%, n=81) (Wave 3= 37.3%, n=72).

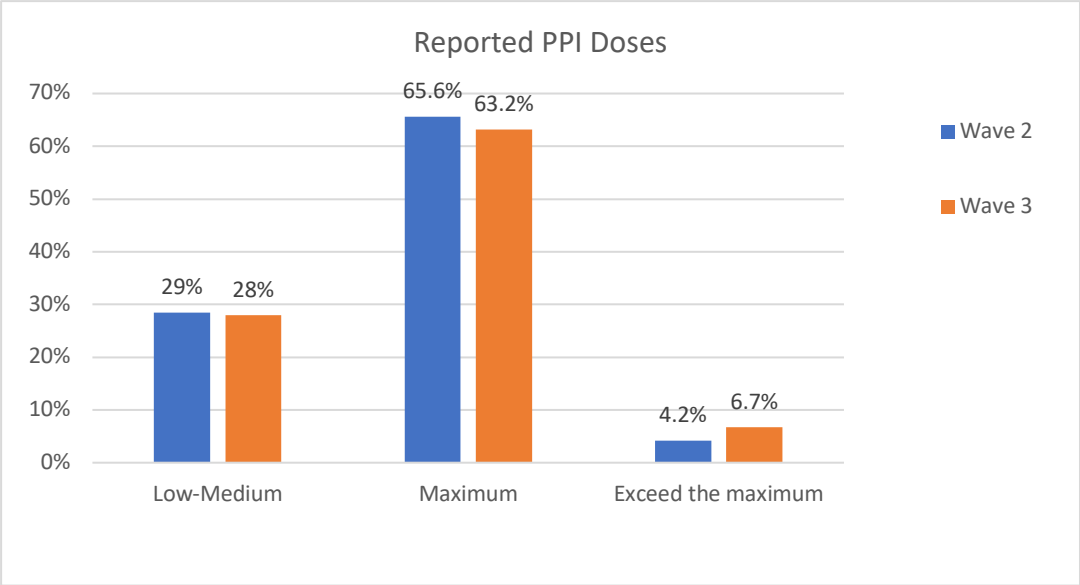

Figure 4-4 Reported PPI dosage information for Wave 2 and Wave 3 IDS-TILDA. Missing values in Wave 2=3, Wave 3= 4)

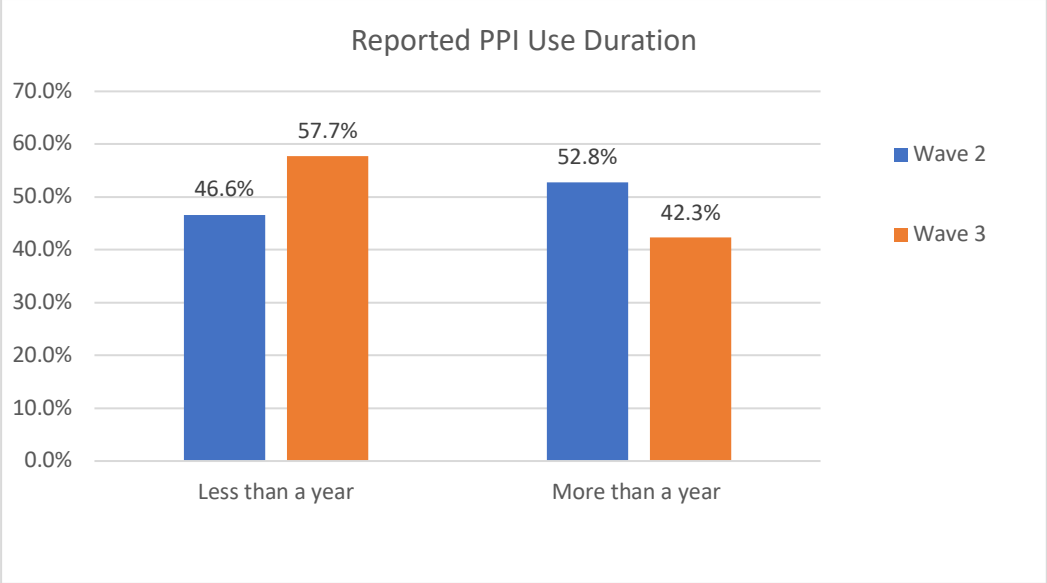

Figure 4-5 Reported PPI use duration for Wave 2 and Wave 3 IDS-TILDA. Missing values in Wave 2: n=59 (31.2%), Wave 3: n=70 (36.3%)

4.3.7. The trend and pattern of PPI use between Wave 2 and Wave 3

PPI users identified in Wave 2 were followed in Wave 3 and the findings (*Table 4-4)* show that from Wave 2, PPI use was continued by 64.5% (n=122) and was discontinued by 9.5% (n=18) in Wave 3. There were 12.5% (n=69) who commenced the use of a PPI at Wave 3.

Table 4-4 PPI use from Wave 2 to Wave 3

	Wave 2	Wave 3	n (%)	Comments
PPI use	Yes	Yes	122 (64.5)[a]	• Still continue PPI use
	Yes	No	67 (35.4)[b]	• 34 have passed away after Wave 2 • 5 withdrawn from participation in Wave 3 • 1 has missing PIQ file • 9 have missing medicine information in Wave 3 • 18 stopped PPI use in Wave 3
	No	Yes	71 (36.8)[b]	• 69 reported PPI use in Wave 3 • 2 new participants in Wave 3 who were not in the 677 Wave 2 cohort

[a] Percentage per Wave 2 population. [b] Percentage per Wave 3 population

4.3.8. Participants who reported PPI use in both Waves

There were 122 participants who reported using a PPI in both waves (Waves 2 and 3) of IDS-TILDA *(Table 4-5)*. Over half (53.3%) of them were female and over half were aged between 50-64 years (53.3-56.6%). About a quarter (24.5%, n=31) of them were aged 65+ years and this proportion increased in Wave 3 to over one third (38.5%, n=47). Moderate and severe/profound level of ID was reported by 42.2% (n=49) and 45.7% (n=53), respectively.

The number of those who live independently or with family reduced from Wave 2 (9.8%, n=12) to Wave 3 (8.2%, n=10) by 2 participants, and number of those who lived in community group homes in Wave 2 was 43 (35.2%) which was decreased in Wave 3 by one participant (n=42 , 34.4%). Over half of this group lived in residential care (55%, n=67 and this was increased to 57.4 (n=70) in Wave 3.

There were over one third (37.7%, n=46) of this group reported GORD in Wave 2 and this proportion increased to over a half in Wave 3 (55%, n=67). Reporting stomach ulcer in this cohort also increased from Wave 2 to Wave 3 by 3.3%, (Wave 2; 17.2%,

n=21) (Wave 3; 20.5%, n=25). Reporting NSAID use represented 10% (n=13) in Wave 2 and this was decreased to 7.4% (n=9) in Wave 3. The proportion of reporting any of the three authorised indications for PPI use increased in Wave 3 (n=78, 64%) as compared to Wave 2 (n=59, 48.4%). Reporting the use of antiplatelet among this group remained at the same percentage in both waves (17.2%, n=21).

Almost two-thirds (65.3%, n=79) of this cohort used maximum doses of PPIs with an increase by 1.6% in Wave 3 (66.4%, n=81) and further 6.6% (n=8) reported using doses exceed the maximum in Wave 2 and this increased by one participant in Wave 3 (7.4%, n=9) *(Table 4-5).*

Table 4-5 Demographics and information on PPI use among participants who reported using PPIs at both waves IDS-TILDA (n=122)

Category	Wave 2 n (%)	Wave 3 n (%)
Gender		
Male	57 (46.7)	
Female	65 (53.3)	
Age, years		
44-49	22 (18)	10 (8.2)
50-64	69 (56.6)	65 (53.3)
65+	31 (25.4)	47 (38.5)
Level of ID (Missing =6)		
Mild	14 (12)	
Moderate	49 (42.2)	
Severe/Profound	53 (45.7)	
Place of residence		
Independent/family	12 (9.8)	10 (8.2)
Community group home	43 (35.2)	42 (34.4)
Residential care	67 (55)	70 (57.4)
PPI dose	(Missing =1)	(Missing =2)
Low – Medium	34 (28)	30 (24.6)
Maximum	79 (65.3)	81 (66.4)
Exceed the maximum	8 (6.6)	9 (7.4)
GORD	46 (37.7)	67 (55)
Stomach ulcer	21 (17.2)	25 (20.5)
NSAID use	13 (10.7)	9 (7.4)
Antiplatelet use	21 (17.2)	21 (17.2)

Category	Wave 2 n (%)	Wave 3 n (%)
Any of the 3 authorised indication	59 (48.4)	79 (64.8)

4.3.9. PPI users who initiated or stopped the PPIs at Wave 3 IDS-TILDA

The demographics and clinical characteristics of those who initiated a PPI or stopped PPIs in Waves 3 is shown in *Table 4-6* and *Table 4-7* respectively. Over two-thirds of those who initiated a PPI at Wave 3 were females (68%, n=47) and similarly among those who stopped PPIs in Wave 3 (66.7%, n=12).

In total, 52.2% (n=36) of those initiated PPIs at Wave 3 were aged 50-64 in Wave 2 and the percentage increased in Wave 3 to 71% (n=49). In total, 18.8% (n=13) of this group were aged 65+ in Wave 2 and this increased in Wave 3 to 23.2% (n=16). Almost half of this group were with moderate level of ID (49.3%, n=33) and 24% (n=16) with severe/profound level of ID. There were 46.4% (n=32) of this cohort living in residential care in Wave 2 and this increased to over a half in Wave 3 (56.5%, n=39). Maximum doses of PPIs were reported by 58% (n=40) of this group with further 5.8% (n=4) reported PPI doses exceed the maximum. NSAIDs use, GORD and stomach ulcer were reported in Wave 2 by 11.6 % (n=8), 7.2% (n=5) and 3% (n=2) respectively with additional 10% (n=7) reported the use of antiplatelet in Wave 2. This however increased in Wave 3 to 16% (n=11) for GORD, 16% (n=11) for antiplatelet use, 13% (n=9) for NSAIDs use and 5.8% (n=4) for stomach ulcer.

Table 4-6 Participants who reported PPI use in Wave 3 but not Wave 2 (Initiated PPI at Wave 3; n=69)

Category	Wave 2 n (%)	Wave 3 n (%)
Gender		
Male		22(32)
Female		47(68)
Age, years		
44-49	20 (29)	4 (5.8)
50-64	36 (52.2)	49 (71)
65+	13(18.8)	16 (23.2)
Level of ID (Missing =2)		

Category	Wave 2 n (%)	Wave 3 n (%)
Mild		18 (27)
Moderate		33 (49.3)
Severe/Profound		16(24)
Place of residence		
Independent/family	6 (8.7)	4 (5.8)
Community group home	31(45)	26 (37.7)
Residential care	32(46.4)	39 (56.5)
PPI dose		(Missing =1)
Low – Medium	-	24(34.8)
Maximum	-	40 (58)
Exceed the maximum	-	4(5.8)
GORD	5 (7.2)	11 (16)
Stomach ulcer	2 (2.9)	4 (5.8)
NSAIDs use	8 (11.6)	9 (13)
Antiplatelet use	7 (10)	11 (16)
Any of the 3 authorised indication	15 (21.7)	22 (32)

Among those who stopped the use of PPIs at Wave 3 *(Table 4-7),* 61% (n=11) and 27.8% (n=5) were aged in Wave 3 between 50 to 64 years and 65+ years respectively. 46.7% (n=7) of this group were with moderate level of ID and one third (33.3%, n=5) with severe/profound level of ID. All of this group were living, in Wave 3, either in community group homes (33.3%, n=6) or in residential care (66.7%, n=12). The majority of this group 76.5% (n=13) reported the use of maximum doses of PPI in Wave 2. GORD was reported in Wave 3 but not Wave 2 by 16.7% (n=3) of this cohort. Any of the three authorised indications was reported in Wave 2 by 33.3% (n=6) of participants which was decreased to 22.2% (n=4) in Wave 3. Similarly, antiplatelet use decreased by 11% (n=2) since Wave 2 *(Table 4-7).*

Table 4-7 Participants who stopped the PPIs in Wave 3 (n=18)

Category	Wave 2 n (%)	Wave 3 n (%)
Gender		
Male		6 (33.3)
Female		12(66.7)
Age, years		

Category	Wave 2 n (%)	Wave 3 n (%)
44-49	4 (22.2)	2 (11)
50-64	9 (50)	11 (61)
65+	5(27.8)	5 (27.8)
Level of ID (Missing =3)		
Mild	3 (20)	
Moderate	7 (46.7)	
Severe/Profound	5 (33.3)	
Place of residence		
Independent/family	0 (0)	0 (0)
Community group home	8 (44.4)	6 (33.3)
Residential care	10 (55.6)	12 (66.7)
PPI dose	(Missing =1)	
Low – Medium	4 (23.5)	-
Maximum	13(76.5)	-
Exceed the maximum	0 (0)	-
GORD	0 (0)	3 (16.7)
Stomach ulcer	1 (5.6)	0 (0)
NSAID use	5 (27.8)	1 (5.6)
Antiplatelet use	4 (22)	2 (11)
Any of the 3 authorised indication	6 (33.3)	4 (22.2)

4.4. Discussion

The prevalence of PPI use among people with ID has been observed to rise among people with ID since the first wave of IDS-TILDA (2009/2010), where the use represented 27% of Wave 1 cohort (72). Although the level of PPI use is still lower than that reported in general older population in Ireland (71), the increase in PPI use shown along the IDS-TILDA waves may hold two possible explanations; it may be associated with new incidence of GORD or any other indications along the three waves, or it could be linked with overprescribing or inappropriate prescribing pattern similar to what have been reported in older general population (160, 165).

While the use of PPI did not differ significantly between males and females along the two waves of IDS-TILDA, a greater proportion were of those in older ages (65+), those with severe/profound level of ID or by those who live in residential care at both waves IDS-TILDA. People with ID at older age or whose ID was within the severe and

profound levels often live in residential settings (20). Nonetheless, after adjusting for confounders, findings from Wave 2 (Chapter 3) indicated that PPI use was significantly associated with severe/profound level of ID and older ages but not place of residence. Residential care is generally an area where polypharmacy/excessive polypharmacy is detected (304) and the quality of medicine use sometimes is of poor level (305). In a study that evaluated medicine use among a group of people with profound level of ID and were living in residential care, drugs for peptic ulcer and GORD (includes PPIs, H2 receptor antagonists or antacids) were of the frequently used therapeutic classes and were used by 52% of participants (205). Another study reported a prevalence of 37.2 % of antiulcer medicines in nursing home resident with ID (68). Although comparison is not valid because of different sample characteristics, this is to suggest that residential care may be commonplace for PPI overuse in people with ID.

Results from the two waves showed that there were a large proportion of participants using PPIs without reporting any indication (Wave 2= 42.8%, n=81) (Wave 3= 37.3%, n=72) and although reporting the indication was slightly increased in Wave 3, the percentage remained concerning and this was also observed among those who used PPIs at both waves *(Table 4-5),* which may be explained by an inadvertent continuation of a no longer indicated PPI. Nonetheless, when investigating the clinical characteristics of those who initiated a PPI in Wave 3 (n=69) (*Table 4-6),* there were 32% (n=22) (in Wave 3) reported any of the three authorised indications for PPI with further addition of those using antiplatelet (16%, n=11), and the remaining proportion (52%, n=36) were initiated the PPIs without clear indications so this may suggest the poor level of documenting the indications related to PPI use as what was reported in another study of people with ID (205). Reporting indications is an important tool in people with ID considering the communication difficulties that they experience and should be always considered by prescribers.

Findings from the two waves IDS-TILDA indicate that there were high proportions of PPIs were used at high doses (Wave 2: 65.6%, n=124), (Wave 3: 63.2%, n=122) and for long term (Wave 2: % 52.8, n=68), (Wave 3: 42.3%: n=52). Since GORD experienced by people with ID may be extensive, becoming severe in some cases (121), the constant use of PPIs may be required with higher doses given to overcome symptoms. Nonetheless, the findings of the two waves show that over a quarter of the high doses

being used for long duration (Wave 2:38%, n=46, Wave 3:28.8%, n=34) and risks from this practice may outweigh the benefits, especially if proved for conditions where the long duration of use is not necessary.

There was a noticed increase in PPI dose by some of the users between Wave 2 and Wave 3 (especially those who used PPIs at both waves, *Table 4-5*) from medium to maximum or even exceed the maximum, and this may be to treat serious acid-related cases such as sever oesophagitis to Barrett's oesophagus. The American Gastroenterological Association (AGA) Clinical Practice Update 1, proposed best practice guidance on the use of PPIs based on specialist opinions and field publication (282). According to the AGA, the dose of long-term PPIs should be periodically revaluated so that the lowest effective PPI dose can be prescribed to manage the condition (282).

There was a reduction in proportion of reporting the use of PPIs for 'more than a year' from Wave 2 (52.8%) to Wave 3 (42.3%) which may attributed to the new PPI users in Wave 3 (n=69). Nonetheless, even among those who used PPI for less than a year, their use remains questioned if being appropriate considering the STOPP criteria which considered the use of full dosses of PPI for more than 8 week as inappropriate (168). Ongoing PPI may be indicated in case of symptoms of GORD have not been resolved or for people with complications associated from GORD and this can be continuous, intermittent or on demand (306).

Among those who stopped PPI by Wave 3, over three-quarters, 76.5% (n=13) reported the use of maximum doses of PPI in Wave 2 and it was not known if they followed the tapering (gradual discontinuation) approach before discontinuing the PPIs in order to prevent the rebound acid hypersecretion (307).

There were some participants who used NSAIDs, antiplatelets or reported GORD without use of a PPI (*Figure 4-3* and *Figure 3-2* in Chapter 3). The GI complications from NSAIDs can be exacerbated with the use of other medicines such as steroids or selective serotonin reuptake inhibitors SSRIs (306). Since these medicines are frequently used by people with ID (71), it is crucial to evaluate the need of acid protecting agent for those participants. In the general older people , it is recommended to give a PPI for those over 75 years if they are on antiplatelet therapy (specific with aspirin) (98). People with ID as they experience early signs of aging and common comorbidity (including the GI),

frequent assessment need to be applied to exclude any risks of gastro-duodenal injury and to evaluate the need for gastroprotection agent accordingly.

As there are an increase in PPI utilisation worldwide among the general population, this poses an issue for many regulatory authorities in terms of increased costs and potential risk of adverse events (162, 306). More recent studies have reported some serious side effects associated with PPI use such as enteric infection (e.g.; *Clostridium difficile*) (308), community acquired pneumonia (222) and malabsorption of nutrient that eventually lead to vitamin B_{12} deficiency or hypomagnesemia and negative effect on bone health (309, 310). The AGA advise that long-term PPI users should not routinely increase their intake of calcium, vitamin B_{12}, or magnesium above the Recommended Dietary Allowance (RDA), nor should they routinely monitor bone mineral density, serum creatinine, magnesium or vitamin B_{12} (282). However, it is not known if these recommendations should also be applied to people with ID considering that they are a vulnerable group who frequently experience other risk factors, multi-morbidity and polypharmacy making them susceptible to adverse effects from medicines more frequently (52).

In Ireland, long-term maximal-dose PPI prescribing is highly prevalent in older adults and is not consistently associated with GI bleeding risk factors (259). As older people with ID in Ireland may be exposed to similar patterns of medicine use, the practice of prescribing PPIs among this vulnerable population must be reviewed to avoid inappropriate long term use, and appropriate strategies in managing persistent conditions such as GORD should be followed especially among those with severe/profound ID. In addition, since people with ID experience poor life style (96), before embarking on PPI long term therapy, there should be other attempts to help in acid suppression such as suitable diet and weight loss (311).

A strength of this study is that the data was derived from a population based representative sample applied in different time point (three years apart). In addition, there were a comprehensive data related to health conditions, medicines use. Furthermore, data of medicines has been cross-checked independently by three pharmacists. A limitation of this study is that the analysis of these temporal trends in PPI use may be subjected to residual confounders which have not been considered.

4.5. Conclusion

In conclusion, the use of PPI among older adults with ID increased and their appropriate use has been subjected to questions specifically seen from the patterns of using high doses, long term use and missing indications. The safety of the long term use of PPIs in this vulnerable population cannot be predicted based on existing knowledge and the use of PPIs inappropriately is not devoid of potential for risks and harms, so all efforts need to be applied in order to individualise treatment with weighing the benefit over the risks of PPI use in the population with ID.

5. Chapter Five: Laxative use and constipation among older adults with intellectual disability: A cross-sectional observational study

5.1. Abstract

Background: Chronic constipation is a prevalent issue in older people with Intellectual Disabilities (ID) and may have a significant negative impact on quality of life. The use of laxatives have not been adequately studied in this population.

Objective: To examine laxatives in relation to prevalence, pattern, dosage, reported indication and correlates.

Setting: Older people with ID who live independently, in community group homes or residential care in Ireland.

Method: Data was extracted from Wave 2 (2013/2014) of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA). Descriptive statistics, bivariate analyses and multiple logistic regression were carried out. Laxative use was analysed using two indicators for chronic constipation, reported doctor's diagnosis of constipation and Rome III criteria.

Main outcome measure: laxative use, constipation and Rome III criteria.

Results: Among the cohort n=677, chronic constipation was reported by 38.5% (n=257). In total 41.5% (n=281) reported 431 used laxatives (mean ± 1.53±0.74), with 74.3% (n=209) of those with laxative use reporting chronic constipation. There were 40% (n=113) who took 2+laxatives, within which, 60% (n=67) were using a combination from same laxative class. Reporting chronic constipation, living in residential care, exposure to anticholinergics and taking soft liquidised food were significantly associated with laxative use.

Conclusion: Chronic constipation and laxative use were highly prevalent in this study of older adults with ID. The treatment of constipation appeared to be unsystematic. Intra-class laxative use was frequent. There is a need for evidence- based treatment guidelines developed for people with ID to provide effective, quality care.

5.2. Introduction

Intellectual Disability (ID) is “a disability characterised by significant limitations in both intellectual functioning and in adaptive behavior, which covers many everyday social and practical skills” (1). Constipation is commonly reported among older adults but in people with ID aged ≥50 years in Ireland, the prevalence has been reported to be more than double of those without ID (17.2% vs. 7.8%, respectively) (71). Adults with ID who have constipation may have prolonged colonic transit time in all segments of the colon, which is linked to neurological disorders (102, 312) and those without constipation may have prolonged recto-sigmoidal colonic transit time suggesting defecation problems (102). In addition, the level of ID is a contributing factor for constipation (101, 103). Older people with ID may be exposed to multiple risk factors for developing constiption such as unhealthy diets, poor health status, low levels of physical activity and polypharmacy (103, 313). People with ID are more frequently exposed to medicines with anticholinergic effects, e.g. antiepileptics and antipsychotics, which may further contribute to constipation (99, 314). A decline in quality of life because of constipation and bowel-related symptoms that is similar to chronic conditions like diabetes has been reported (116, 118, 315). Untreated chronic constipation among adults with ID has led to encopresis, fecal impaction and life threatening consequences (112, 186). In addition, due to communication difficulties in those with ID it may be associated with behavioral changes like restlessness or screaming episodes (95, 101).

In a Dutch study of people with ID 14.3% had laxative prescriptions and 25.7% received a repeat laxative prescription (32). In other studies, laxatives were a significant contributor to polypharmacy (68, 72, 73, 211). A recent systematic review of constipation treatment in adults with ID concluded that laxatives have limited efficacy in this population but remain the most frequent form of treatment (95, 233). Additionally, chronic overuse or multiple use may result in side effects such as dehydration, electrolyte imbalance, diarrhoea or fecal incontinence (316).

The high prevalence of constipation and laxative use with limited effects in people with ID suggests that a detailed investigation of laxative use is required (95, 101, 233).

5.3. Aim of the study

Explore prevalence and patterns of laxative use among older people with ID in Wave 2 IDS- TILDA. The secondary aim was to compare the characteristics of those using laxatives and those reporting chronic constipation using two indicators for constipation. The objectives were to a) Determine the prevalence of use, patterns, dosage, the related indication(s) and combination of laxatives and b) Identify the factors significantly associated with laxative use.

5.4. Ethics approval

The Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA) study received ethical approval (Reference number: 12.10.01) from the Faculty of Health Sciences Ethics Committee, Trinity College Dublin and 138 Intellectual Disability Service Providers in Ireland.

5.5. Method

Data for this study was drawn from Wave 2 of the IDS-TILDA (2013/2014), a representative longitudinal study for older people with ID (20). This study has been previously described in detail elsewhere (20, 43). We have used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting methods and results in this study (255).

5.5.1. Participants

The IDS-TILDA sampling frame was provided from the National Intellectual Disability Database (NIDD) which gathers data for all people with ID in Ireland eligible for, or receiving services. In total, 1,800 participants aged ≥ 40 years were randomly selected from the NIDD and a total of 753 people with ID consented to participate in wave 1 IDS-TILDA (representing 8.9% of the ID population over the age of 40 years). With the average age of mortality in people with ID around 19 years earlier than their non-disabled peers (26, 27), the age of 40 years and over was selected to; reflect the lower longevity of people with ID as they frequently present with older-aged conditions and show signs of functional decline at age earlier than those without ID (28, 179), to offer

an insight into ageing for older adults with ID who age prematurely due to early onset dementia (180) and to ensure a sufficient sample size for later waves of the study.

From Wave 1 (2009-2010), 708 continued participation in Wave 2 (94% retention rate; 2013-2014) with youngest participant was 43 years of age *(Figure 5-1).* For the purpose of this study, we excluded those with missing medicines data and the final number of participants for this study was 677 (95%) with the youngest aged 44 years. The sample of the second wave and the sample of this study were comparable to both the Wave 1 sample and the NIDD database.

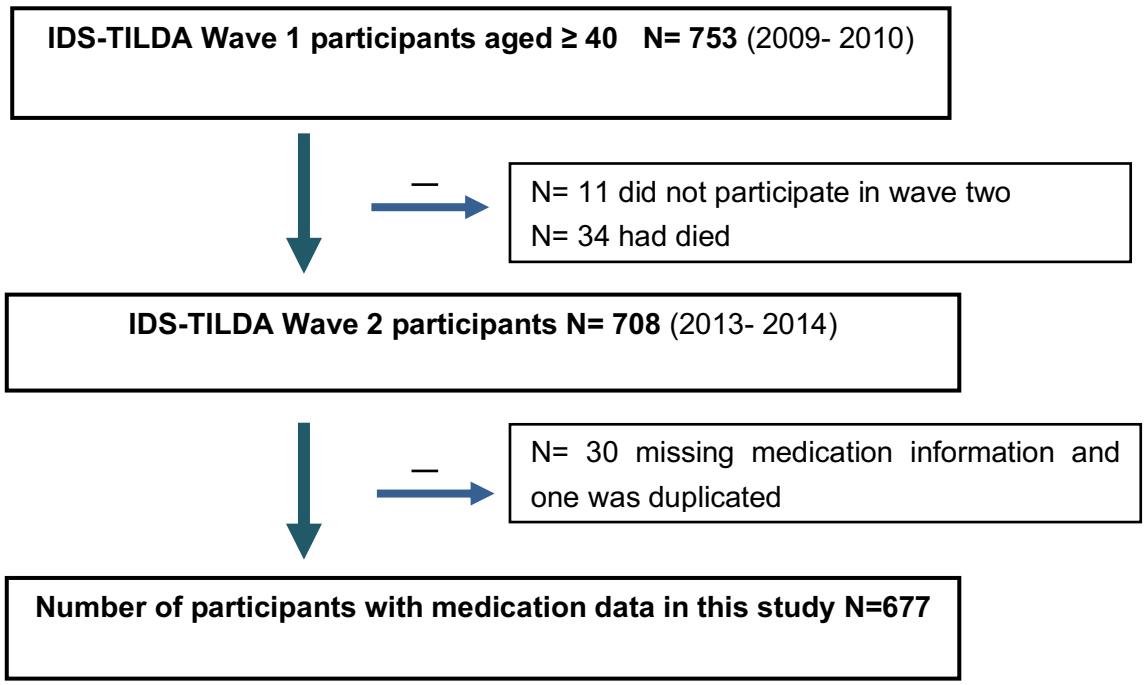

Figure 5-1 Flow of participants from Wave 1 to Wave 2 IDS-TILDA

5.5.2. Data collection

The data collection process has been described comprehensively elsewhere (43). In brief, data collection comprised a Pre-Interview Questionnaire (PIQ) and a face-to-face Computer Assisted Personal Interview (CAPI). The PIQ was sent to each participant and/or proxy/carer at least one week before the interview. This enabled carers/proxies time to gain assistance and support to complete the PIQ and consult their medical files. Different interviewing styles were used during the CAPI, depending on the participant's communication ability and ID level. A respondent-only interview was undertaken

directly with the independent participants, a supported interview was conducted with those participants who wished to have their family member or key worker present or a proxy interview was completed on their behalf of the participant by a family member or key worker. The majority of PIQs (92.8%; n = 628) were recorded by proxies (who had worked with/cared for the participant a minimum of 6 months). Almost all paticipants completed the PIQ and CAPI for Wave 2 (98.7%, n=699).

5.5.3. Medicine and medical conditions

Medicines and health conditions were recorded in the PIQs and crosschecked at the time of CAPI. Laxatives (ATC code A06A), constipation and constipation-related symptoms were the primary outcome of interest for this study. Laxative dosage regimen and doses were recorded. Doses were stratified as standard and high doses based on guidance in the SPC approved by the Health Products Regulatory Authority in Ireland (257) and BNF (317). A list of standard laxative doses for chronic constipation is presented in *Table 5-1.*

Table 5-1 Laxative standard doses per day in adults

Laxative agent	Standard dose per day
Macrogol	1-3 sachets (13.8 gram per sachet)
Lactulose	up to 45ml
Bisacodyl	≤10mg
Senna	≤30mg
Picosulfate	≤10mg (318)
Dantron combination	≤2 capsules
Isphagula	≤2sachets (or 20 ml)
Sterculia	≤4 sachets
Methyl cellulose	≤12 tablets
Linseed oil	≤45ml (319)
Liquid paraffin	10-30 ml

Regular laxative use was stratified by doses in to three groups; standard doses, high doses, or a combination of standard and high doses.

Constipation-related symptoms were straining, lumpy/hard stool, incomplete evacuation, anorectal obstruction, manual manoeuvre and reported defecation of less than three times per week. If the participant reported experiencing at least 25% of defecations with two or more of above symptoms or experiencing rare loose stools without laxative use over the past 6 months and been active for 3 months, the participant meet Rome III criteria for constipation (80).

5.5.4. Other covariates

Demographic and clinical covariates were examined including level of ID, classified into mild, moderate and severe/profound; place of residence, classed as those who live independently or with family, those who live in a community group home and those who resided in residential settings (where ten or more people living together on campus-based accommodation). Level of ID of participants was verified from case notes at Wave 1 of the study. Polypharmacy status (261, 262) and exposure to anticholinergics using the Anticholinergic Component of the Drug Burden Index (AC-DBI) were assessed among laxative users (320). The AC-DBI scores were stratified in to two groups, AC-DBI score = 0 (no exposure to anticholinergics), and AC-DBI score > zero (exposure to any anticholinergics). In addition, Barthel Index (BI; a validated scale for functional assessment in older populations was used to measure dependency in activities of daily living) (321) was also assessed. Each participant was given a composite score from 0 to 20 depending on self/ proxy report of their ability to perform these activities (like bathing, grooming, feeding, dressing, bowels, bladder, mobility, toilet use and stairs). High BI scores indicate more independence (322). Level of physical activity was reported by questioning the participants how many days they had involved in physical activity in the prior week. It is classified into the three categories; low, moderate and high based on International Physical Activity Questionnaire (IPAQ) (323).

Doctor's diagnosis of stroke, diabetes, hypothyroidism, neurological health conditions and mental health conditions that contribute to constipation (324, 325) were assessed among laxative users. Neurological health conditions included Parkinson's disease, multiple sclerosis, Alzheimer's disease, spina bifida, dementia, epilepsy, cerebral palsy and muscular dystrophy. Mental health conditions are depression, anxiety, mood swings, hallucination, emotional conditions, schizophrenia and psychosis.

Type of food was reported by asking participants if they were following soft / liquidised food or using thickened fluids diets.

5.5.5. Statistical analysis

Descriptive statistics and bivariate analyses were used with a statistically significant p-value of <0.05 when using the chi-squared test for categorical variables. Multiple logistic regression was carried out to examine the factors associated with laxative use. The explanatory variables were demographics (gender, age, level of ID, place of residence), reported constipation, and level of physical activity. Exposure to any anticholinergics (AC-DBI score>0) was added because such exposure has been strongly linked to constipation in older people with ID (99). In addition, given that constipation has been linked with neurological conditions (103), any neurological conditions were added to the regression. Finally, it is often suggested that dehydration and insufficient diet may contribute to constipation (88, 326) , so type of food (soft/liquidised/thickening fluid) was added to the regression.

Before applying the regression, multicollinearity between the independent variables was examined, by examining the Spearman's correlation coefficient and Variance Inflation Factor (VIF). According to Dancey and Reidy's categorisation of Spearman's correlation coefficient, any correlation below <0.4, suggests the relevant variables will be weakly correlated (263) and were disregarded. In addition, the VIF was investigated for all the variables, with a cut-off value ≥2 considered as correlated (264). The BI was significantly correlated with the level of ID (Spearman's rho correlation coefficient was 0.44), so was excluded from the regression model. Mental health conditions and the number of medicines variables were excluded from the regression because they showed collinearity with AC-DBI variable (Spearman's rho correlation coefficients was 0.426). Variable categories that had small numbers in subgroups were collapsed. Finally, only those with a verified level of ID (n=624) were included in the regression. All the variables were entered in the regression model simultaneously.

Results were expressed as odds ratio (OR), with the corresponding 95% confidence interval (CI) and significance level of <0.05. The minimum sample size needed for the regression model according to Peduzzi (266) was calculated using the equation: N=10k/p, where p is the smallest of the proportions of negative or positive cases in the

population, k is the number of independent variables. For the regression model, there were 9 covariates and the proportion of positive cases (as laxative use) was 0.41, therefore a minimum sample size (N) of 219 was needed. Given there were data from 583 participants available for regression analyses, the sample size was adequate. Data were analysed using the SPSS statistics version 22 (IBM corporation, New York, United States).

5.6. Results

5.6.1. Demographics of the cohort

Of the population (n=677: *Table 5-2*), more than the half (56.3%, n= 381) were female. The majority the cohort were aged 50-64 (51%, n=346) with 21% aged 65 and over. Almost half reported a moderate level of ID (46%, n=287) and 44% (n=298) lived in community group homes with 40.8% (n=276) in residential care.

Table 5-2 Baseline demographics of the study population (n= 677)

Characteristic	Number (%)
Gender	
Male	296 (43.7)
Female	381(56.3)
Age, years	
44-49	189 (28)
50-64	346 (51)
65+	142 (21)
Level of ID (Missing=53)	
Mild	150 (24)
Moderate	287 (46)
Severe/ Profound	187 (27.6)
Place of residence (Missing=1)	
Independent/Family	102 (15.2)
Community group home	298 (44)
Residential care	276 (40.8)
Gastrointestinal medical conditions	404 (59.6)
Chronic constipation (Missing=8)	257 (38.4)
Meet Rome III criteria (Missing=45)	246 (38.9)
Laxative use	281 (41.5)

Reporting constipation and meeting Rome III criteria were recorded for 38.4% (n=257) and 38.9% (n=246) of participants respectively. Laxative use was reported by 41.5% (n=281) and the cohort's composition in terms of laxative use, constipation and meeting Rome III criteria is illustrated in *Figure 5-2*. There was overlap between reporting of the two constipation indicators and 20.5% (n=139) of participants reported both criteria together with laxative use. Some laxative users reported one or the other: 19.6% (n=55) reported only constipation, and 7% (n=20) only meeting Rome III criteria, while 16% (n=45) of laxative users reported neither constipation nor did they meet the Rome III criteria. In total, 8.9% (n=23) of those who reported constipation reported no laxative use, 24.8 % (n=61) of those who meet the Rome III criteria were not taking laxatives and 3.4% (n=23) who reported both indicators had no laxative use.

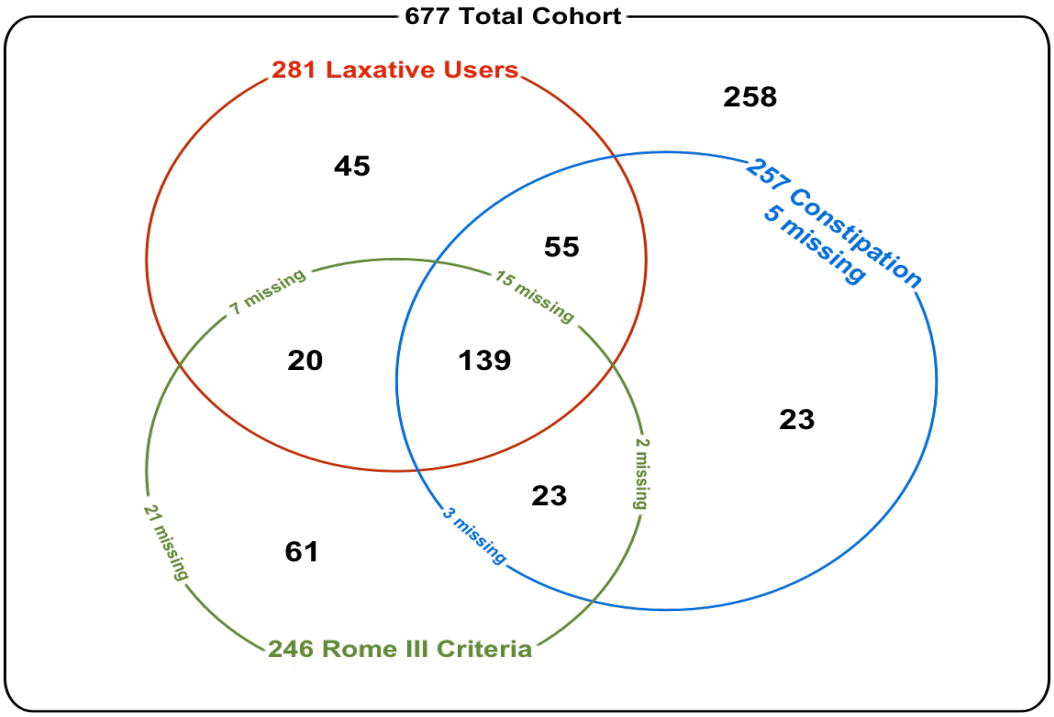

Figure 5-2 The cohort composition in terms of laxative use, chronic constipation and meeting Rome III criteria (n=677)

5.6.2. Characteristics of laxative users and those reported constipation

The characteristics of those using laxatives compared to those who did not report laxative use are shown in *Table 5-3*. The characteristics of those who reported

constipation were compared to those who did not report constipation (*Table 5-4)* and they differed only in antidiarrheal use which was more prevalent among laxative users.

Table 5-3 Bivariate analysis for laxative users and non-users (n=677)

Category	Laxative users (n= 281) n (%)	Laxative non-users (n = 396) n (%)	p-value
Gender			0.357
Male (n=296)	117(39.5)	179 (60.5)	
Female (n=381)	164 (43)	217 (57)	
Age, years			0.019
44-49 (n=189)	78 (41.3)	111 (58.7)	
50-64 (n=346)	130 (37.6)	216 (62.4)	
65+ (n=142)	73 (51.4)	69 (48.6)	
Level of ID (Missing = 53)			<0.001
Mild (n=150)	35 (23.3)	115 (76.7)	
Moderate (n=287)	116 (40)	171 (60)	
Severe-profound (n=187)	116 (62)	71 (38)	
Place of residence			<0.001
Independent /with family (n=102)	5 (5)	97 (95)	
Community group home (n=298)	110 (37)	188 (63)	
Residential care (n=276)	166 (60)	110 (40)	
BMI [a] (Missing = 110)			
Underweight (n=20)	14 (70)	6 (30)	0.001
Normal (n=168)	85 (50.6)	83 (49.4)	
Overweight (n=379)	137 (36)	242 (64)	
BI [b] score (Missing = 42)			<0.001
Complete independence (20) (n=113)	17 (15)	96 (85)	
Mild- moderate dependence (13-19) (n=324)	105 (32.4)	219 (67.6)	
Severe- total dependence (0-12) (n=198)	141(71.2)	57 (28.8)	
Activity level			0.001
Low (n=491)	221 (45)	270 (55)	
Moderate-high (n=177)	54 (30.5)	123 (69.5)	
Medical conditions reported			
Mental health conditions (Missing = 24)	177 (52.2)	162 (47.8)	<0.001

Category	Laxative users (n= 281) n (%)	Laxative non-users (n = 396) n (%)	p-value
Neurological conditions (Missing = 36)	142 (53.8)	122 (46.2)	<0.001
Angina/Heart problems (Missing = 66)	22(45.8)	26 (54.2)	0.58
Stroke (Missing =17)	9 (60)	6 (40)	0.15
Diabetes (Missing =11)	23(44.2)	29 (55.8)	0.67
Hypothyroidism (Missing = 8)	44(48.4)	47(51.6)	0.18
Arthritis (Missing = 20)	31(38.8)	49(61.3)	0.62
Irritable bowel syndrome (Missing = 35)	7(41.2)	10 (58.8)	0.99
Constipation reported (Missing =8)			
Yes (n=257)	209 (81.3)	48 (18.7)	<0.001
No (n=412)	72 (17.5)	340 (82.5)	
Meet Rome III criteria (Missing =45)			<0.001
Yes (n=246)	159 (64.6)	87(35.4)	
No (n=386)	100 (25.9)	286 (74)	
Medicines			
Antiparkinsonian (n=103)	60 (58.3)	43 (41.7)	<0.001
Antiepileptic (n=292)	157 (53.8)	135 (46.2)	<0.001
Antipsychotics (n=305)	148 (48.5)	157(51.5)	0.001
Antidiarrheal (n=60)	34 (56.7)	26 (43.3)	0.013
Opiate analgesics (n=11)	6 (54.5)	5 (45.5)	0.376
AC-DBI [c]			
Zero (n=216)	64 (29.6)	152 (70.4)	<0.001
>zero (n=461)	217 (47)	244 (53)	
Number of medicines			
0-4 (n=256)	35 (13.7)	221 (86.3)	<0.001
Polypharmacy (5-9) (n=258)	127 (49.2)	131 (50.8)	
Excessive polypharmacy (10+) (n=163)	119 (73)	44 (27)	
Type of food			
Soft/liquidised food or thickened fluids (n=95)	70 (73.7)	25 (26.3)	<0.001

[a] Body Mass Index. [b] Barthel Index. [c] Anticholinergic Component-Drug Burden Index

Table 5-4 Patterns of constipation considering clinical and demographic characteristics (n=669 [a])

Category	Participants with chronic constipation (n = 257) n (%)	Participants with no chronic constipation (n = 412) n (%)	p-value
Gender			0.46
Male (n=293)	108 (37)	185 (63)	
Female (n=376)	149 (39.6)	227 (60.4)	
Age, years			0.012
44-49 (n=187)	75 (40)	112 (60)	
50-64 (n=342)	115 (33.6)	227 (66.4)	
65+ (n=140)	67 (48)	73 (52)	
Level of ID (Missing =52)			<0.001
Mild (n=147)	32 (21.8)	115 (78.2)	
Moderate (n=286)	102 (35.7)	184 (64.3)	
Severe-profound (n=184)	107 (58.2)	77 (41.8)	
Place of residence (Missing =1)			<0.001
Independent /with family (n=101)	13 (13)	88 (87)	
Community group home (n=293)	112 (38.2)	181 (61.8)	
Residential care (n=274)	131 (47.8)	143 (52.2)	
BMI [b] (n=560, missing =109)			<0.001
Underweight (n=20)	10 (50)	10 (50)	
Normal (n=167)	83 (49.7)	84 (50.3)	
Overweight (n=373)	121 (32.4)	252 (67.6)	
BI [c] score (Missing= 41)			<0.001
Complete independence (20) (n=112)	21 (18.8)	91 (81.3)	
Mild- moderate dependence (13-19) (n=319)	100 (31.3)	219 (68.7)	
Severe- total dependence (0-12) (n=197)	121(61.4)	76 (38.6)	
Activity level			
Low (n=486)	196 (40.3)	290 (59.7)	0.02
Moderate to high (n=174)	53 (30)	121 (70)	
Medical conditions reported			
Mental health conditions (Missing =23)	156 (46.6)	179 (53.4)	<0.001

Category		Participants with chronic constipation (n = 257) n (%)	Participants with no chronic constipation (n = 412) n (%)	p-value
	Neurological conditions (Missing =29)	125 (47.5)	138 (52.5)	<0.001
	Angina/Heart problems (Missing =62)	16 (33.3)	32 (66.7)	0.43
	Stroke (Missing =15)	8 (53.3)	7 (46.7)	0.23
	Diabetes (Missing =10)	22 (42.3)	30 (57.7)	0.51
	Hypothyroidism (n=91)	37 (40.7)	54 (59.3)	0.63
	Arthritis (Missing =19)	37 (46.3)	43 (53.8)	0.12
	Irritable bowel syndrome (Missing =34)	8 (47)	9 (53)	0.45
Medicines				
	Antiparkinsonian (n=101)	52 (51.5)	49 (48.5)	0.003
	Antiepileptic (n=291)	137 (47)	154 (53)	<0.001
	Antipsychotics (n=300)	128 (42.7)	172 (57.3)	0.04
	Antidiarrheal (n=60)	27 (45)	33 (55)	0.27
	Opiate analgesics (n=11)	7 (63.6)	4 (36.4)	0.08
AC-DBI [e]				
	Zero (n=214)	62 (29)	152 (71)	0.001
	>zero (n=455)	195 (43)	260 (57)	
Number of medicines				<0.001
	0-4 (n=251)	56 (22.3)	195 (77.7)	
	Polypharmacy (5-9) (n=255)	105 (41.2)	150 (58.8)	
	Excessive polypharmacy (10+) (n=163)	96 (59)	67 (41)	
Type of food				
	Soft/liquidised food or thickened fluids (n=93)	56 (60)	37 (40)	<0.001

[a] Missing reported constipation = 8. [b] Body Mass index. [c] Barthel Index. [e] Anticholinergic Component-Drug Burden Index.

5.6.3. Factors associated with laxative use

Reporting a diagnosis of chronic constipation [OR=22.57(13.7-37.03), p<0.001], living in residential care [OR=2.78 (1.70-4.54) p<0.001] and intake of soft food or

thickened fluid [OR=4.32 (2.13-8.75), p<0.001] were all significantly associated with laxative use compared to laxative non-users, after adjusting for confounders in the multiple logistic regression (*Table 5-5*). Exposure to anticholinergics was also significantly associated with laxative use [OR=1.7(1.01-2.85), p=0.04]. There were no significant associations between laxative use and older age, physical activity or reporting neurological conditions.

Table 5-5 Multiple logistic regression of factors associated with laxative use (n=583)

Characteristics	Odds Ratio (95% C.I)	p-value
Gender		
Male	1.00	
Female	0.94 (0.59-1.50)	0.80
Age, years		
44-49	1.00	
50-64	0.89 (0.51-1.55)	0.69
65+	0.84 (0.42-1.65)	0.61
Level of ID		
Mild	1.00	
Moderate	1.27 (0.68-2.35)	0.44
Severe-profound	1.20 (0.59-2.41)	0.60
Place of residence		
Independent/community group home	1.00	
Residential	**2.78 (1.70-4.54)**	**<0.001**
Activity level		
Low	1.00	0.38
Moderate – High	0.78 (0.44-1.36)	
Chronic constipation	**22.57 (13.76-37.03)**	**<0.001**
Neurological health conditions	1.45 (0.90-2.35)	0.12
AC-DBI [a]		
Zero	1.00	
> zero	**1.70 (1.01-2.85)**	**0.04**
Soft liquidised food/thickened fluid intake	**4.32 (2.13-8.75)**	**<0.001**

[a] Anticholinergic component- Drug Burden Index. Cox & Snell R Square=0.425, Nagelkerke R Square= 0.57. Reference categories; Male, 44-49 years, mild level of ID, no chronic constipation, mild level of activity, independent/community group home and zero AC-DBI, no soft liquidised food intake, no neurological health conditions. All explanatory variables were entered into the regression model simultaneously.

5.6.4. Laxative combinations and regimens

Among the 281 laxative users, 431 laxative agents were reported (mean (±SD) 1.53±0.74). Most laxative users reported regular use 63% (n=176) *(Table 5-6)*. Most laxatives (86.3%; n=152) were used at standard doses. Osmotic agents represented the most frequently used class (83.5%, n=147). Two or more laxatives were recorded by 40% (n=113).

Table 5-6 Laxative doses and regimens (n=281)

Laxative [a]	Participants using laxatives n (%)
Laxative used regularly and on demand	41(14.7)
Laxative on demand only	62 (22.2)
Laxative used regularly only	176 (63)
Types used regularly	
Osmotic laxatives (A06AD)	147(83.5)
Stimulant laxatives (A06AB)	33 (19)
Bulk- forming laxatives (A06AC)	31(18)
Stool softeners (A06AA)	6 (3.4)
Doses used regularly [b]	
Standard doses	152 (86.3)
High doses	6 (3.4)
Standard and high doses	9 (5)
Number of laxatives used	
One laxative	168 (60)
Two laxatives	80 (28.5)
Three laxatives	29 (10.3)
Four laxatives	4 (1.4)
Enema use (A06AG)	29 (4)

[a] Missing regimen information =2, [b] missing doses information = 9.

5.6.5. Laxative use in relation to constipation and Rome III criteria

There were no differences in type of combinations or doses of laxatives among those who reported a diagnosis of constipation and met Rome III criteria (*Table 5-7)*. Of those who did not report constipation and did not meet Rome III criteria, there were 30.6% (n=22) and 33% (n=33), respectively, using two of more laxatives and on demand

use was almost twice that in those without a report of a diagnosis (34.7% vs 17.9%) or without Rome III criteria (34.3% vs 14.6%).

Table 5-7 Differences in patterns among laxative users (n=281), self-reporting chronic constipation and those classified according to the Rome III criteria

	Chronic constipation		Rome III Criteria (Missing= 22)	
	Yes (n=209) n (%)	No (n=72) n (%)	Yes (n=159) n (%)	No (n= 100) n (%)
Number of laxatives				
One laxative (n=168)	118 (56.5)	50 (69.4)	88 (55.3)	67 (67)
≥ Two laxatives (n=113)	91(43.5)	22 (30.6)	71 (44.7)	33 (33)
Laxative combination (n=113)	(n= 91)	(n= 22)	(n =71)	(n = 33)
Any intraclass laxatives (n=67)	53 (59.3)	14 (63.6)	40 (56.3)	21 (63.6)
Dose	(Missing=11)	(Missing=4)	(Missing=9)	(Missing=6)
Standard (A)	142 (71.7)	53 (77.9)	110 (73.3)	71 (75.5)
High (B)	9 (4.5)	2 (2.9)	8 (5.3)	2 (2.1)
Combination from (A) and (B)	47 (23.7)	13 (19.1)	32 (21)	21 (22.3)
Frequency	(Missing=2)		(Missing=1)	(Missing=1)
Reg [a]	135 (65.2)	41 (56.9)	107 (67.7)	55 (55.6)
Reg +Prn [b]	35 (16.9)	6 (8.3)	28 (17.7)	10 (10)
Prn	37 (17.9)	25 (34.7)	23 (14.6)	34 (34.3)

[a] Reg: regular use, [b] prn: as needed use

5.6.6. Laxative combination

Interclass combinations were common among laxative users (*Figure* 5-3) with 38 reporting the use of two osmotic agents and further 22 used two osmotic agents together with another laxative class. In total, 15.6% (n=44) reported use of both stimulants and osmotic laxatives and 6% (n=17) a combination of osmotic and bulk-forming laxatives.

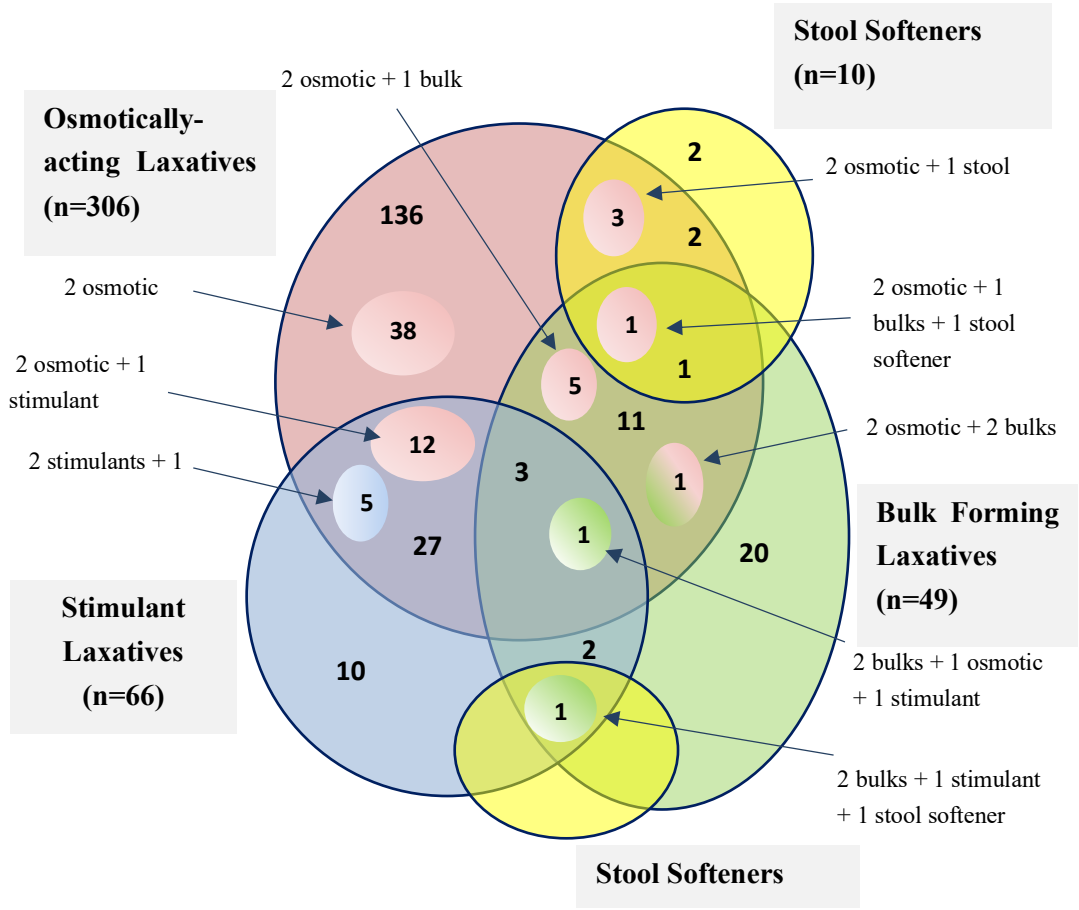

Figure 5-3 Inter-class and intra-class combinations among laxative users n=281; total laxative agents in use = 431

5.7. Discussion

This study has shown that chronic constipation, as assessed by two measures, was prevalent in this population with place of residence being the dominant associated factor and laxative use was not optimal. Laxatives were often used inappropriately and despite their use, criteria indicative of constipation were still reported and in some groups, particularly those living independently, laxative use did not correspond to the reporting of constipation.

The prevalence of laxative use reported in this study (41.5%) is lower than that reported in two studies of people with ID in the Netherlands living in residential care (65-69%) (101, 205). However, regarding those living in residential care in our study, a similar prevalence (60%) of laxative use was found.

Some of the factors associated with laxative use reported by Van Winckel M. *et al.* (non-ambulatory, female gender and medicines use) differ from our findings; while receiving pureed or tube feeding was significantly correlated with laxative use as in our study (211). A severe level of ID, neurological conditions and physical in-activity were reported to be correlated with constipation in some studies (101, 103) but none of these factors were statistically significantly associated with laxative use in our study after adjusting for confounders.

There was a clear gradient in increased constipation and laxative use from those living independently/with family 13% of whom reported constipation compared to 47.8% in residential care. Of those living independently only 5% reported laxative use whereas by contrast 60% in residential care used laxatives. This suggests infrequent or sub-optimal management of constipation in those living independently and easy access to laxatives in residential care perhaps because staff aim to prevent constipation by using laxatives as suggested in other studies (215, 327). Those with higher anticholinergic burden were significantly more likely to report laxative use after adjusting for confounders, which was previously reported from this cohort (99) and among older general population (328).

The main agents reported in this study were macrogol followed by lactulose; these are recommended options for older adults (325) with the former proven effective and less likely than the latter to produce bloating and flatulence (329, 330). Bulking agents

were effective in increasing stool frequency in older patients (331) with normal transit constipation, but not among those with slow transit constipation or with defecation disorders (325, 332) such as many people with ID (102) and consequently the use of bulking agents may not represent an appropriate choice (325). Mineral oil was used by 3.5% of users despite recommendations it should be avoided in older adults due to concerns about aspiration (254).

Several laxative combinations were used by those who used 2+ laxatives. Switching from one agent to another and the use of a laxative combination from different therapeutic classes may be considered if monotherapy is not sufficient (325, 333). However, our findings illustrate that almost one quarter of laxative users received a combination from the same therapeutic class, an approach that is not recommended by any of the existing constipation treatment guidelines (325, 333). This may be because one laxative did not provide relief, resulting in prescribing of an additional laxative (334). However, laxative use in residential care, where the majority of combined use occurred, may be as a result of regular, prescribed laxatives, with the addition of on demand use in response to symptoms, initiated by a nurse or carer when needed (327). This may establish the unstructured approach toward managing constipation in people with ID as a practice norm. The high proportion of participants meeting the Rome III criteria in our study suggests ongoing symptoms despite laxative use and chronic laxative use may not be effective (95, 110, 233) so the prescribing of unnecessary laxatives and of illogical combinations should be discontinued because of the risk of side effects (218).

In our study, laxative users were significantly more likely to follow a soft diet and the participants in this cohort are often edentulous (107) which may lead them to use soft processed food that usually has low fibre content and subsequently increased risk of constipation (335). In addition, as swallowing difficulties are prevalent in people with ID (131), their diet frequently includes thickened fluids which may lead to dehydration, especially when relying on thickened liquids for oral hydration, and this increase the risk of constipation (109).

Constipation significantly affects the quality of life of people with ID (95, 101) and poses a substantial burden to those who care for them. Therefore, optimising all of the available interventions is crucial (233). This study strongly suggests the need for interventions that include frequent and structured medication review by clinical

pharmacists (336) to identify and minimise unnecessary medication use, particularly laxative combinations/regimens and constipating medicines (i.e. anticholinergics). Pharmacists who work in primary care settings need to provide clear advice about the use of laxatives including OTC laxatives in those who live independently.

This study has several key strengths: it is the first investigation of the prevalence, patterns, dose regimen, and factors associated with laxative use among a representative population of older adults with ID so the results may be generalised to the older ID population in Ireland. The large sample provided sufficient power for the statistical analysis and the range of data collected in the study meant that adjustment for relevant confounders was possible in the regression. The use of the participant's report of constipation together with the assessment of the Rome III criteria and comparing these to the reported use of laxatives provided a robust set of data that captured the complexity of the clinical picture. Furthermore, medicine data was inspected and coded independently by two pharmacists. Finally, comprehensive information was available in relation to medicine doses, frequency of dosing and a wide range of covariates, facilitating both a thorough analysis and investigation of laxative use-associated factors.

Among the limitations, medical conditions and medicines data were based on self-report of participants or their proxies, which may lead to misclassification (337) and since the data was not extracted from participant's medical records, which might include additional information related to medicine use, we were not able to identify if there were contraindications to laxative use. Regular medicine use was captured, so some of the 'on demand' laxatives may not have been recorded. Additionally, information about the length of use of laxatives was often missing.

5.8. Conclusion

Constipation and laxative use were both highly prevalent in this representative cohort of older people with ID. Reporting constipation, living in residential care, taking soft food or thickened fluids and exposure to anticholinergics were all significantly associated with the use of laxatives, after adjusting for relevant confounders. Laxative use was complex in this population; combined use of regular and on demand laxatives, single and multiple classes, were all used in various permutations. Use of two agents

from the same pharmacological class was frequent, an approach that may not be appropriate. Furthermore, other medicines and supplements (e.g. iron and calcium supplements) may cause constipation and should be considered in future. Evidence-based guidelines for managing constipation and laxative use specifically for people with ID would improve their quality of life and the quality of healthcare.

6. Chapter Six: Laxative use among older people with ID over three waves IDS-TILDA: Results from Wave 3 and a descriptive comparison with the previous waves.

6.1. Introduction

People with ID experience multi-morbidities and multiple medicine use (52). Constipation is one of these comorbidities and usually identified as common issue in this population (52, 95). Constipation among people with ID often comes with a complex picture in terms of the underlying causes, symptoms, diagnosis and treatment (95). People with ID are exposed to several risk factors that are associated with constipation from the intellectual disability to neurological and mental health morbidities, unhealthy lifestyle and high exposure to anticholinergics (95, 101).

Considering syndrome specific disorders, constipation in people with Down syndrome is likely with all the risk factors that people without Down syndrome might experience such as poor diet, sedentary lifestyle, medicine use etc. Nonetheless additionally, they are susceptible because of conditions that cause constipation such as coeliac disease, hypothyroidism and Hirschsprung disease (338-341).

Behaviours that challenge among people with ID are linked to their communication difficulties. Since constipation is one of several symptoms that causes discomfort and pain, it may be a contributor to or cause of behaviours that challenge (101, 124). In a study of 215 individual with ID in residential care, behavioural problems were observed in 40% of the individuals with constipation compared to 22% of those without constipation, with restlessness and screaming episodes detected even more often (101).

Constipation has a negative impact on quality of life among the general older population with the impact comparable with those reported for other diseases (342) and can lead to mortality among people with ID (112).

There is a growing body of research directed towards evaluating medicine use in this population and high level of polypharmacy and excessive polypharmacy have been detected with some has been linked to GI symptoms (68) and GI medicines such as laxatives (72). To date, the use of laxatives has been given little investigation by studies of large scales in the population with ID despite the high level of constipation in this population (233). O'Dwyer *et al.* identified that laxatives represented the third most frequently reported therapeutic class among older people with ID in Ireland with about

75% of participants who were exposed to excessive polypharmacy reported the use of laxatives (72) and similar frequency has been identified in a Dutch study (32).

In general, the use of laxatives are often the most effective way to manage constipation (343). However, their use has been associated with over-use and perhaps potentially inappropriate use particularly in the older population or those who live in residential care (344). In the population with ID, the long-term use of laxatives may add further complications not only as causing adverse effects but also as being not sufficient to overcome the symptoms of constipation. This is clear from the report of Van Winckel *et al.* who investigated laxative use in 420 institutionalised individuals with ID and reported that 41% of laxative users still had infrequent defecation and stools remained hard in 20% (211).

The use of laxatives in relation to indication has not often been assessed in the population with ID. In one study of people with profound ID, 165 participants (65%) reported laxative use and an indication for such use was reported for only 68% (n=112) of them (205).

Laxative use among people with ID has been independently associated with the use of medicines other than laxatives (211). However, laxative use in relation to specific therapeutic classes is neither clearly nor sufficiently studied considering that there are a wide range of medicines, other than anticholinergics, that can cause constipation and need to be assessed (345, 346).

Among older adults in the general population, laxative use and constipation has been evaluated at different time points in order to assess the trend in use and prevalence (347, 348). However, very few studies evaluate the use of laxatives and constipation over a period among the population with ID.

Findings from Chapter 5 of this thesis (conducted on Wave 2 IDS-TILDA, 2013/2014) indicated that the use of laxatives was complex, was associated with exposure to anticholinergics and yet laxatives were not used by all those who reported constipation. Evaluating the use in further waves of IDS-TILDA will offer a broader picture in this regards and will give an insight into the current practice of laxative use in older people with ID.

The primary aim of this Chapter was to investigate, compare and track the use of laxatives over a 3-year time period, from Wave 2 (2013/2014) to Wave 3 (2016/2017) of

IDS-TILDA. The second aim was to expand the investigation of the clinical and demographic characteristics of laxative users by including data from the first wave IDS-TILDA (2009/2010).

More specifically, the objectives were to;

a. Investigate the use of laxatives in Wave 3 of IDS-TILDA in terms of prevalence, patterns, dosage and indications
b. Include data from the first wave IDS-TILDA to examine laxative users over a 10-year period (from Wave 1 to Wave 3) in terms of their demographics, clinical characteristics, exposure to constipation risk factors
c. Compare these characteristics with those participants who reported doctor's diagnosis of constipation over the three waves IDS-TILDA
d. Compare detailed laxative use in Wave 3 with the findings of previous wave (Wave 2) (Chapter 5)
e. Track laxative users from Wave 2 to Wave 3 to identify those who used laxatives at both waves, those who stopped laxatives at Wave 3, or those who started laxatives at Wave 3-IDS-TILDA
f. Investigate the characteristics, demographics and laxative dosage among those who used laxatives at both Wave 2 and Wave 3, those who stopped or started using laxatives at Wave 3
g. Explore laxative use among participants with Down syndrome in Wave 1-Wave 3 IDS-TILDA
h. Evaluate the use of laxatives and reporting constipation in relation to behaviours that challenge in people with ID in Wave 3 IDS-TILDA
i. Investigate impact of constipation on quality of life in people with ID at Wave 3 IDS-TILDA.

6.2. Methods

6.2.1. Study design

Data of this study was obtained from three waves of IDS-TILDA, a nationally representative, observational, cross-sectional study of older adults with intellectual

disabilities in Ireland. The IDS-TILDA study is composed of waves, one every three years. Wave 1 (2009/2010), Wave 2 (2013/2014) and Wave 3 (2016/2017) have been completed. The study methodology, sampling and data collection are described thoroughly elsewhere for each wave, Wave 1 (20), Wave 2 (43) (refer to Chapter 5) and Wave 3 (182). Ethical approval for the study was granted by the Faculty of Health Sciences Research Ethics Committee in Trinity College Dublin and local and/or regional ethical committee approval was granted from 138 service providers.

6.2.2. Wave 3 IDS-TILDA cohort

Wave 3 is the third and most recent wave completed as part of the nationally representative longitudinal study - the IDS-TILDA- and was conducted in 2016/2017. A cross-sectional observational approach was applied to data from Wave 3. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for cross-sectional studies was used in reporting the findings.

6.2.2.1. Participants of Wave 3

The overall participants of Wave 3 IDS-TILDA was 609 who completed the personal interview of them, 594 completed and returned the pre-interview questionnaire. For the purpose of this study, there were 45 participants with no medicine data have been excluded leaving 549 participants have medicine data (retention rate 90%) and this representted the total population for the analysis of this study. The flow of participants for the current study is presented in *Figure 6-1*.

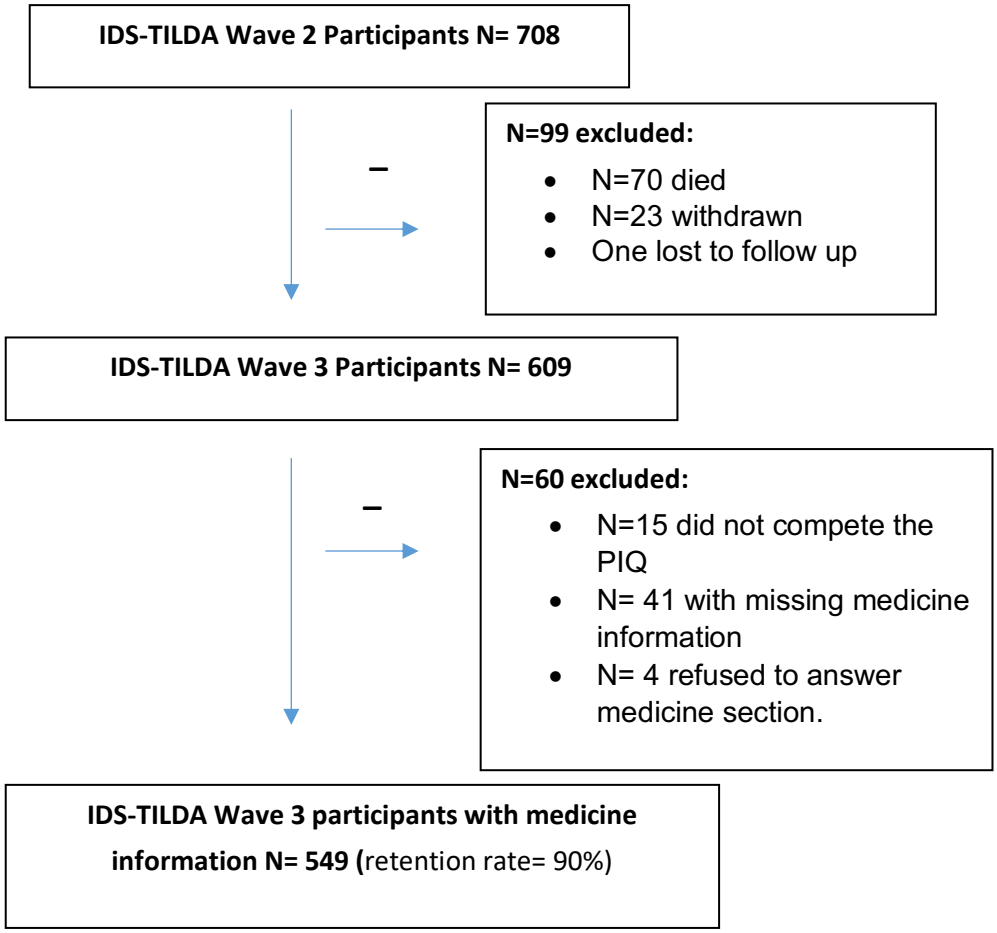

Figure 6-1 Flow of participants from Wave 2 - to Wave 3 IDS-TILDA

6.2.2.2. Data collection

Data collection process continoued in Wave 3 to be gathered using a Pre-Interview Questionnaire (PIQ), an extensive face to face Computer Assisted Personal Interview (CAPI) and health assessments. The PIQ was sent to each participant and/or proxy/carer at minimum one week before the interview. This enabled carers/proxies time to gain assistance and support to complete the PIQ and consult their medical files. The PIQ covered topics such as medications, health service use and frequency, dietary information, and reported challenging behaviour. The CAPI, completed in person, questions like health, social and family circumstances, quality of life, and inter-personal relationships, and was given by a trained interviewer in the location of the respondent's choice.

6.2.2.3. Medicine information

In the PIQ, participants/proxies were asked to fill out questions related to medications. The question was “Can you tell me what medications (including prescribed or over the counter (OTC)) and supplements you take on a regular basis (like every day or every week)?”. Medication data was recorded by brand name/International Non-Proprietary Name (INN), dose, frequency, route of administration and date on which medicine was prescribed. Medicines were coded using the Anatomical Therapeutic Chemical Classification System (ATC) (256) by two pharmacists and this was verified by additional one pharmacist independently. The primary outcome of interest of this section was the use of laxatives (ATC code A06A). Regular or on demand use of laxatives as well as laxative doses were recorded. Doses were stratified similar to the way in the previous chapter (Chapter 5) in to standard and high doses based on guidance in the SPC approved by the Health Products Regulatory Authority in Ireland (257) and BNF (258).

6.2.2.4. Health conditions

At Wave 3, interviews were sought from all respondents who participated in any previous wave and who agreed to be contacted again. Any previous answers in the physical health part in Waves 1 and 2 were “fed forward” and confirmed, or updated, in Wave 3. Two constipation indicators were available in Wave 3 (self-reported of doctors’ diagnosis of constipation and Rome III criteria). Rome III criteria has been created from a list of symptoms related to constipation (refer to Chapter 5). A variable that related to conditions which may cause constipation was created based on reporting the following health conditions; stroke, heart and related problems, diabetes, arthritis, hypothyroidism, neurological and mental health conditions, irritable bowel syndrome.

6.2.2.5. Exposure to anticholinergics

The exposure to anticholinergics in this study were assessed using Anticholinergic Cognitive Burden (ACB) scale. The scale included a list of medicines with anticholinergic activity. Each medicine in the list given a score as following; 1 passible anticholinergic effect, 2 and 3 as owning definite anticholinergic effect and any medicine not in the list are given a score of zero (99). The total ACB score of each participant created by

summing the score of each possible (ACB 1) or definite (ACB 2 or 3). Participants were categorised into two categories, those exposed to any anticholinergic medicine (ACB score $\geq$ 1) and those with no anticholinergic exposure (ACB=0) (99).

6.2.2.6. Medicines that commonly contributed to constipation

Constipation as an adverse effect from medicines can be considered as individual response which depend on other variables like the individual's general health, level of activity, lifestyle and bowel history. Medicines that cause constipation usually described as therapeutic classes which includes a wide range of medicines that vary in their degree in causing constipation. Some medicines are thought theoretically to cause constipation but do not seem to (such as NSAIDs) (85). Paul and Denis reported that anticonvulsants, NSAIDs and antiparkinsonian are less commonly implicated in constipation (87). The search on drugs that contribute to constipation has been expanded to specifically identify a list of medicines that contributed (and commonly contributed) to constipation based on reporting constipation as an adverse effect in the SPC. This list has been used to create 'on medicines contributed to constipation' and 'on medicines commonly contributed to constipation' variables.

I. Method of identifying a list of medicines that may contribute to constipation

A thorough search of the SPC was applied for each medicine among classes that contribute to constipation (see section 1.6.1.3) This involved searching the SPC that are published by the Health Products Regulatory Authority (257) and the SPC from the BNF (317). In the SPC, the reported side effects are derived from clinical trials and post-marketing safety studies. They are also documented from spontaneous reporting for which, after comprehensive evaluation, a causal relationship between the medicine and the side effect is at least sound possibility, according for instance, to their comparative incidence in clinical trials, or to results from epidemiological studies and/or based on an evaluation of causality from case reports (349). Additional sources were searched if the medicine was not found in the HPRA or the BNF (or contained a limited information about side effects of the relevant medicine). These sources were the Medicines and Healthcare products Regulatory Agency (MHRA), publicly accessible data from the Food Drug Administration (FDA) and other online sources (350, 351). The ATC codes from the

WHO was used to assist to identify medicines within the therapeutic classes. Furthermore, we used the anticholinergic list created by O'Connell *et al.* (320) as a guidance for any agent with anticholinergics properties not under the constipating therapeutic classes. Any agent with antimuscarinic properties was considered, after consensus as commonly causing constipation medicine even if there were no reports of constipation as side effect in the SPC. If there was no record of constipation but reported either constipation or consequences such as paralytic ileus was under the precautions, then the medicine was added in the list but not as common. The list of medicines that contributed to constipation was agreed after discussion and consensus with two other pharmacists (MH and MO'D).

II. Results

Appendix 5 summarises medicines and their frequency in causing constipation. The corresponding frequency category for each adverse drug reaction is based on using the following standard: Very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) (317, 349). Once again, the aim of creating the Table in *Appendix 5* was to clearly identify a list of medicines that cause constipation and more specifically medicines which are commonly (≥1/100) causing constipation. All agents under the PPIs and the drugs that are used for urinary frequency and incontinence were found commonly causing constipation. From the other classes, we found 117 medicines with a common or very common frequency in reporting constipation (other than the classes reported in section 1.6.1.3). The majority of medicines commonly causing constipation comes from the antipsychotics (n=21), antidepressants (n=20) and anti-parkinsonian drugs (n=16). The Table shows that not all anticholinergics commonly cause constipation, and this may be specific for the antimuscarinics. Each medicine included in the list was searched for in Wave 3 dataset using all the ATC codes related to the medicine. For example, amitriptyline has two ATC codes; N06AA09 and N06CA01 (in combination with other agents), the two codes were searched for in the medicine dataset.

6.2.2.7. Other covariates

Demographic co-variates examined included level of ID, classified into mild, moderate and severe/profound; place of residence, classed as those who live

independently or with family, those who live in a community group home and those who resided in residential settings (where ten or more people living together on campus-based accommodation). Level of ID of participants was verified from case notes at Wave 1 of the IDS-TILDA study.

Behaviours which challenge are defined as a behaviour that a) is a barrier to a person participating in and contributing to their community, b) undermines directly or indirectly a person's rights, dignity or quality of life, and c) create a risk to the health and safety of a person and those with whom they live and work (352). Behaviours that challenge were assessed in Wave 3 using The Behaviour Problem Inventory-Short Form (BPI-S), an informant-based behaviour rating tool for ID with 30 items and three sub-scales: Self-injurious Behaviour (8 items: self-biting, head or body hitting, self-scratching, pica, inserting objects, hair pulling or teeth grindings), Stereotyped Behaviour (12 items: rocking, sniffing, waving arms, manipulating, hand/finger, yelling, pacing, rubbing self, gazing, bizarre body postures, clapping hands or grimacing) and Aggressive/Destructive Behaviour (10 items: hitting, kicking, pushing, biting, grabbing, scratching, pinching, verbal abusive, destroying or bullying) (353). The tool consists of two Likert-type rating scales per item; a 5-point frequency scale (never = 0, monthly = 1, weekly = 2, daily = 3, hourly = 4) to assess the frequency of the behaviours that challenge and a 4-point severity scale (no problem = 0, a slight problem = 1, a moderate problem = 2, a severe problem = 3) to assess the severity of these behaviours. Participants with any of these behaviour will be assigned as having challenging behaviour and the variable used in the analysis in this chapter was categorised in to two, 'yes' or 'no'.

Quality of life at Wave 3 was assessed using Personal Wellbeing Index – Intellectual Disability (PWI-ID) (354). The index is designed for people with intellectual disability to ask about how happy a person is with 8 life domains; standard of living, personal health, achievement in life, personal relationships, personal safety, community-connectedness, future security, and religion/spirituality. It incorporates a pre-testing protocol to determine whether, and to what level of complexity, respondents are able to use the scale. The comprehensive pre-testing protocol comprises initial screening of potential respondents for acquiescent responding, and a test for response scale competence. It

has simple and concretely worded questions with choice format demonstrated as different levels of outline faces (from very happy to sad) (355).

6.2.3. Comparison with other waves

A descriptive comparison with Wave 2 findings (Chapter 5) has been carried out in terms of laxative use, characteristics, dosage information and reported indications. Data on laxative use, reporting constipation (but not Rome III criteria and exposure to anticholinergics were also available from the first wave of IDS-TILDA so we included these to observe the difference in terms of demographics, laxative use, constipation and exposure to constipation risk factors. Variables related to exposure to any medicines that cause constipation (or commonly cause constipation) were created for Wave 2 and Wave 1 in the similar way described in section 6.2.2.6 of this chapter. Findings related to Wave 1 and Wave 2 were presented in this chapter together with Wave 3 results.

6.2.4. Trends and patterns of laxative use between Wave 2 to Wave 3

Detailed information on laxative use on Wave 2 and Wave 3 allow to follow the use of laxative at the two waves. The identification number for participants who used laxatives has been investigated at both waves using excel sheet to identify; a) those who reported laxative use at Wave 2 and Wave 3, b) those who reported laxative use in Wave 2 but not Wave 3 and c) those who reported the use of laxative at Wave 3 but were not using laxative at Wave 2. After identifying the three groups, a variable for each group has been created in Wave 2 and Wave 3 dataset. This was to further investigate the demographics of each group and to explore the details of laxative use at both waves.

6.2.5. Statistical analysis

Descriptive statistics and bivariate analyses where used in the three waves with a statistically significant p-value of <0.05 when using the chi-squared test. The normality of the distribution of the PWI-ID scores was assessed using two tests; the Kolmogorov-Smirnov and Shapiro-Wilk tests and a nonparametric independent sample Mann-Whitney U test was carried out to compare the difference in the median of PWI scores between constipated and non-constipated participants.

6.3. Results

6.3.1. Demographics of the cohort among the three waves IDS-TILDA 2009-2017

The demographics, laxative use and constipation of the three waves have been presented in *Table 6-1.* As shown in the Table, the proportion of female/male over the three waves was similar with slightly more females in Wave 3 (57%, n=313). As people with ID grow older, fewer people were under the group aged 40-49 years and large proportions of participants aged 50-65 years with percentage ranged from 45.7% to 63%. There was a slight increase in proportion of those aged 65+ from 18.2% in Wave 1 to a quarter in Wave 3 (25.3%). The level of ID was consistent over the three waves with larger proportions classified as having moderate level of ID (46.3-45.6%) and 27.6% to 30.4% with severe-profound level of ID. The percentages of participants in terms of place of residence were also consistent over the three waves with 36 % to 40.6% living in community group homes and 40.8% to 47.4% living in residential care.

6.3.2. Laxative use over the three waves IDS-TILDA

From the first wave IDS-TILDA, there were an increase in proportion of laxative users from 37.5% to 44.4% in Wave 3 *(Table 6-1).* Reporting a doctors' diagnosis of constipation increased from 17.4% in the first wave to 44.6 % in Wave 3. Rome III was available for Wave 2 and Wave 3 and its percentage increased from 38.9% in Wave 2 to 44.4% in Wave 3.

Table 6-1 Demographics of the IDS-TILDA cohort in Wave 1 (n=736) Wave 2 (n=677) and Wave 3 (n=549)

Characteristic	Wave 1 n (%)	Wave 2 n (%)	Wave 3 n (%)
Gender			
Male	330 (44.8)	296 (43.7)	236 (43)
Female	406 (55.2)	381(56.3)	313 (57)
Age, years			
40-49	266 (36)	189 (28)	64 (11.7)
50-64	336 (45.7)	346 (51)	346 (63)
65+	134 (18.2)	142 (21)	139 (25.3)
Level of ID	(Missing=54)	(Missing=53)	(Missing=42)

Mild	163 (23.9)	150 (24)	122 (24)
Moderate	316 (46.3)	287 (46)	231 (45.6)
Severe/ Profound	203 (29.7)	187 (27.6)	154 (30.4)
Type of residence		(Missing=1)	
Independent/Family	122 (16.6)	102 (15.2)	78 (14.2)
Community group home	265 (36)	298 (44)	223 (40.6)
Residential care	349 (47.4)	276 (40.8)	248 (45.2)
		(Missing=8)	
Chronic constipation	128 (17.4)	257 (38.4)	245 (44.6)
		(Missing=45)	(Missing=50)
Rome III criteria	Not available	246 (38.9)	217 (43.5)
Laxative use	276 (37.5)	281 (41.5)	244 (44.4)

6.3.3. Cohort composition of laxative use and constipation indicators at Wave 3 IDS-TILDA

Figure 6-2 illustrated the overlap of laxative use with constipation and Rome III criteria at Wave 3. There were 130 participants who reported constipation, meet Rome III criteria and reported the use of laxatives. There were also some laxatives users without reporting any of these two constipation indicators (n=36) and when compared to Wave 2 results in Chapter 5, this number was slightly decreased since Wave 2 (n=45). There were 24 participants who reported both indicators but did not report use of laxatives and those who reported any of the indicators for chronic constipation without reporting the use of laxatives were 44 participants for each indicator respectively.

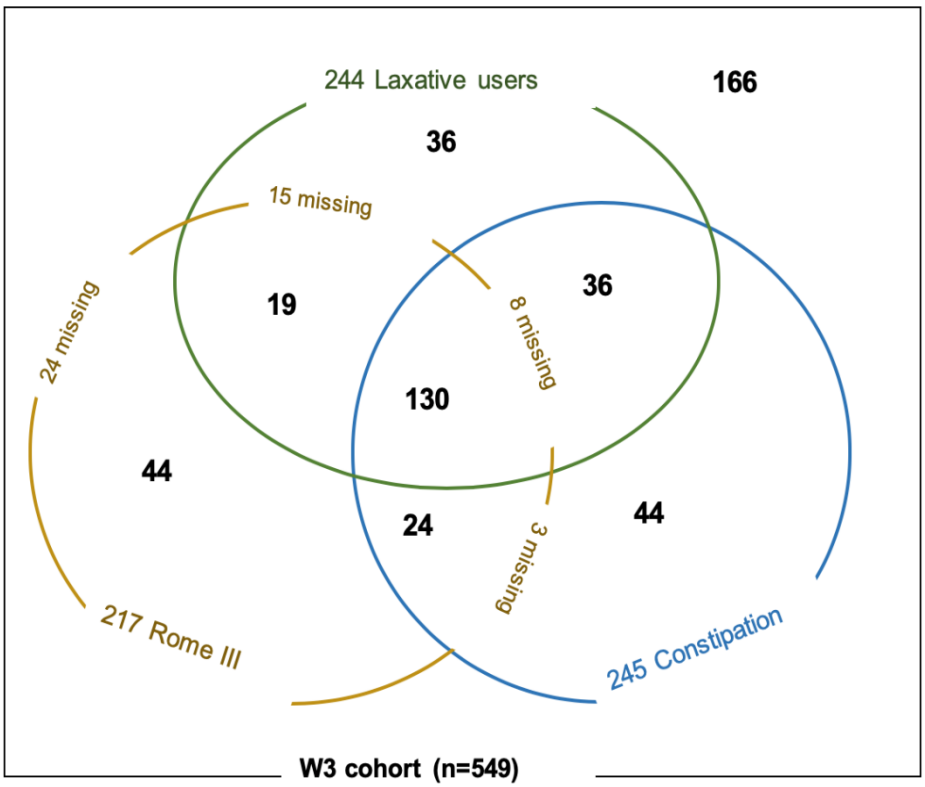

Figure 6-2 Total compositions of Wave 3 cohort in terms of laxative use and two constipation indicators expressed by number of participants

6.3.4. Demographics and clinical characteristics of laxative users in 3 waves of IDS-TILDA

The use of laxatives over the three waves and the difference in demographic and clinical characteristics are presented together in *Table 6-2* with results in bold font indicating a statistically significant difference ($p<0.05$) from the laxative non-users in the relevant wave using a bivariate analysis. Female were using laxatives more than males but the difference was not statistically significant except in the first wave, were 61.2% of female used laxatives compared to 38.8% of males.

A higher proportion of laxative users were aged between 50-64 years over the three waves (43.5%-59%) and 25.7%-31% of laxative users were aged 65+ years. The difference in age among laxative users were statistically significant over the three waves.

Over the three waves, most laxative users had either a moderate (39% - 43.3%) or severe/profound level of ID (43.3% - 47%). There was a slight increase in the proportion of laxative users with mild level of ID from 11.5% in Wave 1 to 15.2% in Wave 3.

Among those who used laxatives, the proportion of those in residential care was significantly higher than those who lived independently or in community group homes with the percentage slightly decreased since the first wave (Wave 1: n=189, 68.5%) (Wave 2: n=166, 59%) (Wave 3: n=151, 62%). There were more laxative users who live independently or with family in the first wave (n=11, 4%) and the percentage decreased to a half or below in the subsequent waves (n=5; 1.7-2%). Most laxative users lived in residential care although as a proportion this group decreased in size. In contrast, the proportion of users living in community group homes increased from 27.5% to 36% from the first to third wave.

Among laxative users (*Table 6-2*), there was an increase in reporting a doctor's diagnosis of constipation in Wave 2 and Wave 3 (71.3%-74.3%) as compared to Wave 1 (41%). Those who used laxatives and meet Rome III criteria increased by 6% in Wave 3 (67.4%) since Wave 2 (61.4%). Among laxative users the percentage of those reported a doctor's diagnosis of constipation is higher than those who met Rome III criteria.

Laxative users over the three waves were more likely to exposed to anticholinergics (81.6%-85%). There were large proportions of laxative users exposed to medicines that contributed to constipation (94.7%-95.9%) and the majority to these medicines are classified as commonly causing constipation (93.5%-95.5% of laxative users, of them 19% on 5+ medicines). Laxative users were also more likely to experience at least one condition that contribute to constipation with the majority attributed to mental (59-65%) and neurological conditions (50-55.7%) which was significantly more than laxative non-users.

The bivariate analysis of laxative users vs non-users *(Table 6-2)* has been compared to results of bivariate analysis between constipated vs. non-constipated participants which are presented for all the three waves in one Table *(Table 6-3).* There was a similar pattern of differences between laxative users vs. non-users and constipated vs. non-constipated participants in terms of the four demographics except for gender in Wave 3, where there were more females reporting constipation than males (63% vs. 37%, $p<0.05$) and this did not differ in terms of laxative use (59.8% vs 40.2%, $p>0.05$). Furthermore, the difference was similar in terms of exposure to anticholinergics, medicines or conditions that contributed to constipation.

For all the three waves, details of each p-value and difference between laxative users vs non-users or constipated vs non-constipated participants considering medicine classes in specific are presented in *Tables 6-4 to Table 6-9*. Over the three waves, participants with constipation more frequently reported use of iron supplements, calcium supplements, PPIs, antipsychotics, anticonvulsants, and antiparkinsonian drugs. While laxative users over the three waves were more likely to use – in addition to the above classes- opioids (except in Wave 2), anti-propulsive agents and NSAIDs (except in Wave 3).

Table 6-2 Differences in demographics and clinical characteristics of laxative users in Wave 1, Wave 2 and Wave 3 IDS- TILDA

Category	Laxative users in Wave 1 **(**n=276, 37.5%) n (%)	Laxative users in Wave 2 (n= 281, 41.5%) n (%)	Laxative users in Wave 3 (n= 244, 44.4%) n (%)
Gender			
Male	**107 (38.8)**	117(41.6)	98(40.2)
Female	**169 (61.2)**	164 (58.3)	146 (59.8)
Age, years			
40-49	**85 (30.8)**	**78 (27.7)**	**24 (9.8)**
50-64	**120 (43.5)**	**130 (46.2)**	**144 (59.0)**
65+	**71 (25.7)**	**73 (26.0)**	**76 (31.0)**
Level of ID	(Missing= 16)	**(**Missing=14**)**	**(**Missing=13)
Mild	**30 (11.5)**	**35 (13.0)**	**35 (15.2)**
Moderate	**108 (41.5)**	**116 (43.3)**	**90 (39.0)**
Severe-profound	**122 (46.9)**	**116 (43.3)**	**106 (46.0)**
Place of residence			
Independent /with family	**11 (4.0)**	**5 (1.7)**	**5 (2.0)**
Community group homes	**76 (27.5)**	**110 (39)**	**88 (36)**
Residential care	**189 (68.5)**	**166 (59)**	**151 (62)**

Category	Laxative users in Wave 1 **(**n=276, 37.5%) n (%)	Laxative users in Wave 2 (n= 281, 41.5%) n (%)	Laxative users in Wave 3 (n= 244, 44.4%) n (%)
Chronic Constipation			
Yes	**113 (41.0)**	**209 (74.3)**	**174 (71.3)**
No	**163 (59.0)**	**72 (25.6)**	**70 (28.7)**
Rome III criteria	Not available	(Missing=22)	(Missing=23)
Yes		**159 (61.4)**	**149(67.4)**
No		**100 (38.6)**	**72 (32.6)**
Number of medicines			
0-4	**41 (15.0)**	**35 (12.5)**	**32 (13.0)**
Polypharmacy (5-9)	**118 (42.8)**	**127 (45.2)**	**100 (41.0)**
Excessive polypharmacy (10+)	**117 (42.4)**	**119 (42.3)**	**112 (46.0)**
ACB score			
Zero	**41 (15.0)**	**47 (16.7)**	**45 (18.4)**
>zero	**235 (85.0)**	**234 (83.3)**	**199 (81.6)**
On medicines that cause constipation			
Total	**264 (95.7)**	**266 (94.7)**	**234 (95.9)**
Categorised			
1-4	**180 (68.2)**	**169 (63.5)**	**143 (61)**
5+	**84 (31.8)**	**97 (36.5)**	**91 (39)**
On medicines that commonly cause constipation			
Total	**258 (93.5)**	**263 (93.6)**	**233 (95.5)**
Categorised			
1-4	**209 (81)**	**213 (81)**	**189 (81)**

Category	Laxative users in Wave 1 **(**n=276, 37.5%) n (%)	Laxative users in Wave 2 (n= 281, 41.5%) n (%)	Laxative users in Wave 3 (n= 244, 44.4%) n (%)
5+	**49 (19)**	**50 (19)**	**44 (19)**
At least one conditions that contributed to constipation	(Missing=28) 247 (99.6)	(Missing=7) **250 (91.2)**	**232 (95)**
Type of food			
Soft liquidised /thickened fluid	**49 (17.8)**	**70 (24.9)**	**76 (31.1)**

Bold numbers are associated with p value <0.05 as compared to laxative non-users in for the relevant wave of IDS-TILDA. ACB: Anticholinergic Cognitive Burden.

Table 6-3 Demographics of constipated participants in Wave 1, Wave 2 and Wave 3

Category	Participants with chronic constipation in Wave 1 (n= 128, 17.4%) n (%)	Participants with chronic constipation in Wave 2 (n= 257, 38.4%) n (%)	Participants with chronic constipation in Wave 3 (n=245, 44.6%) n (%)
Gender			
Male	59 (46)	108(42)	**91(37)**
Female	69 (53.9)	149 (58)	**154 (63)**
Age, years			
40-49	**36 (28)**	**75 (29.2)**	29 (11.8)
50-64	**60 (47)**	**115 (44.7)**	145 (59.2)
65+	**32 (25)**	**67 (26)**	71 (29)
Level of ID	**(**Missing=6)		(Missing=14)
Mild	**14 (11.5)**	**32 (13.3)**	**36(15.6)**
Moderate	**44 (36)**	**102 (42.3)**	**104 (45)**
Severe-profound	**64 (52.5)**	**107 (44.4)**	**91 (39.4)**
Place of residence			
Independent /with family	**6 (4.7)**	**13 (5)**	**11 (4.5)**
Community group homes	**36 (28)**	**112 (43.8)**	**97 (39.6)**
Residential care	**86 (67.2)**	**131 (51.2)**	**137 (56)**
ACB scores			

Category	Participants with chronic constipation in Wave 1 (n= 128, 17.4%) n (%)	Participants with chronic constipation in Wave 2 (n= 257, 38.4%) n (%)	Participants with chronic constipation in Wave 3 (n=245, 44.6%) n (%)
Zero	**16 (12.5)**	**48 (18.7)**	**51 (20.8)**
>zero	**112 (87.5)**	**209 (81.3)**	**194 (79.2)**
On medicines that cause constipation*:*			
Total	**127 (99.2)**	**244 (95)**	**234 (95.5)**
Categorised			
1-4	**86 (67.7)**	**161 (66)**	157 (67)
5+	**41 (32.3)**	**83 (34)**	77 (33)
On medicines that commonly cause constipation:			
Total	**126 (98.4)**	**240 (93.4)**	**233 (95)**
Categorised			
1-4	**101 (80.2)**	**194 (80.8)**	195(83.7)
5+	**25 (19.8)**	**46 (19.2)**	38 (16.3)
At least one conditions contributed to constipation	(Missing=7) 119 (99.2)	(Missing=6) **226 (90)**	227 (92.7)
Type of food			
Soft liquidised /thickened fluid	**29 (22.7)**	**56 (21.8)**	**76 (31)**

Bold numbers are associated with p value <0.05 as compared to laxative non-users in for the relevant wave of IDS-TILDA. ACB: Anticholinergic Cognitive Burden.

Table 6-4 Differences between laxative users versus non-users in Wave 1 (n= 735) considering different drug classes that contribute to constipation

Category	Laxative users (n=276) n (%)	Laxative non-users (n=459) n (%)	p-value
Medicines that contributed to constipation			
Total (n=615)	264 (95.7)	351 (76.5)	<0.001
Categorised			
1-4 (n=467)	180 (68.2)	287 (81.8)	<0.001
5+ (n=148)	84 (31.8)	64 (18.2)	

Commonly causing constipation			
Total (n=594)	258 (93.5)	336 (73.2)	<0.001
Categorised			<0.001
1-4 (n=516)	209 (81)	307 (91.4)	
5+ (n=78)	49 (19)	29 (8.6)	
Drugs that contribute to constipation by class			
Anticonvulsants (n=161)	81 (29.3)	80 (17.4)	<0.001
Antipsychotics (n=325)	148 (53.6)	177 (38.6)	<0.001
Antiparkinsonians (n=126)	66 (24)	60 (13)	<0.001
Iron supplements (n=73)	41(15)	32 (7)	0.001
Calcium supplements (n=133)	73 (26.4)	60 (13)	<0.001
PPIs (n=163)	104 (37.7)	59 (13)	<0.001
NSAIDs (n=72)	41 (15)	31(6.8)	<0.001
Other anticholinergics (n=156)	87 (31.5)	69 (15)	<0.001
Opioids (n=11)	10 (3.6)	1 (0.2)	<0.001
Anti-propulsive agents (n=68)	45 (16.3)	23 (5)	<0.001
Antispasmodics (n=6)	3 (1.1)	3 (0.7)	0.52
Antacid (n=10)	6 (2.2)	4 (0.9)	0.14
Urological anticholinergics (n=23)	11 (4)	12 (2.6)	0.30
Diuretics (n=54)	26 (9.4)	28 (6)	0.09
Antidepressants (n=193)	81 (29.3)	112 (24.4)	0.14
Antihistamine (n=30)	15 (5.4)	15 (3.3)	0.15
Antihypertensives* (n=65)	21 (7.6)	44 (9.6)	0.36
Antilipidemic (n=188)	66 (24)	122 (26.6)	0.422

* Including B-blockers and Calcium Channel Blockers.

Table 6-5 Differences between laxative users versus non-users in Wave 2 (n= 677) considering different drug classes that contribute to constipation

Category	Laxative users (n=281) n (%)	Laxative non-users (n=396) n (%)	p-value
Medicines that contributed to constipations			
Total (n=595)	266 (94.7)	329 (83)	<0.001
Categorised			
1-4 (n=433)	169 (63.5)	264 (80.2)	<0.001
5+ (n=162)	97 (36.5)	65 (19.8)	
Commonly causing constipation			
Total (n=581)	263 (93.6)	318 (80.3)	<0.001
Categorised			
1-4 (n=497)	213 (81)	284 (89.3)	0.005
5+ (n=84)	50 (19)	34 (10.7)	
Drugs that contribute to constipation by class			
Anticonvulsants (n=157)	86 (30.6)	71 (18)	<0.001
Antipsychotics (n=311)	152 (54)	159 (40.2)	<0.001
Antiparkinsonians (n=104)	61 (21.7)	43 (11)	<0.001
Iron supplements (n=82)	50 (17.8)	32 (8)	<0.001
Calcium supplements (n=162)	92 (32.7)	70(17.7)	<0.001
PPIs (n=189)	114 (40.6)	75 (19)	<0.001
NSAIDs (n=57)	34 (12)	23 (5.8)	0.004
Other anticholinergics (n=154)	99 (35.2)	55 (14)	<0.001
Opioids (n=14)	8 (2.8)	6 (1.5)	0.23
Anti-propulsive agents (n=53)	29 (10.3)	24 (6.1)	0.04
Antispasmodics (n=9)	8 (2.8)	1(0.3)	0.004
Antacid (n=3)	2 (0.7)	1 (0.3)	-
Urological anticholinergics (n=25)	9 (3.2)	16 (4)	0.56
Diuretics (n=52)	26 (9.3)	26 (6.6)	0.19
Antidepressants (n=194)	87 (31)	107 (27)	0.26

Category	Laxative users (n=281) n (%)	Laxative non-users (n=396) n (%)	p-value
Antihistamine (n=30)	17 (6)	13 (3.3)	0.08
Antihypertensives* (n=68)	22 (7.8)	46 (11.6)	0.10
Antilipidemic (n=208)	77 (27.4)	131 (33)	0.11

* Including B-blockers and Calcium Channel Blockers.

Table 6-6 Differences between laxative users versus non-users in Wave 3 (n= 549) considering different drug classes that contribute to constipation

Category	Laxative users (n=244) n (%)	Laxative non-users (n=305) n (%)	p-value
Medicines that contributed to constipation			
Total (n=487)	234(95.9)	253 (83)	<0.001
Categorised			
1-4 (n=346)	143 (61)	203(80.2)	<0.001
5+ (n=141)	91 (39)	50 (19.8)	
Commonly causing constipation			
Total (n=480)	233 (95.5)	247 (81)	<0.001
Categorised			
1-4 (n=413)	189 (81)	224 (90.7)	0.002
5+ (n=67)	44 (19)	23 (9.3)	
Drugs that contribute to constipation by class			
Anticonvulsants (n=125)	76 (31)	49 (16)	<0.001
Antipsychotics (n=247)	134 (55)	113 (37)	<0.001
Antiparkinsonians (n=75)	45 (18.4)	30 (9.8)	0.004
Iron supplements (n=63)	37 (15.2)	26 (8.5)	0.01
Calcium supplements (n=182)	100 (41)	82 (27)	<0.001
PPIs (n=193)	118 (48.4)	75 (24.6)	<0.001
NSAIDs (n=35)	19 (7.8)	16 (5.2)	0.22

Category	Laxative users (n=244) n (%)	Laxative non-users (n=305) n (%)	p-value
Other anticholinergics (n=111)	75 (30.7)	36 (11.8)	<0.001
Opioids (n=18)	13 (5.3)	5 (1.6)	0.01
Anti-propulsive agents (n=26)	17 (7)	9(3)	0.02
Antispasmodics (n=4)	3(1.2)	1(0.3)	-
Antacid (n=6)	5 (2)	1 (0.3)	-
Urological anticholinergics (n=29)	17 (7)	12 (4)	0.11
Diuretics (n=37)	19 (7.8)	18 (6)	0.38
Antidepressants (n=184)	87 (35.7)	97 (31.8)	0.34
Antihistamine (n=18)	12 (5)	6 (2)	0.05
Antihypertensives* (n=59)	23 (9.4)	36 (11.8)	0.37
Antilipidemic (n=180)	88 (36)	92 (30.2)	0.14

* Including B-blockers and Calcium Channel Blockers.

Table 6-7 Differences between participants with constipation versus no constipation in Wave 1 (n= 735) considering different drug classes that contribute to constipation

Category	Participants with chronic constipation (n=128) n (%)	Participants with no chronic constipation (n=607) n (%)	p-value
Medicines that contributed to constipation			
Total (n=615)	127 (99.2)	488 (80.4)	<0.001
Categorised			
1-4 (n=467)	86 (67.7)	381 (78)	0.015
5+ (n=148)	41 (32.3)	107 (22)	
Commonly causing constipation			
Total (n=594)	126 (98.4)	468 (77)	<0.001
Categorised			0.012
1-4 (n=516)	101 (80.2)	415 (88.7)	

Category	Participants with chronic constipation (n=128) n (%)	Participants with no chronic constipation (n=607) n (%)	p-value
5+ (n=78)	25 (19.8)	53 (11.3)	
Drugs that contribute to constipation by class			
Anticonvulsants (n=161)	38 (29.7)	123 (20.3)	0.01
Antipsychotics (n=325)	78 (61)	247 (40.7)	<0.001
Antiparkinsonians (n=126)	36 (28)	90 (14.8)	<0.001
Iron supplements (n=73)	25 (19.5)	48 (7.9)	<0.001
Calcium supplements (n=133)	33 (25.8)	100 (16.5)	0.013
PPIs (n=163)	56 (43.8)	107 (17.6)	<0.001
NSAIDs (n=72)	15 (11.7)	57 (9.4)	0.42
Other anticholinergics (n=156)	44 (34.4)	112 (18.5)	<0.001
Opioids (n=11)	2 (1.6)	9 (1.5)	0.94
Anti-propulsive agents (n=68)	10 (7.8)	58 (9.6)	0.53
Antispasmodics (n=6)	2 (1.6)	4 (0.7)	0.30
Antacid (n=10)	2 (1.6)	8 (1.3)	0.82
Urological anticholinergics (n=23)	4 (3.1)	19 (3.1)	0.99
Diuretics (n=54)	13 (10.2)	41 (6.8)	0.18
Antidepressants (n=193)	33 (25.8)	160 (26.4)	0.89
Antihistamine (n=30)	7 (5.5)	23 (3.8)	0.38
Antihypertensives *(n=65)	12 (9.4)	53 (8.7)	0.81
Antilipidemic (n=188)	33 (25.8)	155 (25.5)	0.95

* Including B-blockers and Calcium Channel Blockers.

Table 6-8 Differences between participants with constipation versus no constipation in Wave 2 (n= 677) considering different drug classes that contribute to constipation

Category	Participants with chronic constipation (n =257, 38.4%) n (%)	Participants with no chronic constipation (n =412, 61.6%) n (%)	p-value
Medicines that contributed to constipation			
Total (n=588)	(Missing=7) 244 (95)	(Missing=1) 344 (83.5)	<0.001
Categorised			
1-4 (n=426)	161 (66)	265 (77)	0.003
5+ (n=162)	83 (34)	79 (23)	
Commonly causing constipation			
Total (n=574)	240 (93.4)	334 (81)	<0.001
Categorised			0.009
1-4 (n=490)	194 (80.8)	296 (88.6)	
5+ (n=84)	46 (19.2)	38 (11.4)	
Drugs that contribute to constipation by class			
Anticonvulsants (n=156)	74 (28.8)	82 (20)	0.008
Antipsychotics (n=306)	130 (50.6)	176 (42.7)	0.04
Antiparkinsonians (n=102)	52 (20.2)	50 (12)	0.005
Iron supplements (n=82)	49 (19)	33 (8)	<0.001
Calcium supplements (n=160)	77 (30)	83 (20)	0.004
PPIs (n=189)	105 (41)	84 (20.4)	<0.001
NSAIDs (n=57)	28 (11)	29 (7)	0.08
Other anticholinergics (n=154)	81 (31.5)	73 (17.7)	<0.001
Opioids (n=14)	8 (3)	6 (1.5)	0.14
Anti-propulsive agents (n=53)	23 (8.9)	30 (7.3)	0.43
Antispasmodics (n=9)	7 (2.7)	2 (0.5)	0.01
Antacid (n=3)	2 (0.8)	1 (0.2)	0.31

Category	Participants with chronic constipation (n =257, 38.4%) n (%)	Participants with no chronic constipation (n =412, 61.6%) n (%)	p-value
Urological anticholinergics (n=25)	7 (2.7)	18 (4.4)	0.27
Diuretics (n=51)	23 (8.9)	28 (6.8)	0.30
Antidepressants (n=192)	73 (28.4)	119 (29)	0.89
Antihistamine (n=29)	9 (3.5)	20 (5)	0.40
Antihypertensives* (n=67)	26 (10)	41 (10)	0.94
Antilipidemic (n=205)	77 (30)	128 (31)	0.76

* Including B-blockers and Calcium Channel Blockers.

Table 6-9 Differences between participants with constipation versus no constipation in Wave 3 (n= 549) considering different drug classes that contribute to constipation

Category	Participants with chronic constipation (n =245) n (%)	Participants with no chronic constipation (n=304) n (%)	p-value
Medicines that contributed to constipation			
Total (n=487)	234 (95.5)	253 (83.2)	<0.001
Categorised			
1-4 (n=346)	157 (67)	189 (74.7)	
5+ (n=141)	77 (33)	64 (25.3)	0.06
Commonly causing constipation			
Total (n=480)	233 (95)	247 (81.3)	<0.001
Categorised			
1-4 (n=413)	195(83.7)	218 (88.3)	0.14
5+ (n=67)	38 (16.3)	29 (11.7)	
Drugs that contribute to constipation by class			
Anticonvulsants (n=125)	71 (29)	54 (17.8)	0.002
Antipsychotics (n=247)	125 (51)	122 (40)	0.01

Antiparkinsonians (n=75)	41 (16.7)	34 (11.2)	0.06
Iron supplements (n=63)	42 (17)	21 (7)	<0.001
Calcium supplements (n=182)	92 (37.6)	90 (29.6)	0.049
PPIs (n=193)	112 (45.7)	81 (26.6)	<0.001
NSAIDs (n=35)	12 (5)	23 (7.6)	0.20
Other anticholinergics (n=111)	67(27.3)	44 (14.5)	<0.001
Opioids (n=18)	9 (3.7)	9 (3)	0.64
Anti-propulsive agents (n=26)	14 (5.7)	12 (4)	0.33
Antispasmodics (n=4)	4 (1.6)	0 (0.0)	0.02
Antacid (n=6)	2 (0.8)	4 (1.3)	0.57
Urological anticholinergics (n=29)	15 (6)	14 (4.6)	0.43
Diuretics (n=37)	18 (7.3)	19 (6.3)	0.61
Antidepressants (n=184)	88 (36)	96 (31.6)	0.28
Antihistamine (n=18)	12 (5)	6 (2)	0.05
Antihypertensives* (n=59)	29 (11.8)	30 (10)	0.45
Antilipidaemic (n=180)	87 (35.5)	93 (30.6)	0.22

* Including B-blockers and Calcium Channel Blockers.

6.3.5. Laxative dosage and combination in Wave 3 IDS-TILDA and comparison with Wave 2

Similarly to Wave 2, more than two-thirds (n=162, 68.6%) of laxative users in Wave 3 were using laxatives on a regular basis *(Table 6-10),* with the majority remained using the osmotic laxatives (with or without other classes) (n=141, 87%) and doses were classified as standard. There were lower proportions (n=87, 35%) of participants in Wave 3 using 2+ laxatives as compared to the use in Wave 2 (n=113, 40%). In Wave 3, there were an increase of those who used 4 laxatives (n=8, 3.3%) into the double when compared to Wave 2 (n=4, 1.4%). The percentage of those who used intraclass combination has been decreased to 20% (n=49) in Wave 3 as compared to Wave 2 (n=68, 24%).

Table 6-10 Dosage information of laxatives in both waves Wave 2 and Wave 3

Laxative type [a]	Participants using laxatives in Wave 2 (n=281) n (%)	Participants using laxatives in Wave 3 (n=244) n (%)
Laxatives used regularly or on demand	41(14.7)	34 (14.4)
Laxatives used on demand	62 (22.2)	40 (17)
Laxative used regularly [b]	176 (63)	162 (68.6)
Osmotic laxatives	147(83.5)	141 (87)
Stimulants laxatives	33 (19)	28 (17.3)
Bulk forming laxatives	31(18)	24 (14.8)
Stool softener	6 (3.4)	≤1 (0.6)
Laxatives used in standard doses	152 (86.3)	143 (94)
Laxatives used in high	6 (3.4)	5 (3.3)
Laxatives used in standard and high doses	9 (5)	4 (2.6)
Number of used laxatives		
One laxative	168 (60)	157 (64.3)
Two laxatives	80 (28.5)	61 (25)
Three laxatives	29 (10.3)	18 (7.4)
Four laxatives	4 (1.4)	8 (3.3)
Intraclass laxative combination	68 (24)	49 (20)

[a] Missing regimen information (Wave 2=2), (Wave 3= 8), [b] Missing dose information (Wave 2=9), (Wave 3= 10).

6.3.6. Laxative use from Wave 2 to Wave 3

As shown in *Table 6-11*, participants who used laxatives in Wave 2 were followed in Wave 3 and this identified 63.3% (n=178) of laxative users in Wave 2 reported the use of laxatives in Wave 3. Investigating laxative use was not possible for 22% (n=62) of Wave 2 laxative users because of passing away, withdrawn after Wave 2, missing PIQs or medicine data. There were 14.6% of Wave 2 laxative users did not reported the use of laxatives in Wave 3 (stopped laxatives at Wave 3). Furthermore, new laxative users were identified in Wave 3 but not in Wave 2 (61 participants, 25% of Wave 3 laxative users). There were 5 laxative users in Wave 3 who were not in the total 677 participants of Wave 2.

Table 6-11 Use of laxatives from Wave 2 to Wave 3

	Wave 2 laxative users (n=281)	**Wave 3** laxative users (n=244)	N	Comments
laxative use	Yes	Yes	178	• Still continue on laxatives (Refer to *Table 6-12)*
	Yes	No	103	• 41 have passed away after Wave 2 • 7 withdrawn from participation in Wave 3 • 1 has missing PIQ file • 13 have missing medicine information in Wave 3 • 41 didn't report laxative use in Wave 3 (Refer to *Table 6-14*)
	No	Yes	66	• 61 reported laxative use in Wave 3 (Refer to *Table 6-13*) • 5 new participants in Wave 3 who were not in the 677 Wave 2 cohort

6.3.7. Characteristics of participants who continued using laxatives at Wave 2 and Wave 3 IDS-TILDA (n=178)

The demographics of those who used laxatives at both waves (Wave 2 and 3) (n=178) were investigated and presented in *Table 6-12*. There were more females (60.7%, n=108) in this cohort than males. About 64% (n=114) were aged in Wave 3 between 50-64 years and 22% aged 65+ years and 60% of this cohort living in residential care at Wave 2 and this increased to almost two third (65.2%) in Wave 3. Over one third (n=62, 36.5%) had moderate level of ID and over the half (n=88, 51.8%) with severe-profound level of ID. There were 79.2% (n=141) of this cohort who reported constipation in Wave 2 and the percentage decreased by 5.6% in Wave 3 (n=131, 73.6%). Constant proportion (n= 112, 67.5%) of this cohort who still meet Rome III criteria at both waves. In addition, 81% (n=144) of this cohort were exposed to anticholinergics constantly at both waves. A large proportion of this cohort were exposed to commonly constipating

medicines (Wave 2; 93.8 % and Wave 3; 95.5%) and/or experienced conditions that cause constipation (90.2%-95.5%). Laxatives among this cohort were used on a regular basis by almost the two third (65.5%) and this was increased to 71% in Wave 3. There were 14%-15.3% using combined regimen (regular and as needed laxatives) and 41-41.6% on two or more laxatives. Intraclass laxative combinations reported by 24.2% in Wave 2 and the percentage decreased slightly in Wave 3 to 23%.

Table 6-12 Characteristics and dosage information among participants who used laxatives in Wave 2 and 3 (long term laxative users n=178)

Category	Wave 2 n (%)	Wave 3 n (%)
Gender		
Male	70 (39.3)	
Female	108 (60.7)	
Age, years		
40-49	54 (30.3)	25 (14)
50-64	88 (49.4)	114 (64)
65+	36 (20.2)	39 (21.9)
Level of ID	(Missing =8)	
Mild	20 (11.8)	
Moderate	62 (36.5)	
Severe-profound	88 (51.8)	
Place of residence		
Independent /with family	5 (2.8)	2 (1.1)
Community group homes	68 (38.2)	60 (33.7)
Residential care	105 (59)	116 (65.2)
Reported constipation		
Yes	141 (79.2)	131 (73.6)
No	37 (20.8)	47 (26.4)
Rome III criteria	(Missing= 12)	(Missing= 12)
Yes	112 (67.5)	112 (67.5)
No	54 (32.5)	54 (32.5)
Number of medicines		
0-4	24 (13.5)	28 (15.7)
Polypharmacy (5-9)	83 (46.6)	68 (38.2)
Excessive polypharmacy (10+)	71 (39.9)	82 (46.1)
ACB score		
Zero	34 (19)	34 (19)
>zero	144 (81)	144 (81)

Category	Wave 2 n (%)	Wave 3 n (%)
On medicines that cause constipation:		
Total	168 (94.4)	170 (95.5)
Categorised		
1-4	106 (63)	104 (61.2)
5+	62 (37)	66 (38.8)
On medicines that commonly cause constipation:		
Total	167 (93.8)	170 (95.5)
Categorised		
1-4	131 (78.4)	137 (80.6)
5+	36 (21.6)	33 (19.4)
At least one conditions that contributed to constipation	(Missing=4) 157 (90.2)	170 (95.5)
Mental health conditions	(Missing =6) 113(65.7)	112 (63)
Neurological health conditions	(Missing =2) 93 (52.8)	108 (60.7)
Type of food		
Soft liquidised/thickened fluid	43 (24.2)	58 (32.6)
Type of laxatives		
Osmotic	157 (88.2)	161 (90.4)
Stimulants	40 (22.5)	39 (22)
Bulk-forming	30 (17)	32 (18)
Stool softener	7 (4)	≤1 (0.6)
Laxative combination		
One laxative	104 (58.4)	105 (59)
Two plus laxatives	74 (41.6)	73 (41.0)
Intra class laxative combination	43 (24.2)	41 (23)
Dosage regimen	(Missing =1)	(Missing= 8)
Regular	116 (65.5)	121 (71)
Prn	34 (19.2)	25 (14.7)
Combination	27 (15.3)	24 (14)

ACB: Anticholinergic Cognitive Burden.

6.3.8. Characteristics of those who stopped/started laxatives between Wave 2 - Wave 3

Both those laxative users who started or stopped laxatives in Wave 3 has been investigated in terms of reporting constipation and other characteristics as shown in *Table 6-13* and *Table 6-14* respectively. Among those who started laxatives in Wave 3 (n=61, *Table 6-13*), 21.7% (n=13) reported a doctor's diagnosis of constipation in Wave 2 and the percentage increased to over two-thirds in Wave 3 (n=41, 67.2%). In addition, 31.6% (n=18) meet Rome III criteria in Wave 2 which was doubled in Wave 3 to 64.7% (n=33). While among those who stopped laxatives in Wave 3 (n=41) *(Table 6-14),* 63.4% (n=26) and 41.7 % (n=15) reported constipation and meet Rome III criteria in Wave 2, respectively, and decreased at Wave 3 to 46.3% (n=19) and 30.3% (n=10) for constipation and Rome III criteria, respectively. Of those who started laxatives in Wave 3, exposure to anticholinergics increased from 72% to 83.6% between Wave 2 to Wave 3. While among those who stopped laxatives in Wave 3, 95% were exposed to anticholinergics in Wave 2 and this deceased by 12% in Wave 3 (83%). Most of both groups were exposed to at least one medicine or one condition that contributed to constipation. Among those who started laxatives on Wave 3, there were 82% (n=50) used laxatives as monotherapy, and 18% as laxative combination, within which 45.5% (n=5) used an intraclass laxative combination.

Table 6-13 Wave 2 and Wave 3 clinical characteristics of new laxative users in Wave 3 (n=61)

Category	New laxative users in Wave 3 (n=61)	
	Characteristics in Wave 2 n (%)	Characteristics in Wave 3 n (%)
Gender		
Males	25 (41)	
females	36 (59)	
Age, years		
40-49	12 (19.7)	8 (13)
50-64	33 (54)	32 (52.5)
65+	16 (26.2)	21 (34.4)
Level of ID (Missing= 4)		
Mild	15 (26.3)	
Moderate	27 (47.4)	

Category	New laxative users in Wave 3 (n=61)	
	Characteristics in Wave 2 n (%)	Characteristics in Wave 3 n (%)
Severe-profound	15 (26.3)	
Place of residence		
Independent /with family	5 (8.2)	3 (5)
Community group homes	33 (54)	27 (44.3)
Residential care	23 (37.7)	31 (50.8)
Constipation	(Missing = 1)	
Yes	13 (21.7)	41 (67.2)
No	47 (78.3)	20 (32.8)
Rome III criteria	(Missing = 4)	(Missing =10)
Yes	18 (31.6)	33 (64.7)
No	39 (68.4)	18 (35.3)
ACB scores		
Zero	17(28)	10 (16.4)
≥zero	44 (72)	51 (83.6)
Laxative type		
Osmotic	-	56 (91.8)
Stimulants	-	8 (13)
Bulk-forming	-	6 (9.8)
Stool softener	-	0
One laxative	-	50 (82)
2+ laxatives	-	11 (18)
Intraclass laxative combination	-	5 (8.2)
Regimen		
Reg	-	39 (64)
Prn	-	14 (23)
Reg + prn	-	8 (13)
On medicines that cause constipation		
Total	57 (93.4)	59 (96.7)
Categorised		
1-4	45 (78.9)	35 (59.3)
5+	12 (21.1)	24 (40.7)
On medicines that commonly cause constipation		
Total	57 (93.4)	59 (96.7)
Categorised		
1-4	49 (86.0)	48 (81.4)
5+	8 (14.0)	11 (18.6)

Category	New laxative users in Wave 3 (n=61)	
	Characteristics in Wave 2 n (%)	Characteristics in Wave 3 n (%)
On at least one condition that contributed to constipation	(Missing=3) 52 (89.7)	58 (95)
Neurological diseases	(Missing =6) 21 (38.2)	26 (42.6)
Mental disorders	(Missing =2) 34 (57.6)	(Missing =1) 37 (61.7)
Soft/liquidised diet	8 (13)	16 (26.2)

ACB: Anticholinergic Cognitive Burden.

Table 6-14 Wave 2 and Wave 3 clinical characteristics of Wave 2 laxative users who stopped laxative use in Wave 3 (n= 41)

Category	Wave 2 laxative users who stop laxative in Wave 3 (n=41)	
	Characteristics in Wave 2 n (%)	Characteristics in Wave 3 n (%)
Gender		
Males		17 (41.5)
females		24 (58.5)
Age, years		
40-49	13 (31.7)	7 (17)
50-64	17 (41.5)	22 (53.7)
65+	11 (26.8)	12 (29.3)
Level of ID (Missing= 3)		
Mild		4 (10.5)
Moderate		26 (68.4)
Severe-profound		8 (21)
Place of residence		
Independent /with family	0	1(2.4)
Community group homes	14 (34)	12 (29.3)
Residential care	27 (66)	28 (68.3)
Constipation		
Yes	26 (63.4)	19 (46.3)
No	15 (36.6)	22 (53.7)
Rome III criteria	(Missing= 5)	(Missing= 8)
Yes	15 (41.7)	10 (30.3)
No	21(58.3)	23 (69.7)

Category	Wave 2 laxative users who stop laxative in Wave 3 (n=41)	
	Characteristics in Wave 2 n (%)	Characteristics in Wave 3 n (%)
ACB scores		
Zero	2 (5)	7 (17)
≥zero	39 (95)	34 (83)
Laxative type		-
Osmotic	36 (87.8)	-
Stimulants	4 (9.8)	-
Bulk-forming	5 (12.2)	-
Stool softener	1 (2.4)	-
One laxative	29 (70)	-
2+ laxatives	12 (29.3)	-
Intraclass laxative combination	7 (17)	-
Regimen		
Reg	18 (45)	-
Prn	19 (47.5)	-
Reg + prn	3 (7.5)	-
On medicines that cause constipation		
Total	40 (97.6)	37 (90.2)
Categorised		
1-4	26 (65)	24 (64.9)
5+	14 (35)	13 (35)
On medicines that commonly cause constipation		
Total	40 (97.6)	37 (90.2)
Categorised		
1-4	35 (87.5)	32 (86.5)
5+	5 (12.5)	5 (13.5)
At least one condition that contributed to constipation	(Missing=1) 36 (90) (Missing=2)	37 (90.2)
Neurological diseases	19 (48.7) (Missing=2)	18 (43.9)
Mental disorders	29 (74.4)	30 (73.2)

ACB: Anticholinergic Cognitive Burden.

6.3.9. People with Down syndrome and laxative use from Wave 1 to Wave 3

As may be seen in *Table 6-15*, the demographic characteristics, laxative use and relevant indication were investigated among participants with Down syndrome in Wave 1, Wave 2 and Wave 3 of IDS-TILDA and were compared to those without Down syndrome using a bivatriate analysis with the findings in bold representing a significant statistical difference ($p<0.05$) compared to those without Down syndrome for each wave. There were 19.9% (n=144) participants with Down syndrome in Wave 1 and this was slightly decreased in the subsequent waves (Wave 2: 19.2%, n=127) and (Wave 3: 17.3%, n=93).

There were no statistically signinficant differences in terms of gender between participants with or wihtout Down syndrome over the three waves. In Wave 1, there were over half of participants with Down syndrome at younger ages (40-49 years, 53.5%), however, this propotion decreased as people became older in the subsequent waves with higher proportions aged between 50-64 years. More than half were of a moderate level of ID over the three waves (53.4%-54.5%). The bivariate analysis showed that there were significantly more people with Down syndrom with a moderate to profound level of ID compared to those without Down syndrome in Wave 1 and 2 but the difference was not significant in Wave 3. There were 43.8 % to 51.2% of those with Down syndrom were living in community group homes and one-third or over (33%-37.6%) were living in residential care over the three waves.

Chronic constipation and Rome III criteria among people with Down syndrome were reported by 45.2% and 42.4%, respectively which did not differ compared to those without Down syndrome. However, the use of laxatives did differ with less laxative use among those with Down syndrome (27 % to 31.2%) over the three waves. Participants with Down syndrome exposed to medicines that cause (or commonly cause) constipation was at lower extent than those without Down syndrome ($p<0.05$), but no statistically significant difference between the two groups in term of experiencing at least one condition that cause constipation (85%-99%) was observed. The p values for the difference in demgraphics and clinical characteristics between Down syndrome and no Down syndrome for each wave were presented in *Appendices 6 to 8.*

Table 6-15 Demographics of participants with Down syndrome in Wave 1 Wave 2 and Wave3 IDS-TILDA

Characteristic	Wave 1 Participants with Down syndrome (n=144, 19.9%)[a] n (%)	Wave 2 Participants with Down syndrome (n=127, 19.2%)[b] n (%)	Wave 3 Participants with Down syndrome (n=93, 17.3%)[c] n (%)
Gender			
Male	65 (45)	57 (45)	44 (47.3)
Female	79 (55)	70 (55)	49 (52.7)
Age, year			
40-49	**77 (53.5)**	**58 (45.7)**	**21 (22.6)**
50-64	**64 (44.4)**	**65 (51.2)**	**69 (74.2)**
65+	**3 (2)**	**4 (3)**	**3 (3.2)**
Level of ID	(Missing =10)	(Missing =11)	(Missing =6)
Mild	**20 (14.9)**	**17 (14.7)**	16 (18.4)
Moderate	**73 (54.5)**	**62 (53.4)**	47 (54)
Severe/ Profound	**41 (30.6)**	**37 (32)**	24 (27.6)
Type of residence			
Independent/Family	**27 (18.8)**	20 (15.7)	17 (18.3)
Community group home	**63 (43.8)**	65 (51.2)	41 (44)
Residential care	**54 (37.5)**	42 (33)	35 (37.6)
Chronic constipation	**10 (7)**	40 (31.7)	42 (45.2)
Rome III criteria	-	43 (35.8)	36 (42.4)
Laxative use	**39 (27)**	**39 (30.7)**	**29 (31.2)**
On medicines that cause constipation	**90 (62.5)**	**96 (75.6)**	**71 (76.3)**
On medicines that <u>commonly</u> cause constipation	**85 (59)**	**92 (72.4)**	**69 (74.2)**
At least one condition contributed to constipation	102 (99)	(Missing=7) **84 (70)**	79 (85)
Neurological diseases	**42 (29.2)**	50 (43.5)	43 (46.2)
Mental disorders	**34 (24.6)**	**34 (27.6)**	**26 (28)**

[a] Wave 1 missing cases =12 , [b] Wave 2 missing cases=14 ,[c] Wave 3 missing cases =10. Bold font shows statistically significant at $p<0.05$.

A bivariate analysis was applied to investigate the difference between Down syndrome laxative users in Wave 1 (n=39) Wave 2 (n=39) and Wave 3 (n=29) and Down syndrome laxative non-users as shown in *Table 6-16* with the findings in bold font representing a significant statistical difference ($p<0.05$). The analysis showed that among those with Down syndrome who reported laxative use, there were a statistically significant higher proportion of those with severe/profound level of ID (43.2%-50%, the significant difference was only in Wave 1 and Wave 3). Furthermore, Down syndrome laxative users were more likely to live in residential care (51.4%-62%), to report a doctor's diagnosis of constipation (25% in Wave 1 to 79.3% in Wave 3), meet Rome III criteria (72%-73%) be exposed to anticholinergics or constipating medicines (especially in Wave 1), experience neurological conditions (43.6%-65.5%) and follow a diet of soft food/thickened fluid (25.5%-48.3%). The p values for the difference between Down syndrome laxative users and Down syndrome laxative non-users for each wave were presented in *Appendices 9 to 11.*

Table 6-16 Demographic and characteristics of Down syndrome laxative users in Wave 1-3 IDS-TILDA

Characteristic	Wave 1 Down syndrome laxative users (n= 39) n (%)	Wave 2 Down syndrome laxative users (n= 39) n (%)	Wave 3 Down syndrome laxative users (n= 29) n (%)
Gender			
Male	13 (33.3)	16 (41)	13 (44.8)
Female	26 (66.7)	23 (59)	16 (55.2)
Age, years			
40-49	**11 (28.2)**	14 (36)	6 (20.7)
50-64	**25 (64)**	25 (64)	21 (72.4)
65+	**3 (7.7)**	0 (0)	2 (7)
Level of ID	(Missing =3)	(Missing =2)	(Missing =2)
Mild	**2 (5.6)**	4 (10.8)	**3 (11)**
Moderate	**16 (44.4)**	17 (46)	**11 (40.7)**
Severe/ Profound	**18 (50)**	16 (43.2)	**13 (48)**
Type of residence			
Independent/Family	**1 (2.6)**	**0 (0)**	**0 (0)**
Community group home	**17 (43.6)**	**19 (48.7)**	**11 (38)**
Residential care	**21 (53.8)**	**20 (51.3)**	**18 (62)**

Characteristic	Wave 1 Down syndrome laxative users (n= 39) n (%)	Wave 2 Down syndrome laxative users (n= 39) n (%)	Wave 3 Down syndrome laxative users (n= 29) n (%)
Chronic constipation	**10 (25.6)**	**28 (71.8)** (missing=7)	**23 (79.3)** (missing=8)
Rome III criteria	-	**27 (73)**	**18 (72)**
ACB scores			
Zero	**14 (35.9)**	17 (43.6)	11 (38)
>zero	**25 (64)**	22 (56.4)	18 (62)
On medicines that cause constipation			
Total	**32 (82)**	33 (84.6)	25 (86.2)
Categorised			
1-4	27 (84.4)	27 (81.8)	**17 (68)**
5+	5 (15.6)	6 (18.2)	**8 (32)**
On medicines that commonly cause constipation			
Total	**32 (82)**	32 (82)	25 (86.2)
Categorised			
1-4	29 (90.6)	28 (87.5)	**21 (84)**
5+	3 (9.4)	4 (12.5)	**4 (16**)
Conditions that contributed to constipation	(Missing=6) 33 (100)	(Missing=7) **32 (86.5)**	**28 (96.6)**
Neurological diseases	**17 (43.6)**	**22 (59.5)**	**19 (65.5)**
Mental disorders	(Missing=1) 13 (34.2)	15 (39.5)	9 (31)
Soft food / liquidised/thickened fluid	**10 (25.6)**	**12 (30.8)**	**14 (48.3)**

Bold font shows statistically significant a p<0.05. ACB: Anticholinergic Cognitive Burden.

6.3.10. Constipation, laxative use and behaviours that challenge

As shown in *Table 6-17*, the relationship between behaviours that challenge and both constipation and laxative use has been assessed at Wave 3 IDS-TILDA. Those with challenging behaviour (n= 276) were more likely to report a doctor's diagnosis of constipation (55%), and use laxatives (54.3%) than those with no challenging behaviour.

There were no statistically significant differences in term of meeting Rome III criteria or laxative combination between the two groups.

Table 6-17 Bivariate analysis of challenging behavior in terms of constipation, Rome III criteria and laxative use

Category	Wave 3 Challenging behaviour (Missing =93)		
	Yes (n= 276) n (%)	No (n=180) n (%)	p-value
Constipation reported			≤.001
Yes	152 (55.0)	57 (31.7)	
No	124 (45.0)	123 (68.3)	
Rome III criteria	(Missing= 28)	(Missing= 16)	0.17
Yes	118 (47.6)	67 (41.0)	
No	130 (52.4)	97 (59.0)	
Laxative use	150 (54.3)	62 (34.4)	≤.001
One laxative	96 (64.0)	45 (72.6)	0.22
2+ laxatives	54 (36.0)	17 (27.4)	

6.3.11. Constipation and quality of life

Among the Wave 3 cohort with medicines data (n=549), there were only 275 participants who responded to all parts of the PWI-ID and about half of them (n=139) had the index valid for analysis after removing the answers with acquiescence. The distribution of the scores was not normal when assesed using Kolmogorov-Smirnov and Shapiro-Wilk tests (*Table 6-18*) with a p value <0.05 concluding that the scores significantly deviated from normality. *Figure 6-3* illustrates the distribution of the scores using a histogram.

Table 6-18 Assessment of normality of PWI-ID scores

	Categories	Kolmogorov-Smirnov Test (Sig.)	Shapiro-Wilk test Test (Sig.)
PWI-ID scores	Participants with constipation	0.296 (<0.001)	0.815 (<0.001)
	Participants with constipation	0.286 (<0.001)	0.749 (<0.001)

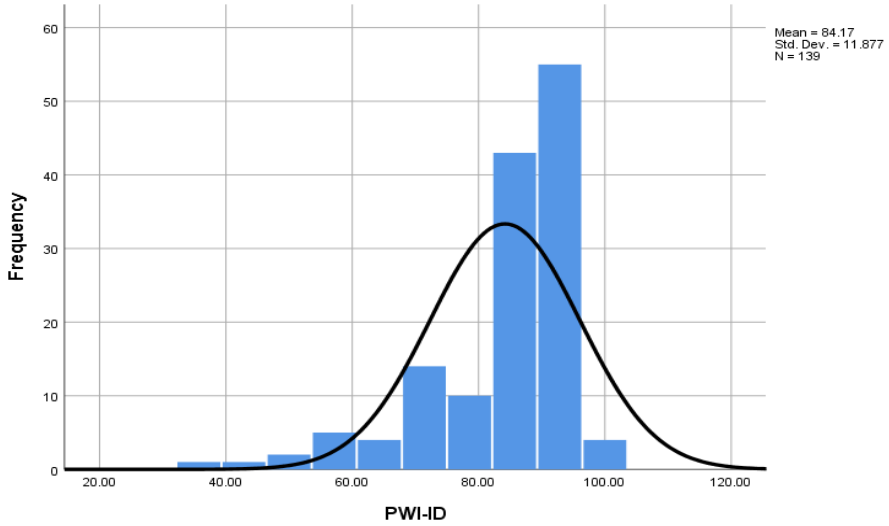

Figure 6-3 Distribution of PWI-ID scores

An independent sample Mann-Whitney U test was applied to compare the differences in median score of PWI-ID for constipated and non-constipated participants. Before this Levene test was used to test for the homogeneity of variances (the equal distribution of the categories) and the results showed an insignificant p value (Levene test = 0.677, p=0.412). The results in *Table 6-19* show that those with constipation had statistically significant lower median of PWI-ID scores than those with out constipation.

Table 6-19 Independent sample Mann-Whitney U test to compare median score of PWI-ID among constipated and non-constipated participants

	N	Median PWI-ID scores	Mean rank (MW)	SD
Participants with constipation	62	85.7	62.17	10.203
Participnats without constipation	77	92.8	76.31	13.067

MW=Mann-Whitney U = 1901.5 (Z =-2.16, p=0.03).

6.4. Discussion

6.4.1. Principal findings

This study evaluated the use of laxatives and two indicators for constipation in a broader way by including data from three waves of a longitudinal study collected at different time points. Our findings in this study indicate that laxative use remained

consistently high in participants over the three waves of the study and appeared complex, with unmet need shown by those who still reported constipation and met Rome III criteria over the three waves. The use of laxatives increased from 37.5% in Wave 1 to 44.4% in Wave 3 in correspondence with reporting constipation which also increased substantially from 17.4% in Wave 1 to 44.6% in Wave 3. The use of two or more laxatives has decreased by 11% since Wave 1. Details of laxative use and Rome III criteria for constipation were available for Wave 2 and 3. Use of intraclass laxative combinations was prevalent at both Waves 2 and Wave 3 representing 24% and 20% of the laxative users respectively. The use of laxatives alone without a report of any of the two constipation indicators occurred at similar percentages in the two waves; Wave 2; 14.2% and Wave 3; 13.5%. The use of laxatives for those with no indication occurred in parallel with the substantial exposure to anticholinergics and constipating medicines.

6.4.2. Changes in demographics over the three waves

The change in demographics among the cohort in Wave 1 to Wave 3 appeared consistent with changes among the total cohort in each wave regardless to availability of medicine data, which was presented in Wave 3 report of IDS-TILDA (182). For example, female to male proportions remained consistent among the three waves IDS-TILDA and this is also seen in the findings of this chapter. Furthermore, there was a decrease in the proportion who were aged 40-49 from Wave 1 to Wave 3 and an increase in number of older groups.

6.4.3. Laxative use and constipation indicators

Reporting a doctor's diagnosis of constipation increased substantially from Wave 1 (17.4%) to Wave 3 (44.6%) and this is consistent with the increase in meeting Rome III criteria from Wave 2 to Wave 3. The findings strongly indicate that constipation is a serious and increasingly concerning issue across the life course in the population with ID. The use of laxatives accordingly increased from Wave 1 (37.5%) to Wave 3 (44.4%) yet, as laxatives supposed to overcome constipation's symptoms, they appeared insufficient based on the ongoing symptoms supporting what has been previously

concluded by Bohmer *et al.* that laxatives usually come with disappointing outcomes among people with ID (101, 233).

To some participants, constipation may be undertreated, and this can be seen from the discrepancies illustrated in *Figure 6-2* (and *Figure 5-2* Chapter 5), where some participants diagnosed with constipation and/or meet Rome III criteria but with no report of laxative use.

There were some laxative users who did not report constipation nor meet Rome III criteria and detailed analysis in relation to exposure to anticholinergics and commonly constipating medicines indicated that laxatives were given prophylactically. We would expect that people with ID are commonly using medicines, acknowledging the high rate of complex multi-morbidity especially the psychiatrics and neurological illnesses (52, 54, 248) and they are frequently exposed in particular to multiple anticholinergics. Nonetheless, investigating the inappropriateness of using some anticholinergics and deprescribing them may be the solution to resolve constipation rather than giving laxatives (60).

6.4.4. Laxative use over the three waves

Females usually use laxatives more frequently in studies in the general old population (356) and found correlated with laxative use in people with ID (211) and this has been observed in the first wave of IDS-TILDA. Nonetheless, the difference was not significant in the subsequent waves suggesting that there were either a possible rise in use of laxatives by males or the proportion of females laxative users reduced in the 2nd and the 3rd wave of IDS-TILDA.

Residential care is usually a commonplace for laxative use for older adult (327, 356, 357) and this can be seen from the findings of this study. People who used laxatives and live in residential care occurred at larger proportion over a 10-year time compared to other living placements. There are no studies in ID population for direct comparison in this matter, however studies in ID population that reported the use of laxative as a frequently used class were conducted in residential care (68, 205).

Among laxative users, there was an increase in the proportions of those who reported constipation in Wave 2 and Wave 3 when compared to Wave 1. This may suggest that there were cases at higher risks of constipation at Wave 1 and the conditions been diagnosed in the subsequent waves. Although the use of laxatives increased from Wave 1 to Wave 3 (Wave 1:37.5%, Wave 2:41.5%, Wave 3: 44.4%), there were much more increase in reporting constipation among laxative users from Wave 1 to Wave 3 (Wave 1:41%, Wave 2: 74.3%, Wave 3:71.3%), suggesting that laxative alone is not sufficient in relieving the symptoms of constipation and that other interventions may have been used.

Over the three waves, laxative users and constipated participants were more likely to use medicines that commonly cause constipation with more exposure to five or more medicines. Considering therapeutic classes, exposure to constipating medicines among laxative users did not differ from those with constipation over the three waves, except in using NSAIDs (Wave 1 and Wave 2), opioids (Wave 1 and Wave 3) and anti-propulsive agents with more laxative users exposed to these classes than non-users and this was not different for constipated versus not constipated participants. There are no studies reporting specific classes that were associated with laxative use in people with ID, but rather in constipated individuals with ID who were more likely to exposed to anticonvulsants, PPIs similarly with findings in this study (101). There was only one study that found that laxative use among people with ID was correlated with all co-medication, either constipating (such as opiates, calcium channel blockers, medicines with anticholinergic effect, calcium and ferrous salts) or non-constipating (211). Laxative users over the three waves were more likely to be exposed to opioids and according to criteria START it is appropriate to give laxatives for older people who used opioids for more than two weeks (260).

6.4.5. Dosage regimen and laxative combination in Wave 2 and Wave 3

The findings on dosage regimen revealed in Wave 2 and Wave 3 tell that there were large proportions of laxative users (around two-thirds) who were using the laxatives on a regular basis with further regular and as needed doses (14%), indicating the constant need for laxatives by older people with ID which attributed to the frequent symptoms

of constipation in this population. The use of osmotic laxatives represented the most commonly used class in both waves (83.5%-87%) and this class has been proved effective and generally well tolerated in the general population and in people with ID (212, 358).

Multiple laxative use was observed in both waves at a range of 35.7%-40% with combinations of three and four laxatives identified. The questions of why combinations of laxative were in use and whether this combination was appropriate to each case were not possible to explore within this study. The general guidelines for managing constipation suggest the use of two laxatives if monotherapy is insufficient (91, 359). Nevertheless, investigating the type of these combinations in this study shows that there were proportions of laxative users were on combination of intraclass laxatives (two from the same laxative class) which we would consider as inappropriate. Although there were observed lower proportions of those who used intraclass laxative combinations in Wave 3 (20%) as compared to Wave 2 (24%) which perhaps reflect the cessation of ongoing laxatives that were not in need anymore, the percentage is still concerning which may cause drawbacks and add further burden to those participants than providing benefits (360). Furthermore, according to the STOPP criteria, duplicate use of drugs from the same class is considered potentially inappropriate in older people (260).

6.4.6. Long term laxative users, those who started or stopped laxatives at Wave 3

Following up the use of laxatives from Wave 2 to Wave 3, identified that 64% (n=178) who were using laxatives at both waves and are considered in this study as being long term laxative users ($\geq$ 3 years). It was interesting to investigate their demographics and to examine the pattern of use. This group consisted of larger proportion of females, older ages (50+), residential care residents, with severe/profound level of ID. Among them, there were proportions who did not report a doctor diagnosis of constipation nor meet Rome III criteria, and our explanation is that they either got benefit from the constant use of laxatives during the three years so that constipation symptoms has been relieved, or basically they did not diagnosed with constipation but rather under a large risk of developing it as they are constantly exposed to anticholinergics or constipating

medicines (*Table 6-12*). Long term use of laxative (≥5 years) among people with ID has been detected in one study (213). We would expect that there are more proportions of participants in this study who are on laxatives for longer time than three years but this was not investigated enough because of many missing data in relation to prescribing date of laxatives. By looking at their laxative regimen that had been followed, 65.5% used laxatives on a regular basis and the percentage increased in Wave 3 to 71%, *(Table 6-12)* with additional 14%-15.3% on combination of regular and on demand laxatives. The use of laxative combination was almost constant among this group at both waves (41.6-41%), and the use of the intraclass laxative combinations which were reported by 24.2% (n=43) at Wave 2, decreased by two participants in Wave 3. Long term laxative use alone may not be the choice for participants who are frequently having constipation acknowledging that their constipation may be as a result of the persistence risk factors that can be avoided or managed and the use of inappropriate combination may add further health consequences and comorbidity to people with ID.

When investigating the characteristics of those who started laxative at Wave 3, findings showed that there was an increase in reporting of constipation from Wave 2 to Wave 3 by 45.5% and increase in proportion who meet Rome III criteria by one third (Wave 2:31.6%, Wave 3: 64.7%). Interestingly, among this group there were an increase in exposure to anticholinergics and constipating medicines, with those who used 5+ medicines had been doubled in Wave 3 (Wave 2: 21%, Wave 3:40.7%). The possible scenario here is that people with ID may be initiated laxatives when constipation was diagnosed without investigating the underlying causes of developing constipation such as the use of anticholinergics, constipating medicines or the dependence on diets with low fibre and liquid content (as seen from the increase in using soft/ liquidised diet or thickened fluid to the double from Wave 2 to Wave 3 among this group). Interestingly, the majority of this group started with using one laxative (82%). Nevertheless, there were few proportion (18%, n=11) who used combination within which, 45% (n=5) were using the inappropriate intraclass laxative combination.

On the other hand, among those who stopped laxatives in Wave 3 (n=41), there were a reduction in reporting constipation and meeting Rome III criteria in Wave 3 by

17% and 11%, respectively *(Table 6-14).* There was a slight decrease in exposure to anticholinergics and constipating medicines although the proportion of exposure to these medicines remained large. It is not known if the discontinuation of laxative in Wave 3 was by healthcare provider or by participants themselves and what the reasons behind this.

6.4.7. Laxatives and Down syndrome

In this study, findings from investigating the prevalence of constipation and Rome III criteria among participants with Down syndrome found that they did not differ from participants without Down syndrome except in Wave 1 (*Table 6-15*). In spite of this, they are less likely to use laxatives over the three waves compared to the other group. The proportion of people with Down syndrome who are exposed to medicines that cause constipation was significant (62.5%-76.3%) although this percentage was statistically significantly lower than participants without Down syndrome.

Those with Down syndrome who used laxatives were more likely to report a doctors' diagnosis of constipation, experience constipation related symptoms (Rome III criteria), have severe/profound level of ID and live in residential care. There were no differences in their exposure to anticholinergics compared to Down syndrome non-users of laxatives (except in Wave 1). However, Down syndrome laxative users were more likely to be exposed to 5+ constipating medicines (in Wave 3) and experience at least one constipating condition (such as neurological conditions) and use soft liquidised diet as compared to Down syndrome laxative non-users (*Table 6-16*).

6.4.8. Challenging behaviour in relation to constipation and laxative user

Findings in this study indicate that those who were diagnosed with constipation are statistically significantly more among those who experience behaviour that challenge. However, it did not differ in terms of meeting Rome III criteria. The difference in diagnosis of constipation but not Rome III criteria may be attributed to the way that constipation was diagnosed (i.e. diagnosis of constipation perhaps was only based on frequency bowel movement/ week) (361). There was a lack of studies that investigated the use of laxatives among those with challenging behaviour in people with ID. The use

of laxatives was significantly more among those with behaviours that challenge. However, those with challenging behaviour did not differ significantly in using 2+ laxatives compared with those without challenging behaviour.

6.4.9. Constipation and quality of life

There are some studies show a negative impact on the quality of life because of constipation in older people and people with ID (117, 118). Untreated constipation was associated with serious side effects which were life-threatening in some cases (112).
Since our findings indicated that constipated participants have lower quality of life scores, the improvement of quality of life should be a vital goal in the treatment of constipation among older people with ID.

6.4.10. Strengths and limitations

The strengths of this study are as follows; first, it is the first study that assess laxative use in older people with ID at different time periods acknowledging that the use of laxatives in details among this vulnerable group have undergone little studies. Secondly, the large sample size, in addition to the representativeness of the national ID population in Ireland implies that these findings have the potential to be generalised to other populations with ID especially with including participants from different types of residence and different level of intellectual disabilities. Thirdly, the availability of comprehensive medication data for the three waves of IDS-TILDA provided for the majority of participants. Fourthly, the availability of two indicators for chronic constipation allowed us to analyse laxative use in relation to indication in a robust way. Fifthly, in the study we expanded the analysis using a variety of risk factors for constipation including exposure to all medicines and conditions that are known to cause constipation and specifically analysing those commonly causing constipation.

Among the limitations, since we did not conduct predictive longitudinal analysis, the change with age or those who withdrew or passed away between waves has not been accounted for in this chapter. In addition, medication data was gathered at three time points, it is possible, for example, that a participant could report a laxative at Wave 2, then stop a laxative for a period and then have resumed a laxative by Wave 3. It was

not possible to account for this in the analysis in this chapter. Further longitudinal statistical analysis should be applied to identify the trend in laxative use considering any residual confounders.

6.5. Conclusion

Over the time of this study, 2009-2017, at three time points, both laxative use and constipation increased among the same cohort of people with ID. The use of laxatives was not only connected to reporting constipation or meeting Rome III criteria, but also linked to exposure to anticholinergics and medicines that contributed to constipation. The burden of exposure of anticholinergics and constipating medicines are significant among people with ID with some maybe inappropriate (60) leading to a prescribing cascade by giving laxatives to treat the side effect of these medicines. In addition, the inappropriate laxative combination observed over two waves (Wave 2 and Wave 3) should be discontinued and managing constipation in this population should be individualised and not restricted only to giving laxatives. The observed increase in reporting constipation which was greater than the increase in laxative shows may indicate that other methods are being used in managing constipation.

7. Chapter Seven: Discussion

7.1. Principal findings

The aims and objectives of the thesis were;

- Explore prevalence and patterns of PPI use among older people with ID in Wave 2 IDS- TILDA and to more specifically; (1) Examine the dosage regimen, length of use and the recorded indications; (2) Explore the patterns of use with respect to clinical and demographic factors; (3) Determine the clinical and demographic factors associated with PPI use.
- Investigating the use of PPIs in Wave 3 IDS-TILDA (2016/2017) and conduct a descriptive comparison of the Wave 3 findings with findings from prior wave (Wave 2). The objectives were to a) Investigate the prevalence and patterns of PPI use by demographics and clinical characteristics at Wave 3 IDS-TILDA (2016-2017), b) Investigate the reported doses and length of use of PPIs at Wave 3, c) Compare the results with findings from Wave 2 IDS-TILDA, d) Track the use of PPIs from Wave 2 to Wave 3 IDS-TILDA to identify those who continue using PPIs at both waves, those who stopped or those who initiated PPIs at Wave 3 and e) Investigate the characteristics, demographics and PPI dosage of those who used PPIs at Wave 2 and Wave 3 continuously, those who stopped or initiated PPIs at Wave 3.
- Explore prevalence and patterns of laxative use among older people with ID in Wave 2 IDS- TILDA. The secondary aim was to compare the characteristics of those using laxatives and those reporting chronic constipation using two indicators for chronic constipation. The objectives were to a) Determine the prevalence of use, patterns, dosage, the related indication(s) and combination of laxatives and b) Identify the factors significantly associated with laxative use.
- Investigate, compare and track the use of laxatives over a 3-year time period, from Wave 2 (2013/2014) to Wave 3 (2016/2017) of IDS-TILDA. The second aim was to expand the investigation of the clinical and demographic characteristics of laxative users by including data from the first wave IDS-TILDA (2009/2010).

More specifically the objectives were, a) Investigate the use of laxatives in Wave 3 of IDS-TILDA in terms of prevalence, patterns, dosage and indications, b) Include data from the first wave IDS-TILDA to examine laxative users over a 10-year period (from Wave 1 to Wave 3) in terms of their demographics, clinical characteristics, exposure to constipation risk factors, c) Compare these characteristics with those participants who reported doctor's diagnosis of constipation over the three waves IDS-TILDA, d) Compare detailed laxative use in Wave 3 with the findings of previous wave (Wave 2) (Chapter 5), e) Track laxative users from Wave 2 to Wave 3 to identify those who used laxatives at both waves, those who stopped laxatives at Wave 3, or those who started laxatives at Wave 3-IDS-TILDA, f) Investigate the characteristics, demographics and laxative dosage among those who used laxatives at both Wave 2 and Wave 3, those who stopped or started using laxatives at Wave 3, g) Explore laxative use among participants with Down syndrome in Wave 1-Wave 3 IDS-TILDA, h) Evaluate the use of laxatives and reporting constipation in relation to behaviours that challenge in people with ID in Wave 3 IDS-TILDA, i) Investigate impact of constipation on quality of life in people with ID at Wave 3 IDS-TILDA.

The principal and novel findings of the thesis indicated that;

- Just over a quarter (28%) of participants in Wave 2 reported use of PPIs. Most of the PPIs were used in higher doses (70%, n=132), for long term with almost over half recorded using the PPIs for more than a year, and with no clear indications (by over 4 in 10). Apart from an indication, the factors associated with PPI use were older ages (≥50 years), severe/profound level of ID.
- PPI use in Wave 3 (after 3 years) increased from the prior wave to one-third (35%) reporting use. Over six in ten of participants reported the use of PPIs at both waves, 9.5% (n=18) discontinued PPIs in Wave 3 and 12.5% (n=69) commenced the use of a PPI at Wave 3. There was still a large proportion of PPIs being used at high doses (70%, n=135) and no clear indications (37.3%) in Wave 3. PPIs were more likely to be used by older ages (65+), those with

severe/profound level of ID or by those who live in residential care at both waves of the study.

- The use of laxatives was reported in Wave 2 by over four in ten of older adults with ID. Constipation was assessed using two indicators; a doctor's diagnosis of constipation which was reported by 38.4% (n=257) of participants and Rome III criteria which was met by 38.9% (n=246). There were four in ten who took two or more laxatives, among them, 60% (n=67) were using a combination from the same laxative class. Laxatives were often potentially inappropriate and despite their use, criteria indicative of constipation were still reported. Reporting chronic constipation, living in residential care, exposure to anticholinergics and taking soft food or thickening fluids were significantly associated with laxative use in regression analysis, after adjusting for confounders.
- There was a corresponding increase in using laxatives and in reporting of the two constipation indicators in the three waves of IDS-TILDA. The reported use of laxative increased from 37.5% in Wave 1 to 44.4% in Wave 3. Reporting a doctors' diagnosis of constipation increased from 17.4% in the first wave to 44.4 % in Wave 3. Rome III was available for Wave 2 and Wave 3 and its prevalence increased from 38.9% in Wave 2 to 44.4% in Wave 3.
- The use of two or more laxatives was prevalent in Wave 3 and intraclass laxative combinations (intraclass polypharmacy) were frequent in both Wave 2 and Wave 3 (Wave 2:24% of all laxative users, n=68) (Wave 3:20% of all laxative users, n=49).
- The use of laxatives in those with no indication appeared as a result of the significant exposure to anticholinergics (Wave 1: 85%, Wave 2: 83.3, Wave 3: 81.6%) and medicines that contribute to constipation (Wave 1: 95.7%, Wave 2: 94.7, Wave 3: 95.9%)

7.2. The use of PPIs in older adult with ID

7.2.1. Patterns in relation to demographics

In some studies in the general older population, females were the majority using PPIs (160). Moreover, female gender was one of the predictors for inappropriate long-

term use of PPIs in the general older population (362). Our findings at both waves (Wave 2 and Wave 3) show that although proportions of females were using PPIs more than males this was not statistically significant different (53.4-59%) vs (41- 46.6%) (P>0.05).

Nonetheless, our findings show that there were statistically significant differences between PPI users and non-users in terms of other demographics. In Ireland and other countries (162), the use of PPIs was most prevalent in the oldest age group (≥65 years) and the findings in both Wave 2 and Wave 3 IDS-TILDA, show that although there were a large proportion of PPI users who were aged between the age of 50-64 years (53.4-59%), the bivariate analysis showed that PPI users were more likely to be by those aged 65 years and over (30.2-33.7%) when compared to PPI non-users (17.4-20.8%) ($p<0.001$). In addition, after controlling for confounders, PPI use appeared more likely to be used by older ages (50+ years) and since older people with ID are usually prone to the phenomenon of polypharmacy/ excessive polypharmacy (72), they are under significant risks of drug-drug interactions especially with using the PPIs that are well known interacting medicines (269). In addition, in our results, PPI users appeared more likely to have a severe/profound level of ID compared to those non-users (37.8-41%) vs (25.7-26%), and even after adjusting for confounders, a severe/profound level of ID was a contributing factor to PPI use in our study (363). The possible reason here is that people with severe/profound levels of ID (IQ <35) are more likely to experience reflux oesophagitis (121) for which PPIs are indicated (364). PPI users were also more likely to live in residential care (54.3-57.5%) than PPI non-users (35.7-38.5%), yet it did not appear as a correlate to PPI use when other factors were adjusted for.

The proportions of PPI users who lived in residential care reported at Wave 2 was 37% (102/276) and increased to 44.7% (111/248) at Wave 3. The prevalence reported in our study (37% - 44.7%) is lower than that reported in another study of people with ID in residential care (52%), nonetheless, that percentage included all medicines for acid related disorders not only PPIs (205). This percentage is higher than the prevalence in other studies in residential care from the general older population (159, 166). In older people, residential care was a predictor for long-term use of PPIs (362) and our findings (Chapter 3) indicated that over half (57.3%) of those who lived in residential care were using PPIs for more than a year, which was slightly higher than of those who lived in

community group homes (51%) but far more than those who live independently or with family (12.5%).

7.2.2. PPI use and clinical indications

Our findings revealed that PPIs were often used to treat GORD with or without other indications (30.7% - 41.5% at both waves) acknowledging that people with ID commonly experience this condition during their life course (121). Reporting any licensed indication for PPIs was observed in 44% to 53.4% in Wave 2 and Wave 3 respectively, and even with the addition of the use of an antiplatelet as an indication, there were 37.3% to 42.8% of PPI users not reporting any clear indication for their use. Moreover, reporting an indication was absent in three in ten of those who reported using PPIs at Wave 2 and Waves 3 continuously. In people with ID, if a PPI without an indication is added to the medication list, this will increase the risk for both drug interactions (61) and potential side effects (365) thus exposing those vulnerable individuals to risk and additional comorbidities (60). There are large number of studies in the older population, of them one conducted in Ireland, that identified the use of PPIs without an indication with a proportion that ranged from 24% to 63% (163, 164, 366, 367).

In a study that assessed the predictors for using PPIs without an appropriate indication for PPI use was mainly linked to the number of medications received (366). In our findings, PPI users were more likely to be exposed to excessive polypharmacy (Wave 2: 45.5% vs 15.8, $p<0.001$). Barreto *et al.* reported that among older people, most PPI use was "probably inappropriately related to a general condition of health vulnerability, reflected by polypharmacy and comorbidities" (159). Moreover, as people with ID are commonly exposed to polypharmacy and a high burden of medicines with anticholinergic properties (99) which may contribute to symptoms like dyspepsia and the lowering of oesophageal sphincter pressure, PPI use without indication in this case may represent a prescribing cascade to overcome these adverse events (368). In the older adults, many factors have been found related to non-guideline recommended prescribing of PPIs such as antidepressants, and anticholinergic drugs, dementia, osteoarthritis, and osteoporosis and the number of chronic diseases (366, 368, 369) and all of these factors were detected in population with ID (27, 72, 76, 99, 180).

Furthermore, it is possible that those who used a PPI without indication had an indication but it was not documented, as what was identified in another study of people with ID (205). Reporting and documenting the indication is an imperative element in the population with ID because they commonly experience communication difficulties which hamper them from reporting or expressing the symptoms (370).

7.2.3. Dosage information and length of use

Almost seven in ten of older adults with ID in this study were using high doses of PPIs which were those assessed as the maximum or those that exceeded the maximum indicated for older adults (257, 258). The use of high doses was also detected in six in ten of the cohort of participants who initiated PPIs in Wave 3, suggesting that prescribing practice of PPIs for older people with ID is similar as in the general adult population. Furthermore, since there were also those PPI users who reported a use of a PPI of more than one year (more than four in ten), the use of high doses accounted for over six in ten of this group. In an Irish study that analysed data from pharmacy claims database in primary care, it indicated that the majority of subjects were on long-term PPI therapy that were continuously prescribed maximum therapeutic dose (275). The practice of giving high doses of PPIs and for a long time may be associated with the popular perception amongst prescribers that PPIs are safe medicines without a serious adverse effects profile, in spite of the growing body of research that identified potential safety concerns linked with the use of PPIs (371). There are a large number of studies that have investigated the appropriateness of using PPIs in the older population (169-171). Assessing the appropriate use of PPIs depends on the doses and the use duration for authorised indications. Full therapeutic doses for more than eight weeks is considered potentially inappropriate for uncomplicated conditions. Maintenance therapy which usually associated with lower PPI doses is always recommended for cases where the long-term use of a PPI is needed such as protection from NSAIDs ulceration of those high-risk patients or to protect the recurrence of GORD and even with these cases, frequent review and evaluation of the doses and the condition itself is always recommended. The high doses of PPIs and for long duration of time will not devoid of risks and harms among those vulnerable populations where multi-morbidity and polypharmacy present frequently.

7.3. The use of laxatives in waves 1-3 of IDS-TILDA

7.3.1. Prevalence and patterns in relation to demographics

The proportion of laxative users increased from 37.5% in Wave 1 to 44.4% in Wave 3. However, some of the increase in laxative use would be expected as this population gets older and we did not account for this factor in this analysis.

The prevalence of laxative use in our study in Wave 3 was close to that reported by another study of an ID population in the Netherlands (43.3%) (52).

In one study of people with ID, female gender was correlated with laxative use (211). While in our findings, when the differences in demographics among laxative users along the three waves IDS-TILDA were assessed, females were significantly more likely to use laxatives than males only in Wave 1 which is also consistent with studies from the general older population (356, 372) and this may be attributed to the higher proportion of females compared to males in the IDS-TILDA cohort.

Age, level of ID and place of residence were shown to be statistically significantly different among laxative users through the three waves with laxative users being more likely to be in the older age group (65+), to have a severe/profound level of ID and to live in residential care. The higher level of laxative use among those with a severe/profound level of ID may be attributed to frequent constipation resulting from gross abnormalities in colonic transit time in this group (101, 213). Studies that have reported the use of laxatives among people with ID were with samples taken from residential care with the reported use prevalence ranging from 49.4% to 69% (68, 101, 205) consistent with our results of laxative use among those living in residential care. Furthermore, the population of two of these studies was characterised by a severe/profound level of ID (101, 205).

7.3.2. The pattern of the two constipation indicators and constipation risk factors

Chronic constipation in our study was evaluated by two indicators; reporting a doctor's diagnosis of constipation and meeting the Rome III criteria which was available only in Wave 2 and Wave 3. Reporting constipation consistently increased since the first wave along with the increase in proportion of laxative users, yet the increase in the

diagnosis of constipation and Rome III criteria was greater than the increase in laxative use suggesting that other measures apart from laxatives may be used or that regular use of laxatives was not being employed.

Although the use of laxatives was prevalent and at an increase since Wave 1, their use was not distributed over all those who reported constipation or meeting Rome III criteria with some who experienced one or both criteria of constipation but without reporting laxative use suggesting the suboptimal and inadequate treatment constipation among people with ID similar to what was reported by Bohmer and colleagues (101) and reported by a systematic review (233). The discrepancy in reporting constipation with less laxative use was specifically observed among those who live independently or with family, where higher proportions reported constipation (13% and 14% in Wave 2 and Wave 3 respectively) compared to laxative users in this group (5% and 6.4% in Wave 2 and Wave 3 respectively).

There were also laxative users who did not report any or both of the constipation indicators. Those participants were exposed to a high burden of constipation risk factors and their laxatives may possibly have been given prophylactically. This may reflect the prescribing cascade where participants were given medications to overcome side effects of other medications (373).

7.3.3. Factors associated with laxative use

The factors significantly associated with laxative use were assessed in Wave 2 IDS-TILDA. Apart from constipation, the findings show that place of residence, taking soft food or using thickened fluid and exposure to anticholinergics were significantly associated with laxative use. Very few studies identified factors that correlated with laxative use among people with ID. In one study, being on pureed or tube feeding was correlated with laxative use similarly to our findings, yet the study reported other factors like non-ambulance, female gender and medicines use (not specific to anticholinergics) (211). Furthermore, it was expected that neurological conditions, a severe/profound level of ID would be linked to laxative use among people with ID, as they are linked to constipation among this population (101, 103). However, the results of the multiple regression did not identify any of these as correlated with laxative use. Investigating the factors associated with laxative use in this population should provide direction for

investigations into the management of constipation and into reducing the burden and risks of polypharmacy among older people with ID to which laxatives contribute significantly (72).

7.3.4. Intraclass Laxative combinations

In Wave 2 and Wave 3, there were over half of those who used laxative combinations received inappropriate combinations and not those based on guidelines. There were some studies among people with ID who identified the use of laxative combination (127, 211). However, none reported such intraclass laxative combination that were identified in our study. These combinations not only add burden of polypharmacy but also exposing those vulnerable people to additional side effects such as diarrhoea. This may link to our results in the bivariate analysis where laxative users were more likely to use anti-diarrheal medicines. Managing constipation in people with ID should not be by abusing laxatives, but choosing the type, combinations should be tailored appropriately for each individual case in population with ID (233, 374).

7.3.5. Management of constipation among people with ID

Prior to applying treatment approaches, thorough assessments should always applied and should include reviewing medical and medication history to identify the underlying causes. Approaches in managing constipation should involve combination of both non-pharmacological and pharmacological. Non-pharmacological such as patient education (whenever possible) regarding normal bowel habit and following healthy life style (e.g. exercise and sufficient fibre or fluid intake). Pharmacological treatment includes the use of laxatives that have different mechanism of action in treating constipation. Choosing the laxative depends on patient health status, medical and medication history, constipation type as well as patient tolerability and preference. The laxatives are traditionally categorised into osmotic, stimulants, bulk forming and stool softeners, with each group has different mechanism of action, and thus requires different information about their proper use. Laxatives are generally recognised to have good efficacy and safety profile in the older population (375-379). However, chronic over use of laxative may cause side effects such as dehydration, electrolyte imbalance,

anatomic and physiologic changes in the colon (specific to stimulant laxatives), diarrhoea and faecal incontinence (316).

There are no evidenced based studies evaluating a stepwise approach to laxative therapy in old population, and the existent European guidelines have been issued for the general population (91). Although some of these guidelines incorporate what can be applied to elderly, they are not specific for older people (359, 380-383). Nevertheless, recommendation for laxatives that applied for older general population are the same as for adults but with some modification and precautions (384), and what applied for the general older population should be applied to people with ID until new guidelines or approaches that targeted older people with ID is created (385). Initiating bulk forming laxatives as a first line laxative type is usually recommended, unless contraindicated. If no improvement osmotic laxatives, then stimulants if required (325). Combined laxative /in addition to enema may be considered in cases if refractory patient or sever constipation (386). There are preference toward using the osmotic laxative macrogol (polyethylene glycol) or senna combination (with bulk forming) as being more effective in old people compared to other laxative types (387). A recent consensus statement includes a treatment panel to manage constipation in older people, has been released by a group of European healthcare professionals in gastroenterology, geriatrics, nursing and pharmacology. In the statement, osmotic laxatives are likely to be the most suitable class for older people with macrogol preferred over lactulose. In the statement, the team discourages the use of bulk forming laxative for older people because of an accompanied need to increase fluid intake, which is not usually feasible to older people. Combination of different laxative classes maybe sometimes considered. If laxative combination does not alleviate the symptoms after 8 weeks, even at high doses, then prucalopride or lubiprostone or naloxegol (in case of opioid-incduced constipation) is to be considered. Among those with swallowing difficulties (dysphagia), if the syrup- based osmotic laxative are ineffective, rectal administration of stimulant with /without stool softener is the alternative (345). Laxatives need to be titrated gradually until optimal bowel function is achieved and for those with poor response to treatment, referral to specialised care may be the best choice. Considering different mechanism of actions for different laxative class, each class has its own proper use instruction accordingly. For example, bulk-forming laxatives should be taken with plenty of fluids; otherwise, it may

cause mechanical obstruction such as faecal impaction. In addition, they should not be taken immediately before going to sleep. On the other hand, most of stimulant laxatives are instructed to be taken at night (257). Therefore, enough instructions and clear counselling should be given to people with ID or their proxies for the proper laxative administration as well as assessment of whether or not people with ID are following these instructions properly.

7.4. Recommendation and implication for practice

Considering the novel findings in this thesis, a number of recommendations can be made that are relevant to healthcare providers, pharmacists, carers and older adults with ID aiming for the best quality of care delivered to people with ID.

7.4.1. Involvement of multidisciplinary team

Due to the complexity of gastrointestinal health conditions experienced by people with ID arise from childhood, the quality of care given to people with ID can be enhanced by involvement of multidisciplinary team as an integrated care system and this would include pharmacists/clinical pharmacist, experts in the field of intellectual disabilities, psychiatrists or neurologists as well as gastroenterologists. The role of psychiatrists or neurologists are to assess the need for medicines with anticholinergic properties such as antipsychotics, antiparkinsonians or antiepileptics which are contributing to constipation. Gastroenterologists will help in early detection and management of GI conditions, provide better advice on laxative use based on constipation type, suggest alternatives to constipating medicines and constantly evaluate the need for PPIs. Pharmacists can play a vital role in primary assessment process. Pharmacists can positively contribute in evaluating and assessing the quality and safety of the medication use process, provide advice in relation to side effects and drug-drug interaction and give proper counselling for people with ID in relation to medicine administration (388, 389). The team should also involve dietitian/ nutritionists to afford non-pharmacological plan related to healthy diets that help in managing or reducing the extent of constipation and GORD in this population.

Considering the communication difficulties among people with ID, involvement of team which bring together the relevant healthcare professionals and practitioners will

promote the collaboration and coordination between each member in relation to the medical history and treatment plan for people with ID.

Constant output from a multidisciplinary team will positively impact on quality of life for people with ID and effectively meet their needs as they age by understanding more about the ageing process and developing interventions which do not only tackle one area.

7.4.2. Implementing guidelines specialised for people with ID

The prevalence of GI conditions in people with ID, particularly constipation, as observed from findings of this thesis add further to the complexity of healthcare and comorbidity in people with ID. Development of guidelines for these conditions will guide the healthcare providers and practitioners for the best treatment options and will facilitate the management of these conditions in a structured and planned way.

To date, there are limited guidelines for managing constipation or GORD in the population with ID and even if they existed, the evidence is mainly brief reports and so not good enough. The Public Health England (PHE) released a report presenting some strategies to be considered when managing constipation in people with ID (385). The approach suggest involvement of family/carers, learning disability nurses, GPs, physiotherapists, occupational therapists and dietitians. The strategy includes the follows; diet, exercise, training in toileting, abdominal massage and physical health/medication review (385). There is a need for evidence-based guidelines for using laxatives in this population. The guidelines should emphasise that constipation should be actively considered in people with ID and to direct the health professional and practitioner to also consider and tackle the risk factors of constipation which this research has identified. The guidelines must discuss different cases of ID - those with cerebral palsy, Down syndrome - so that therapy will be tailored to each case accordingly.

7.4.3. Developing tools to evaluate the appropriateness of prescribing for people with ID

There are many tools that are used to assess the appropriateness of prescribing in the older population such as STOPP/START (Screening Tool of Older Person's

Prescriptions/Screening Tool to Alert to Right Treatment), STRIP (Systematic Tool to Reduce Inappropriate Prescribing) and ACOVE (Assessing Care of Vulnerable Elders). These tools may be used in people with ID (390). Nonetheless, because people with ID experience earlier signs of functional decline, earlier mortality, poorer health outcomes, higher frailty and polypharmacy compared with the general population, applying tools specific for them will be of crucial value to support the carer and heath care providers to avoid any prescribing practice that could be inappropriate, with attention to anticholinergics, laxatives and PPIs. The tools should include assessment of indication-related problems, such as lack of indication or unclear indication, for a person with ID, since this is an important element for those with communication difficulties. Evaluating the quality of GI medicine use in people with ID may require developing a comprehensive list of quality indicators related to effective medicine use and ascertain experts opinions (Delphi process) such as those established by Flood and Henman that aim to measure the quality of the medication use process for people with ID and behaviour disorders (391).

7.4.4. Awareness of the potential of prescribing cascade among all healthcare professionals

Exposure to anticholinergic medicines was detected frequently in people with ID in this thesis exposing them to additional adverse effects such as dry mouth, constipation, confusion, dizziness or urinary retention (93). It was found that the anticholinergic burden was associated with constipation in the older population with ID (99), so it is possible in some cases that high use of laxatives and also the PPIs in our findings may represent a prescribing cascade. With the deinstitutionalisation and integration of people with ID in to the community, there will be a greater use of primary rather than specialised care in the community which creates more challenges to heath care professionals and pharmacists in order to provide best quality of care to this vulnerable population (392), so raising the awareness about the potential of the prescribing cascade may help in limiting this phenomenon in people with ID. Pharmacists could play a proactive role in performing medication reviews and in the active education of other healthcare professionals in terms of medicines that associated with bowel alterations and constipation which may provide important clues for

caregivers to prevent or reduce constipation. In addition, constant education of the safety concerns associated with PPIs is another important role for pharmacist. However, pharmacist should specifically educated to perform these roles. The Public Health England approach to manage constipation in people with ID would be suggested by pharmacists as a good starting point for all practitioner in primary care (385).

7.4.5. Medication review and deprescribing strategies

Given that people with ID have a large burden of polypharmacy and excessive polypharmacy (72), with some being used for long-term to manage comorbid chronic conditions, frequent and structured medication review may optimise and improve the quality of medicine use by identifying and reducing that used inappropriately. This may be done periodically and could be applied in the community by accredited pharmacists (home medicines review) (393). In a study, a structured medication review was performed to 55 patients with ID and identified a prevalence of drug-related problems (DRP) of 34% of the overall prescribed medicines with the commonest DRP identified was giving medicines with no or unclear indication. In this study, the pharmacist and psychiatrist contributed to develop a care plan with 60% of recommended actions were executed (336). Prescription errors have been detected in older people with ID with a prevalence of errors reached 47.5% (394). Since our findings identified some PPI use without clear indication and a use of inappropriate laxative combinations, reviewing the use of these two classes periodically would be of great value to optimise their use in this population.

Deprescribing approaches have been given more attention in older population (395-397) with some specifically targeted deprescribing the anticholinergics (398). Deprescribing is a planned and supervised process of dose reduction or discontinuation of medicines that might be causing harm or might no longer be providing benefit (399, 400). The aim of deprescribing is to reduce the medication burden and harm while maintaining or improving quality of life. Deprescribing in the population with ID has been directed to reduce psychotropic medicines (401) which was challenging as being not devoid from withdrawal side effects (60). In terms of GI medicines, there is many research suggested deprescribing of PPIs in the general older population given their high prevalence of use and overuse (402, 403). It is likely that deprescribing may fail in cases

of refractory stages of GORD despite PPI treatment. In addition, the patient may be reluctant to stop therapy, likely due to symptoms associated with acid rebound hypersecretion after discontinuation especially for long term PPI users (404). According to Rochoy *et al.*, daily exposure to PPIs for more than 4 weeks is likely to trigger a rebound of acid hypersecretion about 15 days after discontinuation, and lasting from a few days to several weeks depending on the duration of the exposure (404). Deprescribing should be restricted to one medicine at a time with slow tapering to allow for gentle physiological adjustments (405, 406). An evidence-based clinical practice guideline to deprescribe PPIs in the older population has been developed to provide practical recommendations for making decisions about when and how to reduce the dose of or stop PPIs (281, 407, 408). Pharmacists should always encourage the prescriber to routinely re-evaluate repeat PPI prescribing practices and to deprescribe PPIs when clinically appropriate.

7.4.6. Standard and periodic follow up assessments

Given that GI conditions such as constipation, *H. pylori* and GORD are common in people with ID, a follow up monitoring process to evaluate the ongoing symptoms is important for good quality of care. This also includes assessment of the effectiveness of therapy to provide the lowest effective dose, particularly with the PPIs. In a study of people with ID, recurrence of *H. pylori* infection after thirty-six months was high after successful treatment course which includes PPIs (136). GI conditions need periodic follow up assessments among people with ID.

7.5. Further research

A key recommendation for future research is longitudinal analysis to examine the trend in both PPIs and laxatives among people with ID using statistical analysis that can adjust for any residual confounder between the waves of IDS TILDA such as missing data or withdrawn participants. This will further provide a comprehensive insight into resultant changes as people age and move into community settings. In addition, repeating the multiple regression analysis for laxative use and PPIs for each wave IDS-TILDA would help to identify any further correlates for their use in this population.

An important tool for future analysis would be linking the medicines dispensed under the Primary Care Reimbursement Service in Ireland (in particular the General Medical Services and Long-Term Illness schemes) to the data in IDS-TILDA. This would give a robust information for medicines that are used on a regular and as needed basis and would allow accurate analysis of the length of use of both laxatives and PPIs without missing information. This would also help in assessing the appropriateness of prescribing of PPIs using the available validated tools particularly in relation to doses, length of use and reporting the indications.

Moreover, since there are a large proportion of participants were using PPIs for a long time and given that there are growing safety concerns with PPI use, it would be crucial to assess the side effects of PPIs among long-term PPI users.

In addition, since the use of drugs for functional GI disorders (A03) (such as antispasmodics, antidiarrheal and propulsive) among people with ID was more than that reported in older population (1.8% of IDS-TILDA vs 0.5% of people in TILDA)(71), it would be worth investigating their use and their relevant indication in details especially that this class include a number of medicines with anticholinergic properties.

Fibre and fluid intake will be captured in Wave 4 IDS-TILDA as a subjective measure using an open-source self-completed computerised dietary recall system based on multiple-pass 24-hour recall called *Intake24* (409) together with sending a template diary page with the invitation letter to all participants in order to complete it the day before their CAPI. Including accurate information related to fibre and fluid intake in the future analysis would answer more questions related to using the non-pharmacological treatment with/without laxative use in managing constipation in this population. Furthermore since physical activity has an impact on constipation, in Wave 4, in addition to the International physical activity questionnaire (IPAQ), there will be an accurate measurement of sedentary behaviour using the *ActivPAL* accelerometer (410) which will allow better investigation of constipated and laxative users in terms of physical activity.

In addition, given that dental health has an impact on maintaining a healthy diet that does not predispose to constipation, and since our findings shows that using a soft diet is one of the correlates of laxative use, an objective measure of oral health status

assessment including dental assessment would provide robust data for future analysis of those who have dental issues in terms of using laxatives.

Assessing the use and pattern of laxatives and PPIs considering specific groups who commonly experience constipation and GORD among people with ID such as those with cerebral palsy would be worthwhile future research. Moreover, since those with Down syndrome experience constipation but are less likely to use laxatives than others in the cohort, it would be of value to investigate the factors behind this suboptimal practice.

7.6. Conclusion

With the increase in longevity, deinstitutionalisation and community integration among people with ID, there is a high burden on healthcare providers, practitioners, policy makers, carers and pharmacists to provide all the means to improve the quality of life of this vulnerable population. There is a need to raise the education and awareness of health professionals in primary care on the unique medical and pharmaceutical care needs of people with ID.

Knowing that people with ID are experiencing polypharmacy it would be useful to further investigate all groups of medicines that contribute to this phenomenon. Evaluating the use of two GI classes, the PPIs and laxatives, shows that their use is not based on evidence and was not sufficient to meet the needs to manage the relevant GI conditions among people with ID. Also there are some suboptimal practices in relation to constipation although the use of laxatives was prevalent. The practice of just prescribing laxatives without investigating the current medical history to identify the associated constipation risk factors will lead to treatment failure and persistent symptoms of constipation in this population. The substantial exposure to constipation risk factors observed by frequently experiencing conditions that contribute to constipation and high rates of exposure to anticholinergics or constipating medicines should be tackled before embarking on treatment or depending on only the long-term use of laxatives. Using irrational combinations of laxatives for a long period of time exposes those vulnerable individuals to side effects and to further constipation and contributes to the problem rather than solving it.

Investigating the use of PPIs in this population has suggested that inappropriate prescribing practice occurs which is seen from the long term of use, high doses and without clear indications. Given that PPIs are associated with many side effects, whenever clinically appropriate, PPI should be tapered gradually and deprescribed based on the deprescribing guidelines and their use should be individualised according to the individual needs.

List of Appendices

1. Appendix 1: IDS-TILDA Study Ethical Approval

THE UNIVERSITY OF DUBLIN
TRINITY COLLEGE

SCHOOL OF MEDICINE
FACULTY OF HEALTH SCIENCES

Trinity College, Dublin 2, Ireland
Tel: +353 1 896 1476
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Professor Dermot Kelleher, MD, FRCPI, FRCP, F Med Sci
Head of School of Medicine
Vice Provost for Medical Affairs

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School Administrator
Email: fmcnamar@tcd.ie

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

10th July, 2008

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

Dear Prof. McCarron,

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

Yours sincerely,

Dr. Orla Sheils
Chairperson
Faculty of Health Sciences Ethics Committee

2. Appendix 2: Medication data collection form in the PIQ

144. MEDICATIONS 

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 and herbal and alternative medicines.
PLEASE WRITE DOWN ALL MEDICATIONS/TABLETS YOU TAKE AND HOW OFTEN YOU TAKE THEM, PLEASE USE ONE LINE PER MEDICATION

Don't know what medication I take, record by proxy ☐ 1 PLEASE COMPLETE MEDICATION FORM

Don't take any medication 1 GO TO QUESTION 145

Name of Medication	Dosage Strength	Frequency	Route	Date First Prescribed
Examples of medication completion form :				
Epilim Chrono	200mgs	Twice a day (BD)	Orally(PO)	Sept 2009
One touch ultra test strip(blood glucose)	1 strip	Before meals	-	June 2010
Neo-cytamen Injection(hydroxycobalamin)	1000micrograms	Monthly	IM	Nov 2010
Xalatan eye drops	2 drops (left eye)	Nocte (At night)	Instill	June 2010
Emulsifying Ointment		PRN	Topically	Jan 2009
Vegepa (Omega fishoil)		2 daily	PO	June 2005
Ensure Plus		1 daily	PO	Oct 2007

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COLÁISTE NA TRÍONÓIDE

Name of Medication	Dosage Strength	Frequency	Route	Date Prescribed
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				

59

3. Appendix 3: IDS-TILDA data protection policy

IDS-TILDA DEPARTMENTAL DATA PROTECTION MANAGEMENT POLICY

Purpose of the Policy

The purpose of this policy is to assist members of IDS-TILDA to fulfil their responsibilities with respect to the collection, storage and retention of data and records associated with, and arising from, their research activities.

This policy establishes uniform data management standards and identifies the shared responsibilities for assuring that IDS-TILDA has integrity and that it efficiently and effectively serves the needs of the department.

This policy will cover the day to day access requirements of IDS-TILDA paper data, electronic data and the equipment that gives access to the data.

Objectives of the Policy

Raise awareness that data constitute an important resource and that the value of data as a department resource is increased through its widespread and appropriate use while its value is diminished through misuse, misinterpretation, or unnecessary restriction to its access.

Help ensure that data comply with all relevant legislation such as the Data Protection Act and the Freedom of Information Act;

Raise awareness of data access v. privacy issues and formalise procedures for access management.

Improve ease of access. Assure that data is easily located, easily accessed once located, and that people have enough information about the data to understand what they have found.

Facilitate database integration.

Reduce the redundancy of the data by defining an official record of reference.

Data Classification

All data to be collected, processed and stored in IDS-TILDA should be identified and classified using the college data classification table below or similar.

Data Classification	Information	Description	Examples	Handling
Non Confidential	Public	Such data is available to anyone to see, and is often made available to public via the college website,	Publications, Articles, Presentations	Access to this data is not usually restricted.
	University Internal	Such data is generally available to all staff and students in College	Publications, Articles, Presentations	Access is usually restricted to members of College Staff
Confidential	Restricted	Personal data. This data is only made available to authorised members of IDS-TILDA	Participants Name, address, telephone numbers,	Access is restricted to IDS-TILDA members only
	Critical	Sensitive personal data.	Information relating to the mental & physical health of individuals	Access to such data is tightly controlled

Data sets related to individual study participants.

Where data sets are collected relating to individuals you may also want to label data sets with regard to whether the data is.

Personal data means any information about a living individual who can be identified from that information and other information which is in, or likely to come into, the data controller's possession.

Anonymised data is data prepared from personal data but from which the person cannot be readily identified by the recipient of the information.

Coded data is identifiable personal data in which the details that could identify someone are concealed in a code, but which can readily be decoded by those using the personal data. Such coded data is not anonymised data.

Linked data is typically used when it may be necessary to refer back to the original recodes for further information, or for verification. Unlinked data usually ensures confidentiality but prevents follow-up, verification or feedback.

With both linked and unlinked anonymised data it is sometimes possible to deduce an individual's identity through combinations of information. The most important identifiers are:

- Unusual disease or treatment;
- Partial address, geocode or similar;
- Details of health professionals responsible for care;
- Specific/unusual occupation or place of work;
- Combinations of details such as birth date, place of birth etc.

Data Handling Procedures

Once data has been classified, appropriate handling procedures should be agreed on and documented.

#	Data Type	Handling Procedures
1	Critical Data	• Is authorised for use by the Data Manager, Project director only. • May not be removed from premises • Must be encrypted at all times • Must never be transported on insecure USB media
2	Restricted Data	• Is authorised for use by the Data Manager, Project Director & research staff • Must be encrypted at all times • May not be removed from premises
3	Coded Data	• Is authorised for use by Data Manager, Project Director & research staff • Must be encrypted at all times
4	Participant Contact Records	• Is authorised for use by the Participant's signed consent form. • Must be encrypted when stored & transferred • Can be transmitted by Email but only if fully encrypted
5	Public Data	• No requirement for encryption • Approved for public distribution

Daily Data Management

It is the responsibility of all members of IDS-TILDA to adhere to the following office policy.

- All members of IDS-TILDA are issued with their individual secure login and password.
- Each member is responsible for their login and password and should never give this out for other people to use.
- All members have access to an encrypted laptop or desktop.
- The laptops are in a secured press in office 1. It is the responsibility of each member of staff to ensure they leave the laptop back in the press when they are finished. The press is to be locked and the key put back in the designated area.
- The Muse has five hot desks which have five encrypted desktops for members of IDS-TILDA to use. IDS-TILDA has a secure and dedicated link for accessing the required data.
-

Responsibilities

Project Director

- Responsible for ensuring project compliance with all relevant legislation
- Responsible for Data Management Policy content
- Responsible for ensuring compliance with data management policy

Data Manager

- Responsible for backup and recovery of all project data
- Responsible for promoting ongoing awareness of data management policy among project staff
- Responsible for ensuring the integrity of dataset

Researchers

- Responsible for compliance with Data Management Policy

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

An Intellectual Disability Supplement to The Irish Longitudinal Study on Ageing

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

Interdisciplinary Post Graduate Training Opportunities

Research Student information and Agreement Protocol

Intellectual Disability Supplement to TILDA,
The University of Dublin, Trinity College,
School of Nursing & Midwifery, 24 D'Olier Street,
Dublin 2,
Ireland

Telephone: (01) 8963186 / (01) 896 3187
Fax: (01) 8963001

Email: idstilda@tcd.ie

Developed	Date	Review Date
Prof. Mary McCarron, Prof. Philip McCallion, Eilish Burke	2013	
Reviewed		
Eilish Burke, MaryAnn O'Donovan, Prof Philip McCallion, Prof Mary McCarron		13.5.2016

Table of Contents

Introduction

The Intellectual Disability Supplement to The Irish Longitudinal Study on Ageing (IDS-TILDA) is a longitudinal study of the ageing of a random and representative sample of over 700 people with intellectual disability aged 40 and over is now entering its third wave of data collection. There are opportunities to analyze the data and there may be opportunities to access data from the main TILDA project to use in comparative studies. The first and second waves of data have already supported the theses of several PhD, MSc. and MD students. Applications are currently being considered for PhD theses that may utilize either waves of data further.

Definitions of terms

Students: Refers to full/part-time PhD, MSc, MD, interns or students on placement. Herein after referred to as student.

Investigators: Refers to the principal investigator and co-principal investigator of the IDS-TILDA study; Prof Mary McCarron and Prof Philip McCallion.

Core IDS-TILD team: Please refer to governance structure of the IDS-TILDA project in

Critical Considerations

There are several critical considerations:

1. The investigators (PIs) and the core IDS-TILDA team have already identified and are continuing to identify a number of research questions that the research team itself will be addressing. Understandably pursuit of these questions will not be appropriate for a PhD or MD thesis. In addition, as the investigators agree to additional specific PhD, MSc. and MD theses this will further narrow the scope of available research questions. It is therefore important that the unique questions for a particular PhD, MSc. or MD thesis be defined and approved by the PIs/Project Manager early in any process. No work using IDS-TILDA data may proceed without this approval.
2. With reference to interns and/or students on placement it is essential that agreement of area for investigation is obtained prior to commencement of placement.
3. All Students must attain placement deliverables within the specific time and to the appropriate standard as designated by the project manager/supervisor and the principle investigators.
4. Consistent with funder goals for student training and with the investigators' own commitment to postgraduate education, participation in IDS-TILDA by students is designed to offer **research experience** as well as access to data. There will be an expectation that students will participate in trainings, data collection where appropriate (dependent on stage of project and status of student) and data analyses and any other work within the IDS-TILDA team necessary to work within the research team advancing the entire project

5. For students completing a thesis using IDS-TILDA data and for achievement of advanced academic qualification, the IDS-TILDA investigators will be members of the thesis committee, preferably with the PI as the main supervisor, to ensure that all data protections and data sharing understandings are fully respected.
6. For students accessing IDS-TILDA data from another university outside Trinity College the investigators will be part of their supervisory team.
7. IDS-TILDA is a critical study whose data is already informing public policy debates and decision-making. As such the timely delivery of data is of critical concern and requires that expectations be agreed with students about timelines for completion of any agreed publications and theses.
8. Publication of findings from IDS-TILDA data must comply with Data Use Policy of the Intellectual Disability Supplement of The Irish Longitudinal Study on Ageing (see accompanying protocol).
9. Confidentially and data management protocols must be complied with at all times including restrictions on use of data outside of IDS-TILDA offices and password protected computers.

Rationale

It is precisely because the IDS-TILDA dataset offers a unique and exciting opportunity for multiple interdisciplinary students to experience being part of a national and international research team and to develop theses that are on the cutting edge of research knowledge of the ageing of people with ID that guidelines for their participation are necessary.

Expectations and Opportunities

To address the outlined considerations and to enrich the students training and placement experience there are a number of expectations and opportunities with regards the initial proposal, training, and timely publication

The Proposal

Applicants are encouraged to propose unique research questions allied to the main IDS-TILDA study and or they may be invited to undertake a structured PhD on an investigator- identified topic:

- Students should review the IDS-TILDA report to see the range of data available to begin the process of identifying research questions and considering if there is sufficient data to help answer those questions.
- Students will have the opportunity of undertaking an internship under the guidance of the PIs and direct supervision of a designated team member to help them better understand the data and develop their own unique research question. The type and duration of the internship will be worked out on an individual basis with each potential student.
- The internship will be guided by the key performance indicators specific for each student.

- Students beginning during the period between waves of data collection may have an opportunity to suggest additional protocol questions but this will not be possible at other times and any additions agreed will be limited so as not to overburden participants. Investigators decisions will be final.
- Often students may wish to add qualitative components to the protocol. These too are possible but the over-riding concern for the investigators will be the level of burden on participants and the need to preserve the sample for future waves of data collection. Investigators decisions will be final.
- A proposal in a format agreed with the investigators must be presented to the investigators who will then consider it for approval. It is likely that a face-to-face meeting will be required and students should expect that some changes to the proposal will be necessary before approval.
- In order to ensure that each students' work and the research studies being undertaken by the research team are unique, students may only access and use data that the investigators have agreed is necessary to answer the research question and study objectives identified in the proposal.
- For all students only the agreed data may be accessed as per the IDS-TILDA data protection protocol.
- As part of the proposal approval process, the student and the investigators will agree a time frame for the completion of the various components of the thesis including trainings and data collection and the student will commit to adhering to this agreed schedule. All placement students will adhere to their agreed key performance indicators and timeline as agreed on commencement of placement.
- It is recognized that there may be unforeseen circumstances influencing completion of aspects for the thesis/ placement work and it is the responsibility of the students to keep the supervisory team informed of concerns and to work with the team to agree on plans to address any such issues.
- Should issues arise a review process will be agreed upon to address the issues that have arisen. Regardless of who is the main thesis supervisor, the IDS-TILDA PI will be the final arbitrator of whether sufficient progress is being made to permit continued access to and use of IDS-TILDA data.
- It is understood that data collected as part of IDS-TILDA, even where used for a thesis becomes part of the IDS-TILDA dataset.

PhD/MD, MSc, Intern or MSc. Placement Training

IDS-TILDA offers opportunities for PhD/MD /MSc /Intern /Placements level research training likely to support the development of students for a future research career. Students whether they are F/T or P/T will commit to:

- Attendance at the full training programme or formal induction with the IDS-TILDA team offered to all field workers/and all students in the administration of the IDS-TILDA protocol and research process.
- Collection of data on 40-60 study participants under the supervision of the research team. --Where possible and /or appropriate students will be assigned

subjects to reflect their research interests, for example family carer's, or geographical regions where specific research questions are likely to be better captured.
- Participation in developing materials responsive to ethical approval requirements by various sites
- Participation in the preparation of materials to be forward to study participants and study sites, for example assist in photocopying of materials and preparation for postage in line with the 'Keeping in Touch' Strategy of the IDS-TILDA project.
- Adherence to the highest ethical principles and the meeting of requirements for confidentially, storage of data, accessing data, consent and maintenance of data integrity.
- Preparation, cleaning and entry of data.
- Assisting with analysis of data.
- Development of publications in a timely manner.
- Appropriate acknowledgment to participants and funders in all publications.

In furtherance of their preparation students will also:

- Schedule regular supervisory meetings as agreed with the supervisory team and keep record of all meetings.
- Attend PhD monthly meetings and master classes where applicable.
- Access grant writing, statistical and other training opportunities in College.
- Submit work for review on a schedule agreed with the supervisory committee.
- Submit all poster/ oral presentations, journal articles and any other publications to PIs for review prior to submission.

Timely Publication

To ensure that project needs as well as student needs are met:

1. Students must commit and adhere to the overall goals and targets of the main project as set out by the PI and project manager and research team.
2. Students must complete work on their own research question within a timeframe negotiated with their supervisory team. There will be an expectation that student transfers to PhD status will be timely and the thesis will be completed within 3-4 years. The PI cannot guarantee beyond the four year timeframe that others may not be permitted to pursue a similar question.
3. The PhD/MD/MSc student will have the opportunity to be first author on all publications resulting from the thesis with the understanding that the PIs and project staff (as determined by the PI) will be co-authors.
4. Should it not be possible for the PhD/MD/MSc student to submit articles from the thesis within one year of a successful viva/completion of the thesis in the case of MSc, the investigators may assign the first authorship to someone else with the PhD/MD/MSc student as a co-author.

5. In the case of student intern/placement the publication must be at an appropriate standard judged by the IDS-TIILDA supervisor/PI, be delivered within the agreed timeframe relative to the number of week's placement and at minimum first draft level.

Agreement

I _____ have read the above principles document and have had the opportunity to discuss the contents with PI/Project Manager/IDS-TILDA Supervisor, and have all my questions satisfactory answered. I understand the commitments inherent within the document and I agree to fulfil and adhere to these.

_____	_____	_____
Student Signature	Principal Investigator	IDS-TILDA Supervisor
Date _____	Date_____	Date_____

Copy to be retained by Research student and copy to be retained by the IDS-TILDA office

4. Appendix 4: Crowe Critical Appraisal Tool (Page1)

Crowe Critical Appraisal Tool (CCAT) Form (v1.4) Reference Reviewer

This form must be used in conjunction with the CCAT User Guide (v1.4); otherwise validity and reliability may be severely compromised.

Citation

	Year

Research design (add if not listed)

❑ Not research		Article | Editorial | Report | Opinion | Guideline | Pamphlet | …
❑ Historical		…
❑ Qualitative		Narrative | Phenomenology | Ethnography | Grounded theory | Narrative case study | …
❑ Descriptive, Exploratory, Observational		A. Cross-sectional | Longitudinal | Retrospective | Prospective | Correlational | Predictive | …
		B. Cohort | Case-control | Survey | Developmental | Normative | Case study | …
Experimental	❑ True experiment	Pre-test/post-test control group | Solomon four-group | Post-test only control group | Randomised two-factor | Placebo controlled trial | …
	❑ Quasi-experiment	Post-test only | Non-equivalent control group | Counter balanced *(cross-over)* | Multiple time series | Separate sample pre-test post-test [no Control] [Control] | …
	❑ Single system	One-shot experimental *(case study)* | Simple time series | One group pre-test/post-test | Interactive | Multiple baseline | Within subjects *(Equivalent time, repeated measures, multiple treatment)* | …
❑ Mixed Methods		Action research | Sequential | Concurrent | Transformative | …
❑ Synthesis		Systematic review | Critical review | Thematic synthesis | Meta-ethnography | Narrative synthesis | …
❑ Other		…

Variables and analysis

Intervention(s), Treatment(s), Exposure(s)	Outcome(s), Output(s), Predictor(s), Measure(s)	Data analysis method(s)

Sampling

Total size		Group 1		Group 2		Group 3		Group 4		Control	
Population, sample, setting											

Data collection (add if not listed)

Audit/Review	a) Primary | Secondary | … b) Authoritative | Partisan | Antagonist | … c) Literature | Systematic | …	Interview	a) Formal | Informal | … b) Structured | Semi-structured | Unstructured | … c) One-on-one | Group | Multiple | Self-administered | …
Observation	a) Participant | Non-participant | … b) Structured | Semi-structured | Unstructured | … c) Covert | Candid | …	Testing	a) Standardised | Norm-ref | Criterion-ref | Ipsative | … b) Objective | Subjective | … c) One-on-one | Group | Self-administered | …

Scores

Preliminaries		Design		Data Collection		Results		Total [/40]	
Introduction		Sampling		Ethical Matters		Discussion		Total [%]	

General notes

4. Appendix 4: Crowe Critical Appraisal Tool (Page 2)

Appraise research on the merits of the research design used, not against other research designs.

Category Item	Item descriptors [☑ Present; ☒ Absent; ■ Not applicable]	Description [Important information for each item]	Score [0–5]
1. Preliminaries			
Title	1. Includes study aims ❑ and design ❑		
Abstract (assess last)	1. Key information ❑ 2. Balanced ❑ and informative ❑		
Text (assess last)	1. Sufficient detail others could reproduce ❑ 2. Clear/concise writing ❑, table(s) ❑, diagram(s) ❑, figure(s) ❑		
		Preliminaries [/5]	
2. Introduction			
Background	1. Summary of current knowledge ❑ 2. Specific problem(s) addressed ❑ and reason(s) for addressing ❑		
Objective	1. Primary objective(s), hypothesis(es), or aim(s) ❑ 2. Secondary question(s) ❑		
	Is it worth continuing?	**Introduction [/5]**	
3. Design			
Research design	1. Research design(s) chosen ❑ and why ❑ 2. Suitability of research design(s) ❑		
Intervention, Treatment, Exposure	1. Intervention(s)/treatment(s)/exposure(s) chosen ❑ and why ❑ 2. Precise details of the intervention(s)/treatment(s)/exposure(s) ❑ for each group ❑ 3. Intervention(s)/treatment(s)/exposure(s) valid ❑ and reliable ❑		
Outcome, Output, Predictor, Measure	1. Outcome(s)/output(s)/predictor(s)/measure(s) chosen ❑ and why ❑ 2. Clearly define outcome(s)/output(s)/predictor(s)/measure(s) ❑ 3. Outcome(s)/output(s)/predictor(s)/measure(s) valid ❑ and reliable ❑		
Bias, etc	1. Potential bias ❑, confounding variables ❑, effect modifiers ❑, interactions ❑ 2. Sequence generation ❑, group allocation ❑, group balance ❑, and by whom ❑ 3. Equivalent treatment of participants/cases/groups ❑		
	Is it worth continuing?	**Design [/5]**	
4. Sampling			
Sampling method	1. Sampling method(s) chosen ❑ and why ❑ 2. Suitability of sampling method ❑		
Sample size	1. Sample size ❑, how chosen ❑, and why ❑ 2. Suitability of sample size ❑		
Sampling protocol	1. Target/actual/sample population(s): description ❑ and suitability ❑ 2. Participants/cases/groups: inclusion ❑ and exclusion ❑ criteria 3. Recruitment of participants/cases/groups ❑		
	Is it worth continuing?	**Sampling [/5]**	
5. Data collection			
Collection method	1. Collection method(s) chosen ❑ and why ❑ 2. Suitability of collection method(s) ❑		
Collection protocol	1. Include date(s) ❑, location(s) ❑, setting(s) ❑, personnel ❑, materials ❑, processes ❑ 2. Method(s) to ensure/enhance quality of measurement/instrumentation ❑ 3. Manage non-participation ❑, withdrawal ❑, incomplete/lost data ❑		
	Is it worth continuing?	**Data collection [/5]**	
6. Ethical matters			
Participant ethics	1. Informed consent ❑, equity ❑ 2. Privacy ❑, confidentiality/anonymity ❑		
Researcher ethics	1. Ethical approval ❑, funding ❑, conflict(s) of interest ❑ 2. Subjectivities ❑, relationship(s) with participants/cases ❑		
	Is it worth continuing?	**Ethical matters [/5]**	
7. Results			
Analysis, Integration, Interpretation method	1. A.I.I. method(s) for primary outcome(s)/output(s)/predictor(s) chosen ❑ and why ❑ 2. Additional A.I.I. methods (e.g. subgroup analysis) chosen ❑ and why ❑ 3. Suitability of analysis/integration/interpretation method(s) ❑		
Essential analysis	1. Flow of participants/cases/groups through each stage of research ❑ 2. Demographic and other characteristics of participants/cases/groups ❑ 3. Analyse raw data ❑, response rate ❑, non-participation/withdrawal/incomplete/lost data ❑		
Outcome, Output, Predictor analysis	1. Summary of results ❑ and precision ❑ for each outcome/output/predictor/measure 2. Consideration of benefits/harms ❑, unexpected results ❑, problems/failures ❑ 3. Description of outlying data (e.g. diverse cases, adverse effects, minor themes) ❑		
		Results [/5]	
8. Discussion			
Interpretation	1. Interpretation of results in the context of current evidence ❑ and objectives ❑ 2. Draw inferences consistent with the strength of the data ❑ 3. Consideration of alternative explanations for observed results ❑ 4. Account for bias ❑, confounding/effect modifiers/interactions/imprecision ❑		
Generalisation	1. Consideration of overall practical usefulness of the study ❑ 2. Description of generalisability (external validity) of the study ❑		
Concluding remarks	1. Highlight study's particular strengths ❑ 2. Suggest steps that may improve future results (e.g. limitations) ❑ 3. Suggest further studies ❑		
		Discussion [/5]	
9. Total			
Total score	1. Add all scores for categories 1–8		
		Total [/40]	

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5. Appendix 5: Medicines that contributed to constipation classified by frequency

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
Medicines with anticholinergic properties						
Alprazolam (N05BA12)	No		Yes (C/VC)	Yes (C)		Yes (C)
Atropine (S01FA01)			Systemic side-effects can occur, particularly in children and the elderly			Yes
Baclofen (M03BX01)		Yes (C/VC)	In the antimuscarinic list	Yes (VC)		Yes (VC)
Tizanidine (M03BX02)		No		No	Yes (411)	Yes
Cyclobenzaprine (M03BX08)		NA		NA	Yes (412)	Yes
Methocarbamol(M03BA03)		No		NA		No
Cimetidine (A02BA01)	Yes (C/VC)	-		No		Yes
Diazepam (N05BA01) PO	No	Yes	Yes (UC)	Yes (UC)		Yes (UC)
Digoxin (C01AA05)			No	No		No
Dipyridamole (B01AC07)			No	No		No
Fentanyl (N02AB03)			No	Yes (C)		Yes (C)
Ipratropium(R03BB01)		Yes	GI motility disorders (C/VC). (in the antimuscarinic list)	Yes (UC)		Yes (UC)

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
Tiotropium(R03BB04)		Yes	GI disorders (C/VC)	Yes (UC)		Yes (UC)
Nefopam (N02BG06)			No (antimuscarinic side-effects may be troublesome)	No		Yes (C)
Prednisolone (H02AB06)			No	No		No
Ranitidine (A02BA02)	Yes (C/VC)	No		Yes (UC) (mostly improved during continued treatment)		Yes (UC)
Scopolamine(hyoscine hydrobromide)(A04AD01)			GI disorder (UF) antimuscarinic agent			Yes (C)
Theophylline (R03DA04)			No	No		No
Warfarin (B01AA03)			No	No		No
Cinnarizine(N07CA02)			No	Yes		Yes
Clorazepate (N05BA05)			NA	NA	No(413)	No
Colchicine (M04AC01)			No	No		No
Isosorbide mononitrate (C01DA14)			No	No		No
Diuretics						
Bendroflumethiazide (C03AA01)	Yes (C/VC)	-	Gastrointestinal disorder	Yes (C)		Yes (C)
Hydrochlorothiazide(C03AA03)	Yes (C/VC)		-	Yes		Yes (C)

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
Cyclopenthiazide (C03AA07)	Yes (C/VC)	-	No	NA	Yes (R)(414)	Yes (R)
Chlortalidone (C03BA04)	Yes (C/VC)		No	Yes (R)		Yes (R)
Metolazone (C03BA08)	Yes (C/VC)		-	NA	Yes(415)	Yes
Xipamide (C03BA10)	Yes (C/VC)		No	NA	Yes (C)(416)	Yes (C)
Indapamide (C03BA11)	Yes (C/VC)		No	Yes (R)	Yes (R)(417)	Yes (R)
Furosemide(C03CA01)	No	Yes	No	Yes (UC)		Yes (UC)
Bumetanide (C03CA02)	No	Yes	-	Yes (UC)		Yes (UC)
Torasemide (C03CA04)	No	Yes		NA	Yes (C)(418)	Yes (C)
Piretanide (C03CA03)	NA	Yes	NA	No		No
Spironolactone (C03DA01)	-	Yes	No	No	No(419)	No
Amiloride (C03DB01)	-	Yes	Yes	No	Yes(420)	Yes
Triamterene (C03DB02)	-		-	NA	No(421)	No
Tolvaptan (C03XA01)	-	-	Yes (C/VC)	Yes (C)		Yes (C)
Aldosterone antagonist						
Eplerenone (C03DA04)	-	-	Yes (C/VC)	Yes (C)		Yes (C)
Antipsychotics						
Chlorpromazine (N05AA01)	Yes (C/VC)	Yes	- (antimuscarinic effect)	Yes (VC)		Yes (VC)
Levomepromazine (N05AA02)	Yes (C/VC)	Yes	No	Yes		Yes (VC)

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
			(antimuscarinic effect)			
Promazine (N05AA03)	Yes (C/VC)	-	No	NA	Yes (422) has antimuscarinic effect	Yes (C)
Fluphenazine (N05AB02)	-	Yes	No	NA	Yes (423)	Yes
Perphenazine (N05AB03)	-	-	No (antimuscarinic effect)	NA	Yes (424)	Yes (C)
Prochlorperazine (N05AB04)	Yes (C/VC)	Yes	No (antimuscarinic effect)	Yes		Yes (C)
Trifluoperazine (N05AB06)	Yes (C/VC)	Yes	No (antimuscarinic effect)	Yes		Yes (C)
Periciazine (N05AC01)	Yes (C/VC)		No	NA	Yes (425)	Yes (C)
Haloperidol (N05AD01)	Yes (C/VC)		No (antimuscarinic effect)	Yes (C)		Yes (C)
Benperidol (N05AD07)	Yes (C/VC)		No	NA		Yes
Droperidol (N05AD08)	Yes (C/VC)		No	No		Yes
Ziprasidone (N05AE04)	Yes (C/VC)		NA	Yes (C)		Yes (C)

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
Molindone (N05AE02)	NA		NA	NA	Yes (426)	Yes
Flupentixol (N05AF01)	Yes (C/VC)		No	Yes (C)		Yes (C)
Zuclopenthixol (N05AF05)	Yes (C/VC)		No	Yes (C)		Yes (C)
Pimozide (N05AG02)	Yes (C/VC)		No (antimuscarinic effect)	NA		Yes (C)
Clozapine (N05AH02)	Yes (C/VC)		No (antimuscarinic effect)	Yes (VC)		Yes (VC)
Olanzapine (N05AH03)	Yes (C/VC)		No (antimuscarinic effect)	Yes (C)		Yes (C)
Quetiapine (N05AH04)	Yes (C/VC)		No	Yes (C)		Yes (C)
Asenapine (N05AH05)	Yes (C/VC)		No	No	No(427)	No
Sulpiride (N05AL01)	Yes (C/VC)		No	Yes (C)		Yes (C)
Amisulpride (N05AL05)	Yes (C/VC)		No	Yes (C)		Yes (C)
Aripiprazole (N05AX12)	Yes (C/VC)		No	Yes (C)		Yes (C)
Paliperidone (N05AX13)	Yes (C/VC)		No	Yes (C)		Yes (C)
Risperidone (N05AX08)	Yes (C/VC)		No	Yes (C)		Yes (C)
Cariprazine (N05AX15)	NA		NA	Yes (C)	Yes (C) (428)	Yes (C)
Antidepressant						
Tricyclic antidepressant						
Amitriptyline (N06AA09, N06CA01)	-	Yes	Yes (UF)	Yes (VC)		Yes (VC)
Clomipramine (N06AA04)	-	Yes	Yes (C/VC)	Yes (VC)		Yes (VC)

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
Dosulepin (N06AA16)	-	Yes	Yes	Yes (C)		Yes (C)
Doxepin (N06AA12)			Yes	NA	Yes (C)(429)	Yes (C)
Trimipramine (N06AA06)		Yes	Yes	Yes must be used with caution in elderly patients more susceptible to chronic constipation (risk of paralytic ileus)		Yes
Lofepramine (N06AA07)		Yes	Yes	Yes		Yes
Nortriptyline (N06AA10)			Yes	Yes (VC)		Yes (VC)
Amoxapine (N06AA17)	NA		NA	NA	Yes (430)	Yes
Desipramine (N06AA01)	NA		NA	NA	Yes (431)	Yes
Imipramine (N06AA02)			Yes antimuscarinic	NA	Yes (VC)(432)	Yes (VC)
MAO inhibitors						
Tranylcypromine (N06AF04)	Yes (UF)	Yes	-	No		Yes
Phenelzine (N06AF03)	Yes (UF)	-	-	NA		Yes
Isocarboxazid (N06AF01)	Yes (UF)	-	-	NA		Yes

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
Moclobemide (N06AG02) (selective MAOI)	Yes (UF)	Yes	Yes (C/VC)	Yes (VC)		Yes (VC)
Selective serotonin reuptake inhibitors						
Citalopram (N06AB04)	Yes (C/VC)	Yes	No	Yes (VC)		Yes (C)
Escitalopram (N06AB10)	Yes (C/VC)	Yes	No	Yes (C)		Yes (C)
Paroxetine (N06AB05)	Yes (C/VC)	Yes	No	Yes (C)		Yes (C)
Fluvoxamine (N06AB08)	Yes (C/VC)	Yes	No (not in the antimuscarinic medicines BNF lists)	Yes (C)		Yes (C)
Fluoxetine (N06AB03)	Yes (C/VC)	Yes	No	No		Yes
Sertraline (N06AB06)	Yes (C/VC)	Yes	No	Yes (C)		Yes (C)
Other antidepressants						
Mirtazapine (N06AX11) (tetracyclic antidepressant)	-	-	Yes (C/VC)	Yes (C)		Yes (C)
Trazodone (N06AX05)	-	Yes	Yes	Yes		Yes
Venlafaxine (N06AX16) (serotonin and noradrenaline re-uptake inhibitors)	-	Yes	Yes (C/VC)	Yes (VC)		Yes (VC)
Bupropion (N06AX12, A08AA62)	-	-	Yes (C/VC)	Yes (C)		Yes (C)

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
Duloxetine (N06AX21) (Serotonin and noradrenaline re-uptake inhibitors)	-	Yes	Yes (C/VC)	Yes (VC)		Yes (VC)
Reboxetine (N06AX18) (Noradrenaline reuptake inhibitors)	-	Yes	Yes (C/VC)	Yes (VC)		Yes (VC)
Vortioxetine (N06AX26)	-	-	Yes (C/VC)	Yes (C)		Yes (C)
Mianserin (N06AX03)	-	-	Yes (in the caution section)	NA	Yes (VC)(433)	Yes (VC)
Agomelatine (N06AX22) Melatonin receptor agonists	-	-	Yes (C/VC)	Yes (C)		Yes (C)
Antihistamine						
Diphenhydramine (R06AA02)	No enough information	Yes	No enough information	Yes (UF)		Yes
Dimenhydrinate (is the salt produced by interaction of the antihistaminic base diphenhydramine with an acidic compound) In the HPRA : it comes in combination with cinnarizine N07CA52. constipation is associated with cinnarizine not Dimenhydrinate	No information		No information (in the antimuscarinic BNF lists)	No		Yes (C)

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
Chlorpheniramine(Chlorphenamine) (R06AB04)	-	Yes	Has antimuscarinic activity (in the side effect : it cause GI disturbances)	No but included as anticholinergic medicines		Yes (C)
Brompheniramine (R06AB01)	No enough information	Yes	No enough information	No		Yes
Alimemazine (R06AD01)	-		No (it is not in the BNF antimuscarinic list)	No (it has mild anticholinergic effect)		Yes
Meclozine (R06AE05)	NA		NA	Limited information in HPRA but in general reference, it cause constipation	Yes (434)	Yes
Cyclizine (R06AE03, R06AE53)	-		Yes (UF) (antimuscarinic effect)	Yes (UF) It has anticholinergic effect		Yes (C)
Hydroxyzine (N05BB01)	-	Yes	Yes (UF) Caution : reduce GI motility Antimuscarinic effects	NA		Yes (C)
Promethazine(R06AD02)		Yes	No but reported: Elderly patients are more	No		Yes (C)

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
			susceptible to anticholinergic side-effects from this drug (it has antimuscarinic effects)	May produce anti-cholinergic side effects		
Cyproheptadine (R06AX02)	-	-	Yes (antimuscarinic effects)	NA		Yes (C)
Carbinoxamine (R06AA08)			NA	NA		Yes
Clemastine (R06AA04)			Yes (R/VR) (antimuscarinic effects)	NA		Yes (C)
Cetirizine (R06AE07) (is a selective antagonist of peripheral H1-receptors and is relatively free of anticholinergic activity)			No (not in the antimuscarinic list)	No		No
Desloratadine (R06AX27)			No (no antimuscarinic effect)	No		No
Levocetirizine (R06AE09)			Yes (C/VC in children) in children. It is not in the antimuscarinic list	Yes in children		Yes
Loratadine (R06AX13)			No	No		No
Doxylamine (R06AA09)			No enough information	No enough information	Yes(435)	Yes

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
Buclizine (R06AE01)	-		A product in combination with codeine reported to cause constipation	(Yes) has an antimuscarinic action		Yes (C)
Triprolidine (R06AX07)	-	Yes	No enough information	No (possesses minimal anticholinergic activity		Yes
Fexofenadine (R06AX26) (metabolite of terfenadine)			No	No		No
Ketotifen (R06AX17)			No	No		No
Acrivastine (R06AX18)			No	NA		No
Mizolastine (R06AX25)			No	NA		No
Rupatadine (R06AX28)			Yes (UC) no antimuscarinic activity	Yes (UC)		Yes (UC)
Bilastine (R06AX29)			No (no antimuscarinic activity)	No		No
Antispasmodic						
Dicycloverine (A03AA07)	No as side effect but it mentioned that it reduce		No	Yes (R) Antimuscarinic effect		Yes (C)

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
	intestinal motility as antimuscarinic agent					
Propantheline(A03AB05)	Yes antimuscarinic effect	-	No	NA		Yes (C)
Butylscopolamine (Hyoscine butylbromide) (A03BB01)	-		No But it has antimuscarinic effect	Yes (UC)		Yes (C)
Alverine (A03AX08) (direct relaxants of intestinal smooth muscle)	No		No	No		No
Mebeverine (A03AA04) (direct relaxants of intestinal smooth muscle with no effect on normal gut motility)	No		No	No		No
Glycopyrronium bromide (A03AB02)	It is antimuscarinic agent but used either as inhalation (where systemic absorption is		No	Yes (UF) if inj No if inhalation		No

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
	poor) or as injection					
Clidinium (A03CA02)			NA	NA		Yes
Antihypertensive						
Clonidine (C02AC01)			Yes (C/VC)	Yes (C)		Yes (C)
Captopril (C09AA01)	Yes (C/VC)	-	No	Yes (C)		Yes (C)
Doxazosin (C02CA04)			Yes (UC)	Yes (UC)		Yes (UC)
Calcium channel blockers						
Amlodipine(C08CA01)	GI disorders (VC)		Yes (C/VC)	Yes (C)		Yes (C)
Felodipine (C08CA02)	GI disorders (VC)		Not enough information	No	Yes (436)	Yes
Clevidipine (C08CA16)	GI disorders (VC)		Yes (UC)	NA		Yes (UC)
Lacidipine (C08CA09)	GI disorders (VC)		Abdominal discomfort (C/VC)	NA	No(437)	No
Lercanidipine (C08CA13, C09BB02)	GI disorders (VC)		GI discomfort (UC)	No	No (438)	No
Nicardipine (C08CA04)	GI disorders (VC)		No	NA	No (439)	No
Nimodipine (C08CA06)	GI disorders (VC)		No	No		No

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
Nifedipine (C08CA05)	GI disorders (VC)		Yes (C/VC)	Yes (C)		Yes (C)
Diltiazem (C08DB01)	GI disorders (VC)		Yes (C/VC)	Yes (C)		Yes (C)
Verapamil (C08DA01)			Yes (UF)	Yes (C)		Yes (C)
Beta adrenoceptor antagonists						
Oxprenolol (C07AA02)	Yes (C/VC)		No	NA	Yes (VC)(440)	Yes (VC)
Pindolol (C07AA03)	Yes (C/VC)		No Side effects : GI disorders	NA	Yes (441)	Yes
Propranolol (C07AA05)	Yes (C/VC)		No	No (GI disturbances as uncommon side effect and no constipation mentioned)	Yes (442)	Yes
Timolol (C07AA06)	Yes (C/VC)		No	No		No
Sotalol (C07AA07)	Yes (C/VC)		No	No		No

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
Nadolol (C07AA12)	Yes (C/VC)		No	NA	Yes (443)	Yes
Metoprolol (C07AB02)	Yes (C/VC)	Yes (C)	No	Yes (C)		Yes (C)
Atenolol (C07AB03)	Yes (C/VC)	Yes (C)	No Side effects : GI disorders (C/VC)	No Side effect : GI disturbances (C)		Yes (C)
Acebutolol (C07AB04)	Yes (C/VC)		No Side effects : GI disorders (C/VC)	NA	No (444)	No
Bisoprolol (C07AB07)	Yes (C/VC)	Yes (C)	No	Yes GI complaint including constipation (C)		Yes (C)
Celiprolol (C07AB08)	Yes (C/VC)	Yes (C)	No	No		No
Nebivolol (C07AB12)	Yes (C/VC)	Yes (C)	No	Yes (C)		Yes (C)
Carvedilol (C07AG02)	-		No	Yes (UC)		Yes (UC)
Labetalol (C07AG01)	-		No	No		No
Antiarrhythmic						
Disopyramide (C01BA03)	-	Yes	Yes			Yes
Propafenone (C01BC03)			Yes (C/VC)	Yes (C)		Yes (C)
Flecainide (C01BC04)		No	Yes (UC)	Yes (UC)		Yes (UC)
Amiodarone (C01BD01)			Yes (C/VC)	Yes (C)		Yes (C)

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
Dronedarone (C01BD07) (is a multi-channel blocking anti-arrhythmics	-		No	No		No
Lipid modifying agents						
Bezafibrate (C10AB02)			Yes (UC)	NA		Yes (UC)
Gemfibrozil (C10AB04)			Yes (C)	Yes (C)		Yes (C)
Fenofibrate (C10AB05)			No	No		No
Ciprofibrate (C10AB08)			No	NA		No
Lomitapide (C10AX12)			Yes (C/VC)	Yes (C/VC)		Yes (C/VC)
Acipimox (C10AD06)			No	NA		No
Ezetimibe (C10AX09)			Yes (UF)	Yes (UF)		Yes (UF)
Omega-3 ethyl ester (C10AX06)			Yes (C/VC)	Yes (C)		Yes (C)
Evolocumab (C10AX13)			No	No		No
Alirocumab (C10AX14)			No	No		No
Statins (HMG CoA reductase inhibitors)						
Simvastatin (C10AA01)	Yes (C/VC)		-	Yes (R)		Yes (R)
Pravastatin (C10AA03)	Yes (C/VC)		-	Yes (UC)		Yes (UC)
Fluvastatin (C10AA04)	Yes (C/VC)		-	No	Yes (445)	Yes
Atorvastatin (C10AA05)	Yes (C/VC)		-	Yes (C)		Yes (C)
Rosuvastatin (C10AA07)	Yes (C/VC)		-	Yes (C)		Yes (C)
Pitavastatin (C10AA08)	Yes (C/VC)		NA	Yes (C)		Yes (C)
Anticonvulsant						
Phenobarbital (N03AA02)	-	No	No	No		No

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
Primidone (N03AA03)	-	No	No	No		No
Phenytoin (N03AB02)	-		Yes	Yes		Yes
Fosphenytoin (N03AB05)			Yes (UF)	Yes (UF)		Yes (UF)
Ethosuximide (N03AD01)			No	No		No
Clonazepam (N03AE01)			No	No		No
Carbamazepine (N03AF01)			Yes (UC)	Yes (UC)		Yes (C)
Oxcarbazepine (N03AF02)			Yes (C/VC)	Yes (C)		Yes (C)
Rufinamide (N03AF03)			Yes (C/VC)	Yes (C)		Yes (C)
Eslicarbazepine (N03AF04)			Yes (UC)	Yes (UC)		Yes (UC)
Valproic acid (N03AG01)			No	No		No
Vigabatrin (N03AG04)			No	No		No
Tiagabine (N03AG06)			No	No		No
Lamotrigine (N03AX09)			No	No		No
Topiramate (N03AX11)			Yes (C/VC)	Yes (C)		Yes (C)
Gabapentin (N03AX12)			Yes (C/VC)	Yes (C)		Yes (C)
Levetiracetam (N03AX14)			No	No		No
Zonisamide (N03AX15)			Yes (C/VC)	Yes (C)		Yes (C)
Pregabalin (N03AX16)			Yes (C/VC)	Yes (C)		Yes (C)
Lacosamide (N03AX18)			Yes (C/VC)	Yes (C)		Yes (C)
Perampanel (N03AX22)			No	No		No
Brivaracetam (N03AX23)			Yes (C/VC)	Yes (C)		Yes (C)
Stiripentol (N03AX17)			No enough information	No		No
Retigabine (N03AX21)			No enough information	Yes (C)		Yes (C)

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
NSAIDs						
Acetylsalicylic acid (N02BA01) High doses			No	Yes		Yes
Indomethacin (M01AB01)			Yes	NA		Yes
Sulindac (M01AB02)			Yes	NA		Yes
Diclofenac (M01AB05)			Yes (R/VR)	Yes (VR)		Yes (VR)
Etodolac (M01AB08)			Yes	NA		Yes
Acemetacin (M01AB11)			Yes (R/VR)	NA		Yes (VR)
Aceclofenac (M01AB16)			Yes (UC)	Yes (UC)		Yes (UC)
Piroxicam (M01AC01)			Yes (C/VC)	Yes (C)		Yes (C)
Tenoxicam (M01AC02)			Yes (C/VC)	NA		Yes (C)
Meloxicam (M01AC06)			Yes (C/VC)	Yes (VC)		Yes (C)
Ibuprofen (M01AE01)			Yes (R/VR)	Yes (C)		Yes (C)
Naproxen (M01AE02)			Yes	Yes (C)		Yes (C)
Ketoprofen (M01AE03)			Yes (UC)	Yes (UC)		Yes (UC)
Dexketoprofen (M01AE17)			Yes (UC)	Yes (UC)		Yes (UC)
Fenoprofen (M01AE04)			Yes	NA		Yes
Flurbiprofen (M01AE09)			Yes (UF)	Yes (UC)		Yes (UC)
Tiaprofenic acid (M01AE11)			Yes	NA		Yes
Dexibuprofen (M01AE14)			Yes (R/VR)	NA		Yes (R)
Mefenamic acid (M01AG01)			Yes	Yes (less frequent)		Yes
Tolfenamic acid (M01AG02)			Yes	NA		Yes
Celecoxib (M01AH01)			Yes (UC)	No		Yes (UC)

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
Parecoxib (M01AH04) (selective cox2 inhibitor)			Yes (C/VC)	Yes (C)		Yes (C)
Etoricoxib (M01AH05)			Yes (C/VC)	Yes (C)		Yes (C)
Nabumetone (M01AX01)			Yes (C/VC)	Yes (C)		Yes (C)
Glucosamine (M01AX05)			Yes (C/VC)	Yes (C)		Yes (C)
Lornoxicam (M01AC05)	NA		NA	No		No
Antiparkinsonian						
Trihexyphenidyl (N04AA01)			Yes (antimuscarinic effect)	NA		Yes (C)
Benzatropine (N04AC01)			NA	NA		Yes
Biperiden (N04AA02)	NA		NA	Yes (VR)		Yes (VR)
Procyclidine (N04AA04)			Yes (C/VC) (antimuscarinic effect)	Yes (C)		Yes (C)
Orphenadrine (N04AB02)			Yes (UC) (antimuscarinic effect)	NA		Yes (C)
Levodopa (N04BA01) /levodopa and decarboxylase inhibitor (N04BA02): Co-beneldopa (Benserazide+levodopa) Co-careldopa (Carbidopa+ levodopa)		No	No Yes (UF)	No Yes (UC)		Yes (UC)
levodopa, decarboxylase inhibitor and COMT inhibitor (N04BA03)		No	Yes (C/VC)	Yes (C)		Yes (C)
Amantadine (N04BB01) (dopamine agonist)	-		Yes	NA	Yes (C)(446)	Yes(C)

	Reported Constipation as a class		Reported Constipation SPC			Conclusion
Drug (ATC code)	BNF (258)	HPRA(257)	BNF(258)	HPRA (257)	Other	
Bromocriptine (N04BC01, G02CB01)		Yes	Yes (C/VC)	Yes (C)		Yes (C)
Pergolide (N04BC02)			Yes	NA		Yes
Ropinirole (N04BC04)		Yes	No	Yes (C)		Yes (C)
Pramipexole (N04BC05)		Yes	Yes (C/VC)	Yes (C)		Yes (C)
Cabergoline (N04BC06, G02CB03)		Yes	Yes (C/VC)	Yes (C)		Yes (C)
Apomorphine (N04BC07)		Yes	No	No (inj)		No
Rotigotine (N04BC09)		Yes	Yes (C/VC)	No (inj)		Yes
Monoamine oxidase B inhibitors: Selegiline (N04BD01)			Yes (C/VC)	No		Yes (C)
Rasagiline (N04BD02)			No	Yes (C)		Yes (C)
Safinamide (N04BD03)			Yes (UC)	Yes (C)		Yes (C)
Dopaminergic agents: Tolcapone (N04BX01)		Yes	Yes (C/VC)	Yes (C)		Yes (C)
Entacapone (N04BX02)		Yes	Yes (C/VC)	Yes (C)		Yes (C)
Opicapone (N04BX04)			Yes (C/VC)	Yes (C)		Yes (C)
Tetrabenazine (N07XX06)			Yes (C/VC)	Yes (C)		Yes (C)

C/VC: common/ very common. R/VR: rare/ very rare. UC: uncommon. UF: unknown frequency. The underlined are medicines with anticholinergic properties

6. Appendix 6: Demographics of participants with Down syndrome in Wave 1 (n=144)*

Characteristic	Participants with Down syndrome (n=144, 19.9%) n (%)	Participants without Down syndrome (n=580, 80%) n (%)	p-value
Gender			
Male	65 (45)	258 (44.5)	0.88
Female	79 (55)	322 (55.5)	
Age, year			<0.001
40-49	77 (53.5)	182 (31.4)	
50-64	64 (44.4)	268 (46.2)	
65+	3 (2)	130 (22.4)	
Level of ID	(Missing =10)	(Missing =43)	0.02
Mild	20 (14.9)	138 (25.7)	
Moderate	73 (54.5)	242 (45)	
Severe/ Profound	41 (30.6)	157 (29.2)	
Type of residence			0.03
Independent/Family	27 (18.8)	93 (16)	
Community group home	63 (43.8)	199 (34.3)	
Residential care	54 (37.5)	288 (49.7)	
Chronic constipation	10 (7)	116 (20)	<0.001
Rome III criteria	-	-	-
Laxative use	39 (27)	234 (40.3)	0.003
On medicines that cause constipation	90 (62.5)	515 (88.8)	<0.001
On medicines that commonly cause constipation	85 (59)	500 (86.2)	<0.001
At least one condition contributed to constipation	102 (99)	466 (99.8)	0.24
Neurological diseases	42 (29.2)	221 (38)	0.04
Mental disorders	34 (24.6)	313 (56)	<0.001

*Missing cases =12.

7. Appendix 7: Demographics of participants with Down syndrome in Wave 2 (n=127)*

Characteristic	Participants with Down syndrome (n=127, 19.2%) n (%)	Participants without Down syndrome (n=536, 80.8%) n (%)	p-value
Gender			
Male	57 (45)	231 (43)	0.71
Female	70 (55)	305 (57)	
Age, year			<0.001
40-49	58 (45.7)	128 (24)	
50-64	65 (51.2)	272 (61.2)	
65+	4 (3)	136 (25.4)	
Level of ID	(Missing =11)	(Missing =39)	0.04
Mild	17 (14.7)	127 (25.6)	
Moderate	62 (53.4)	223 (45)	
Severe/ Profound	37 (32)	147 (29.6)	
Type of residence			0.11
Independent/Family	20 (15.7)	78 (14.6)	
Community group home	65 (51.2)	227 (42.4)	
Residential care	42 (33)	230 (43)	
Chronic constipation	40 (31.7)	215 (40.6)	0.06
Rome III criteria	43 (35.8)	201 (40.2)	0.37
Laxative use	39 (30.7)	237 (44.2)	0.005
On medicines that cause constipation	96 (75.6)	488 (91)	<0.001
On medicines that commonly cause constipation	92 (72.4)	479 (89.4)	<0.001
At least one condition contributed to constipation	84 (70)	441 (85.3)	<0.001
Neurological diseases	50 (43.5)	211 (41.2)	0.65
Mental disorders	34 (27.6)	298 (57.6)	<0.001

* Missing cases =14.

8. Appendix 8: Demographics of participants with Down syndrome in Wave 3 (n=93)*

Characteristic	Participants with Down syndrome (n=93, 17.3%) n (%)	Participants without Down syndrome (n=446, 82.7%) n (%)	p-value
Gender			
Male	44 (47.3)	187 (42)	0.34
Female	49 (52.7)	259 (58)	
Age, year			<0.001
40-49	21 (22.6)	43(9.6)	
50-64	69 (74.2)	268 (60)	
65+	3 (3.2)	135 (30.3)	
Level of ID	(Missing =6)	(Missing =43)	0.24
Mild	16 (18.4)	102 (24.7)	
Moderate	47 (54)	184 (44.6)	
Severe/ Profound	24 (27.6)	127 (30.8)	
Type of residence			0.16
Independent/Family	17 (18.3)	56 (12.6)	
Community group home	41 (44)	180 (40.4)	
Residential care	35 (37.6)	210 (47)	
Chronic constipation	42 (45.2)	200 (44.8)	0.95
Rome III criteria	36 (42.4)	178 (44)	0.78
Laxative use	29 (31.2)	211 (47.3)	0.004
On medicines that cause constipation	71 (76.3)	408 (91.5)	<0.001
On medicines that commonly cause constipation	69 (74.2)	404 (90.6)	<0.001
At least one condition contributed to constipation	79 (85)	388 (87)	0.59
Neurological diseases	43 (46.2)	192 (43)	0.57
Mental disorders	26 (28)	260 (58.4)	<0.001

*Missing cases =12.

9. Appendix 9: Down syndrome laxative users (n=39) versus Down syndrome laxative non-users (n=105) in Wave 1 IDS-TILDA

Characteristic	Down syndrome laxative users (n= 39) n (%)	Down syndrome laxative non-users (n=105) n (%)	p-value
Gender			
Male	13 (33.3)	52 (49.5)	0.08
Female	26 (66.7)	53 (50.5)	
Age, years			<0.001
40-49	11 (28.2)	66 (63)	
50-64	25 (64)	39 (37)	
65+	3 (7.7)	0 (0)	
Level of ID	(Missing =3)	(Missing =7)	0.007
Mild	2 (5.6)	18 (18.4)	
Moderate	16 (44.4)	57 (58.2)	
Severe/ Profound	18 (50)	23 (23.5)	
Type of residence			0.004
Independent/Family	1 (2.6)	26 (24.8)	
Community group home	17 (43.6)	46 (43.8)	
Residential care	21 (53.8)	33 (31.4)	
Chronic constipation	10 (25.6)	0 (0)	≤0.001
Rome III criteria	-	-	
ACB scores			
Zero	14 (35.9)	67 (63.8)	0.003
>zero	25 (64)	38 (36.2)	
On medicines that cause constipation			
Total	32 (82)	58 (55.2)	0.003
Categorised			
1-4	27 (84.4)	54 (93)	0.18
5+	5 (15.6)	4 (7)	
On medicines that <u>commonly</u> cause constipation			
Total	32 (82)	53 (50.5)	0.001
Categorised			
1-4	29 (90.6)	52 (98)	0.11
5+	3 (9.4)	1 (1.9)	

Characteristic	Down syndrome laxative users (n= 39) n (%)	Down syndrome laxative non-users (n=105) n (%)	p-value
Conditions that contributed to constipation	(Missing=6) 33 (100)	(Missing=35) 69 (98.6)	0.49
Neurological diseases	17 (43.6)	25 (23.8)	0.02
Mental disorders	(Missing=1) 13 (34.2)	(Missing=5) 21 (21)	0.10
Soft food / liquidised/thickened fluid	10 (25.6)	10 (9.5)	0.01

10. Appendix 10: Down syndrome laxative users (n=39) versus Down syndrome laxative non-users (n=88) in Wave 2 IDS-TILDA

Characteristic	Down syndrome laxative users (n= 39) n (%)	Down syndrome laxative non-users (n=88) n (%)	p-value
Gender			
Male	16 (41)	41 (46.6)	0.56
Female	23 (59)	47 (53.4)	
Age, years			0.09
40-49	14 (36)	44 (50%)	
50-64	25 (64)	40 (45.5)	
65+	0 (0)	4 (4.5)	
Level of ID	(Missing =2)	(Missing =9)	0.19
Mild	4 (10.8)	13 (16.5)	
Moderate	17 (46)	45 (57)	
Severe/ Profound	16 (43.2)	21 (26.6)	
Type of residence			0.001
Independent/Family	0 (0)	20 (22.7)	
Community group home	19 (48.7)	46 (52.3)	
Residential care	20 (51.3)	22 (25)	
Chronic constipation	28 (71.8)	12 (13.8)	≤0.001
Rome III criteria (Missing=7)	27 (73)	16 (19.3)	≤0.001
ACB scores			
Zero	17 (43.6)	44 (50)	0.50
>zero	22 (56.4)	44 (50)	
On medicines that cause constipation			
Total	33 (84.6)	63 (71.6)	0.11
Categorised			
1-4	27 (81.8)	59 (93.7)	0.07
5+	6 (18.2)	4 (6.3)	
On medicines that <u>commonly</u> cause constipation			
Total	32 (82)	60 (68.2)	0.17
Categorised			
1-4	28 (87.5)	58 (96.7)	0.09
5+	4 (12.5)	2 (3.3)	

Characteristic	Down syndrome laxative users (n= 39) n (%)	Down syndrome laxative non-users (n=88) n (%)	p-value
Conditions that contributed to constipation (Missing=12)	32 (86.5)	52 (62.7)	0.009
Neurological diseases	22 (59.5)	28 (36)	0.01
Mental disorders	15 (39.5)	19 (22.4)	0.050
Soft food / liquidised/thickened fluid	12 (30.8)	11 (12.5)	0.01

11. Appendix 11: Down syndrome laxative users (n=29) versus Down syndrome laxative non-users (n=64) in Wave 3 IDS-TILDA

Characteristic	Down syndrome laxative users (n= 29) n (%)	Down syndrome laxative non-users (n=64) n (%)	p-value
Gender			
Male	13 (44.8)	31 (48.4)	0.74
Female	16 (55.2)	33 (51.6)	
Age, years			0.45
40-49	6 (20.7)	15 (23.4)	
50-64	21 (72.4)	48 (75)	
65+	2 (7)	1 (1.6)	
Level of ID	(Missing =2)	(Missing =4)	0.01
Mild	3 (11)	13 (21.7)	
Moderate	11 (40.7)	36 (60)	
Severe/ Profound	13 (48)	11 (18.3)	
Type of residence			0.001
Independent/Family	0 (0)	17 (18.3)	
Community group home	11 (38)	30 (47)	
Residential care	18 (62)	17 (26.6)	
Chronic constipation	23 (79.3)	19 (29.7)	≤0.001
Rome III criteria (Missing=8)	18 (72)	18 (30)	≤0.001
ACB scores			
Zero	11 (38)	35 (54.7)	0.13
>zero	18 (62)	29 (45.3)	
On medicines that cause constipation			
Total	25 (86.2)	46 (72)	0.13
Categorised			
1-4	17 (68)	42 (91.3)	0.01
5+	8 (32)	4 (8.7)	
On medicines that <u>commonly</u> cause constipation			
Total	25 (86.2)	44 (68.8)	0.07
Categorised			0.03
1-4	21 (84)	43 (97.7)	
5+	4 (16)	1 (2.3)	

Characteristic	Down syndrome laxative users (n= 29) n (%)	Down syndrome laxative non-users (n=64) n (%)	p-value
Conditions that contributed to constipation	28 (96.6)	51 (79.7)	0.03
Neurological diseases	19 (65.5)	24 (37.5)	0.01
Mental disorders	9 (31)	17 (26.6)	0.72
Soft food / liquidised/thickened fluid	14 (48.3)	13 (20.3)	0.006

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