Drug Burden Index to Define the Burden of Medicines in Older Adults with Intellectual Disabilities: An Observational Cross-Sectional Study

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Summary

Aims: The Drug Burden Index (DBI) is a dose-related measure of anticholinergic and sedative drug exposure. This cross-sectional study described DBI in older adults with intellectual disabilities (ID) and the most frequently reported therapeutic classes contributing to DBI and examined associations between higher DBI scores and potential adverse effects as well as physical function.

Methods: This study analysed data from Wave 2 (2013/2014) of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA), a representative study on the ageing of people with ID in Ireland. Self- and objectively-reported data was collected on medication use and physical health, including health conditions. The Barthel Index was the physical function measure.

Results: The study examined 677 individuals with ID, of which 644 (95.1%) reported taking medication and 78.6% (n = 532) were exposed to medication with anticholinergic and/or sedative activity. 54.2% (n = 367) were exposed to high DBI score (≥1). Adjusted multivariate regression analysis revealed no significant association between DBI score and daytime dozing, constipation or falls. After adjusting for confounders (gender, age, level of ID, comorbidities, behaviours that challenge, history of falls), DBI was associated with significantly higher dependence in the Barthel Index (p = 0.002).

Conclusions: This is the first time DBI has been described in older adults with ID. Scores were much higher than those observed in the general population and higher scores were associated with higher dependence in Barthel Index activities of daily living.

What is already known about this subject

- The Drug Burden Index is a tool which quantitatively evaluates the exposure of an individual to medications with anticholinergic and sedative activity.
- Higher Drug Burden Index scores have been associated with poorer physical and cognitive function in community dwelling older people without intellectual disabilities.

What this study adds

- We evaluated Drug Burden Index in older adults with intellectual disabilities using data from a nationally representative study in Ireland.
- The Drug Burden Index of older people with intellectual disabilities is higher than that of the older general population, particularly the anticholinergic component, and this reflects the different pattern of multimorbidity of the intellectual disabilities population, in particular higher levels of mental health and neurological morbidities.
- Higher Drug Burden Index scores were significantly associated with having higher levels of dependence as measured by the Barthel Index after adjusting for relevant confounders.

Introduction

People with intellectual disabilities (ID) may be exposed to high levels of polypharmacy, including medicines with sedative and anticholinergic effects [1, 2]. People with ID become multimorbid with age and as a result they may be exposed to a high burden of medications [3]. This multimorbidity includes a high prevalence of mental health conditions (such as depression, schizophrenia, bipolar affective disorder and anxiety disorders), neurological disease (such as epilepsy and dementia) and gastrointestinal disease (such as gastro-oesophageal reflux disease and peptic ulcer disease) [4].

Medications with sedative and/or anticholinergic activity may have a significant negative impact on the health of older people. Sedative medications commonly produce adverse cognitive and psychomotor events, increased falls and fractures liability and daytime fatigue – effects which become clinically significant in those with additional risk factors for falls and cognitive impairment [5-10]. Use of medications with sedative effects has been associated with frailty and poorer performance in instrumental activities of daily living in older adults [11, 12].

Older adults in the general population can be particularly sensitive to medications with anticholinergic effects, and the classic adverse effects such as dry mouth, reduced gastric motility, blurred vision and sedation can be compounded in this population to produce difficulties in communication, constipation and falls [13, 14].

A high burden of medicines with anticholinergic properties has been reported in two-thirds of older adults with ID, with high levels of Anticholinergic Cognitive Burden (ACB) exposure in three in ten older adults with ID [1, 2]. In contrast, community-dwelling older adults without

ID have reported a total ACB exposure of 23% [13]. Use of neuroleptic and antipsychotic medication in the ID population have been reported at between 21 – 50%, while sedative exposure has been reported at between 10 – 24% [2, 15-18] and total exposure to central nervous system (CNS) agents has been reported as high as 60%, compared to 10 – 25% in the population without ID [19]. This burden in people with ID has been associated with a number of adverse effects, including chronic constipation and daytime drowsiness [1].

A number of alternative scales are available to quantify anticholinergic and sedative load separately. The ACB scale categorises medications as having absent (ACB Score 0), possible (ACB Score 1) or definite (ACB Score 2 or 3) anticholinergic properties [1]. The Sedative Load model classifies medications as primary sedatives (Group 1), drugs with sedation as a prominent side effect (Group 2), drugs with sedation as a potential adverse effect (Group 3) and drugs with no known sedative effect (Group 4) [20]. The Drug Burden Index (DBI) is a tool which quantitatively evaluates the burden of both anticholinergic and sedative medications on an individual. The DBI offers a dose-related measure of burden, unlike these other indices available, by taking into account the relationship between prescribed dose and the dose response curve. Scores from the relevant medications are added together to give a total DBI score for the individual [21, 22]. Associations between DBI scores and objective function measures have been analysed in order to identify the effect of these types of medications on cognitive and physical performance in older adults. A higher DBI score has been associated with a number of negative outcomes: poor cognitive and physical performance; reduced gait speed and grip strength; poorer performance in instrumental activities of daily living (IADLs); frailty; and falls [21-28].

The DBI can be tailored to evaluate appropriate prescribing in a number of settings, and has been validated internationally [22, 29]. The index includes a range of medications with sedative properties, offering a broader evaluation than previous research which only examined single classes of sedatives [11]. A recent systematic review identified the DBI as the most suitable tool for use in the evaluation of anticholinergic burden in longitudinal studies of older adults [30].

Failure to identify the side effects of anticholinergics in older people in the general population occurs due to reduced health expectations and misinterpretation of side effects as age related illness [13], a difficulty which is further compounded in the population with ID due to their additional difficulties in communication and diagnostic overshadowing [31, 32]. Even though people with ID have a high drug burden, there is a lack of research into specific measurement of drug burden of sedative and anticholinergic medicines and guidance for intervention in this population. Given evidence to date of high sedative and anticholinergic burden in older adults with ID, the aim of this study was to evaluate and describe the cumulative drug burden for older people with ID.

In Ireland, similar to the practice in other developed countries, current policy emphasises deinstitutionalisation of people with ID. This specifically aims to encourage movement from congregated settings (i.e. housing units of 10 or more people) into community housing alongside the general population. While community based models appear to achieve better outcomes for people with ID, loss of specialist medical services and greater utilisation of general primary care practices may mean the medical needs of people with ID as they age are not fully addressed [2, 33].

The primary objectives of this study were:

1) To create an inventory of medications with clinically significant anticholinergic and sedative activity for use in the study setting;
2) To determine the characteristics in an older population with ID that are associated with the drug burden measured by the DBI;
3) To describe the drug burden in older adults with ID and the most frequently reported therapeutic classes contributing to total burden;
4) To examine the association between drug burden and potential adverse effects (daytime dozing, chronic constipation and falls) and Barthel Index activities of daily living.

Methods

Study Population

The data for this study was drawn from Wave 2 (2013/2014) of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA); a large scale, nationally representative longitudinal study which examines the ageing of persons with ID. This study has been described in detail elsewhere [33, 34]. The National Intellectual Disability Database (NIDD) collates information for all people in the Republic of Ireland with an ID eligible for or receiving services and it provided the sampling frame for Wave 1 of the study. A total of 1,800 personal identification numbers (PINs) were randomly selected by staff at NIDD. An invitation pack was sent to each potential participant with a consent form. Whereby an individual was unable to provide consent independently, a family member/guardian could sign a letter of agreement for their family member to participate. Participants lived independently/with family, in community group homes or in residential settings. A total of 753 individuals participated in Wave 1 of the study (2009/2010). Participants were aged 40 years or older to account for the reduced life expectancy and presentation of older age conditions at a younger age in people with ID [35]. Approval for the study was granted by Faculty of Health Sciences Research Ethics Committee in Trinity College Dublin. In addition, local and/or regional ethical committee approval was granted from each service provider (n = 138).

All living Wave 1 participants (n = 719) were invited to participate in Wave 2 (2013/2014). The study population with available medication data was 677 (95.6%) (Figure 1).

Participants were invited to complete a Pre-Interview Questionnaire (PIQ) and these answers were confirmed in the face-to-face interview with a computer-assisted personal interview (CAPI). The PIQ contained a section on medication use. The design of this medication data

section was improved from Wave 1 to Wave 2 of the study to collect more consistent, accurate information on dose and frequency data. To further facilitate data capture, the PIQ was sent to each participant/carer one week in advance of interview to allow time to access medical files if necessary. In the majority of cases (92.8%; n = 628), this data was recorded by proxy (key worker or family member known to participants for at least six months).

Field researchers came from a variety of backgrounds but all had experience in working with people with ID. They were provided with three full training days in data collection and a further refresher day prior to beginning interviews. A pharmacist (MO'D) provided medication data capture training to all field researchers. Several interview styles were utilised – direct interview with the participant, assisted interview where a proxy assisted the participant and interview where questions were answered by a proxy only, with or without the participant present.

In addition, a health assessment was included to obtain objective physical health measures which included body mass index (BMI) and Lunar Achilles GE Quantitative Ultrasound (QUS) [33]. The health assessments were conducted separate from the main interview by a registered nurse in intellectual disability who was a researcher in the IDS-TILDA study. Each of the Wave 2 participants were invited to take part and to facilitate and support the individual's participation, adaptable and accessible materials and methods were developed. This component has been described in detail elsewhere, for further details see Burke et al., 2014, 2016a & 2016b [33, 36, 37].

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for cross-sectional studies were used [38, 39].

Medication Exposure

Participants/proxies were asked: “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)?”

The participant/proxy recorded their medication data by brand name/International Non-Proprietary Name (INN), dose, frequency, route of administration and date on which medicine was initiated in the PIQ.

Medications were categorised by Anatomical Therapeutic Chemical (ATC) code and verified by two pharmacists [40]. Medicines recorded for indications which were not regular (for example: treatments for pre-dental/medical procedures, pre-phlebotomy treatments, alternate month usage of antihistamines) were excluded from the calculations. As per previous studies, “as required” or “prn” medications were also excluded from DBI calculations because the contribution to the burden of anticholinergic and/or sedative activity from the intermittent use of these medications cannot be reliably estimated [21, 41, 42].

Medication Inventory of Sedative and Anticholinergic Medicines

Medications with clinically significant anticholinergic and/or sedative activity were identified by reference to relevant studies [1, 12, 20, 21, 25, 43] in addition to detailed examination of the licenced product information (Summary of Product Characteristics, SmPC) for the Republic of Ireland as available from the Health Products Regulatory Authority (HPRA)[44]. The final list of 258 medications (117 anticholinergic, 141 sedative) was decided upon by consensus by three pharmacists (MH, MOD & JOC) (Figure 2).

Table 1 represents a summary of the search terms used to identify sedative potential during review of the SmPC. The list of search terms which were used were modelled on those used in the Sedative Load Model: "sedating, sedative, drowsiness, sleepiness, lassitude, exhaustion, tiresome, fatigability."[20]

This inventory of medications was categorised according to the nature of the burden. Medications with both anticholinergic and sedative effects were classified primarily as anticholinergic as per previous studies [21, 23, 45, 46].

- Prochlorperazine was recoded from the ATC code N05AB04 (Antipsychotics) to A04A (Antiemetics and Antinauseants) as the dosages reported by this population exclusively fell within the total daily dosage range used for treatment of Ménière's syndrome, nausea and vomiting (10 – 40mg according to the Irish SmPC) as opposed to those indicated for psychotic episodes (75 – 100mg).
- Depot preparations administered less frequently than weekly (intramuscular flupentixol, fluphenazine, risperidone, zuclopenthixol) were also included due to their release profile.
- Topical products were excluded for the purposes of this analysis due to insignificant systemic effects. The only exception was ophthalmological atropine which was considered to have clinically significant systemic anticholinergic properties [47].
- Inhaled anticholinergic preparations (ipratropium and tiotropium) were excluded due to low prevalence of users (n = 11; 1.6%) and high proportion of missing dose information for these preparations (n = 7; 64%).

- Medicines for which the primary indication is acute seizure control (rectal diazepam, buccal midazolam) and migraine (sumatriptan), are used on an intermittent basis and were excluded as the DBI measures exposure to regularly used medications.

Calculation of Drug Burden Index

The accepted standard approach to calculation of the Drug Burden Index was utilized [21]. Scores were calculated for each individual according to the formula:

$$Total\ Drug\ Burden = B_{AC} + B_S$$

where B_{AC} indicates the anticholinergic burden and B_S indicates the sedative burden [21]. A model of pharmacological effect (E) was developed which assumes that the anticholinergic and sedative burdens of individual drugs are additive linearly:

$$\frac{E}{\alpha} = \sum \frac{D}{D + DR_{50}}$$

α is a proportionality constant, D is the daily dose and DR_{50} is the daily dose to achieve 50% of maximal contributory effect at steady state [22]. As the DR_{50} of anticholinergic and sedative activity is not easily identifiable, the Minimum Daily Dose (MDD) is used as a substitute. MDDs were selected based on the lowest effective daily dose listed in the Irish medicinal product authorisation from the HPRA.

The final version of the DBI calculation is as follows:

$$Drug\ Burden\ Index = \sum \frac{D}{\delta + D}\ [21]$$

where δ is the MDD.

DBI scores for participants were calculated as a continuous variable and then transformed into a categorical variable with three levels: DBI score 0 (no DBI exposure), DBI score 0 > 1

(low) and DBI score ≥1 (high). This reflects the categories used elsewhere in the literature [21, 23-28, 42, 48, 49].

Missing Dose Information

When dose information was missing for a medication (n = 43), a median dosage figure was used. This is consistent with the strategy used in preceding DBI studies [21, 23, 24, 26]. For one medication (diphenhydramine), no median dose was available, therefore the MDD was substituted.

Physical Function Measure

The Barthel Index is a measure of assessing disability in those receiving rehabilitation for neuromuscular and musculoskeletal conditions and has become a reliable method of measuring function in older populations. It consists of an ordinal scale of ten instrumental activities of daily living (range 0 – 20) [50, 51]. It takes into account the level of dependence an individual has with regard to mobility, using stairs, dressing, bathing, grooming, feeding, transfer, toileting and bladder and bowel continence. A modified form of Barthel Index activities of daily living was created for this population (Supporting Information Table S1). Each participant was given a composite score between 0 and 20 based on their self-/proxy-report of difficulty experienced with each activity. Lower scores indicated poorer physical function. Barthel Index scores were categorised as per Wade & Collin (1988) classifications: total dependence (0 – 4), severe dependence (5 – 12), moderate dependence (13 – 18), mild dependence (19) and total independence (20) [52].

Participants with two or more missing values (i.e., those who answered "don't know", gave an unclear response or preferred not to answer) were excluded from the Barthel Index evaluation (n = 42). This method of handling missing data was as per a previous study [53].

Covariates

Demographic Characteristics: Covariates were gender, age range (44 – 49 years; 50 – 64 years; 65+ years), level of ID (mild; moderate; severe/profound), type of residence (independent, community group home, residential care) and behaviours that challenge (yes/no).

Level of ID is correlated by intelligence quotient (IQ) scores as follows; mild (50 – 55 to approx. 70), moderate (35 – 40 to 50 – 55) and severe/profound (below 35 - 40) and correct classification was obtained from case notes for each participant [54]. Those with unverified level of ID (n = 53) were excluded from regression analysis.

Community group homes are in a community setting with staff support for small groups of people with ID. Residential settings were defined as living arrangements where ten or more people share a single living unit or where the living arrangements are campus based.

Behaviours that challenge were defined as any behaviour which "(1) is a barrier to a person participating in and contributing to their community (including both active and passive behaviours); (2) undermines directly or indirectly a person's rights, dignity or quality of life, and (3) poses a risk to the health and safety of a person and those with whom they live and work" [55]. Behaviours that challenge were measured by response to a question on verbal aggression, physical aggression, destructive behaviour, self-injurious behaviour or other behaviours that challenge. A more detailed description of the definition of behaviours that challenge is available in Supplementary Information Description SD1. Behaviours that

challenge were included as a covariate to adjust for potential confounding by indication due to evidence which already exists in the literature reporting the extensive use of psychotropic medication in the management of behaviours that challenge in the ID population [18, 56-58].

Potential adverse effects: Three potential adverse effects were selected for assessment due to previous associations identified in the general population in DBI studies and in Anticholinergic Cognitive Burden (ACB) studies of older adults with ID [1, 27].

1) *Daytime dozing:* This was identified by asking participants and/or proxies "How likely are you to doze off and fall asleep during the day?" Where a participant answered "most of the time" or "sometimes", they were considered to have daytime dozing (yes), while "rarely" and "never" indicated no daytime sleep problem (no) [59].
2) *Chronic constipation:* Participants/proxies were asked "have you ever had a doctor's diagnosis of chronic constipation?" to which they answered "yes", "no" or "don't know".
3) *Fall in the previous 12 months:* Participants/proxies were asked "in the past year have you had any fall including a slip or trip in which you lost your balance and landed on the floor or ground or lower level?" to which they answered "yes", "no" or "don't know".

Functional Comorbidity Index: A modified Functional Comorbidity Index (FCI) (Supporting Information Table S2) was developed for the population and provided a continuous score between 0 and 16 by summing the presence of a reported doctor's diagnosis (in response to the question "have you ever had a doctor's diagnosis of…") for the following conditions: arthritis; osteoporosis/osteopenia (self-/proxy-report of doctor's diagnosis and/or objective

evidence from QUS); asthma; lung disease; angina; congestive heart failure (or heart disease); myocardial infarction; neurological disease; stroke or transient ischaemic attack; diabetes mellitus type I or II; upper gastrointestinal disease (e.g. ulcer, hernia, reflux); depression (unipolar or bipolar); anxiety or panic disorder; visual impairment (e.g., cataracts, glaucoma, macular degeneration); hearing impairment; overweight/obese (data obtained from health assessment). Similar modified versions of the FCI have been used in a number of previous DBI studies adapted for the populations being studied [24, 27, 45, 46, 60]. Participants with two or more missing conditions were excluded from the FCI score evaluation, reflecting the method used in a previous study [53]. Table 4 (multivariate regression analysis) and Figure 3 (analysis of covariance for Barthel Index) were adjusted for comorbidities using the FCI.

Polypharmacy: This was measured as a categorical variable. Definitions were as follows:

- *Excessive polypharmacy:* Concurrent use of ten or more different drugs.
- *Polypharmacy:* Use of five to nine drugs.
- *No polypharmacy:* Use of four or less drugs (included those taking no medicines)[2].

Statistical Analyses

Analyses were performed using Microsoft Excel 2010 (Microsoft Corporation) and Statistical Package for Social Sciences (SPSS) version 21.0 (IBM Corporation). Statistical significance was set at $p < 0.05$.

Descriptive statistics (percentages and 95% confidence intervals) described the characteristics of the study populations. Medians and interquartile range (IQR) were reported as the data was not normally distributed. Univariate analysis was used to examine the associations between the three DBI levels (0, 0 > 1, ≥1) (the dependent variable) and the demographic and

clinical variables. For the categorical variables, chi-squared (χ^2) tests for independence were used to test for significant associations between the three DBI levels.

Multinomial logistic regression was carried out to identify the relationship between DBI scores of 0 > 1 and ≥1 and potential adverse effects. The reference category was set as those with DBI score = 0. The model was adjusted for demographic variables – age, gender, level of ID, type of residence, behaviours that challenge, comorbidities (FCI) and number of non-DBI medicines; potential adverse effects included were daytime dozing, chronic constipation and fall in the previous 12 months. Those with unverified level of ID (n = 53) were excluded from the regression analysis. Those living independently (n = 102) or in community group homes (n = 298) were combined as a single group (n = 400) due to small numbers in the subgroups.

To test for multicollinearity between the independent factors, two strategies were employed. Variance Inflation Factors (VIF) and Spearman's correlation coefficients of the independent variables were examined. A VIF cut-off of >2 was employed [61]. If the VIF for one of the variables is greater than 2, there is collinearity associated with that variable. All VIFs were below the threshold of 2. Spearman's correlation coefficients were interpreted using Dancy and Reidy's categorisation [62]. Here, correlations of ±1 are interpreted as a perfect correlation, values between ±0.7 to ±0.9 are interpreted as strong correlations, values in the range ±0.4 to ±0.6 are categorized as moderate correlations, values between ±0.1 to ±0.3 are weak correlations and a value of 0 is zero correlation, implying there is no correlation. All of the correlations fell below 0.4, indicating only weak correlations and thus not of concern.

Analysis of covariance (ANCOVA) was used to compare the adjusted mean of the continuous variable for the Barthel Index between subjects exposed to three different levels of Drug Burden Index ranges (means were adjusted for gender, age, level of ID, behaviours that challenge, comorbidities (FCI) and history of falls). This reflected the practice used in a similar study of DBI and physical function measures [24].

Sample size calculation for the logistic regression was based on the guideline of Peduzzi et al [63], (for a minimum number of cases (N) needed for the study; N = 10k/p, where p is the smallest of the proportions of negative or positive cases in the population and k is the number of covariates (independent variables) [63]. For the multinomial logistic regression, there were 10 covariates and the proportion of negative cases (DBI 0) was 0.21, therefore a minimum sample size (N) of 476 was needed, which our sample size (n = 484) exceeded.

Missing Data

Missing data for the Barthel Index and Functional Comorbidity Index analyses are described in Supporting Information Table S3. Higher rates of missing data were observed in those with mild level of ID (26.8%; n = 40), those living in independent settings (32.4%; n = 33) and those in the younger age group (44 – 49 years; 24.6%; n = 46) for the Functional Comorbidity Index. Less data was missing overall for Barthel Index and the profile was slightly different, with more people with moderate ID (7.0%; n = 20), living in community group homes (7.7%; n = 23) and in the older age group (65+ years; 7.7%; n = 11) missing Barthel Index scores.

Results

Of the 708 participants who partook in Wave 2, 677 (95.6%) had available medication data. Of the study population (n = 677), 56.1% (n = 380) were female and 44.1% (n = 298) lived in a community group home (Table 2). The median number of medications per participant was 6.00 (IQR 6.00). Of the 677 participants, 95.1% (n = 644) reported taking medicines. Overall, 78.6% (n = 532) of the population were exposed to medications with anticholinergic and/or sedative effects (DBI Score > 0) and the median number of DBI medications was 2.00 (IQR 3.00) (Table 2). 51.3% (n = 347) of participants were exposed to anticholinergic medications only and 32.1% (n = 217) were exposed to sedative medications only. Median number of comorbidities (FCI) was 3.00 (IQR 2.00) and 41.2% (n = 264) of participants reported having neurological disease. With respect to potential adverse effects, 34.9% (n = 232) reported daytime dozing, 38.4% (n = 257) reported chronic constipation and 28.5% (n = 190) reported having a fall in the previous 12 months. 52.0% (n = 352) reported behaviours that challenge. Level of polypharmacy was high, with 62.2% (n = 421) reporting taking 5 or more medications. 21.4% (n = 145) of participants had no exposure to anticholinergic or sedative medications (DBI score = 0), while 24.4% (n = 165) had a DBI score 0 > 1 and 54.2% (n = 367) had a score of 1 or higher.

Table 3 displays the exposure of participants to at least one member of the individual therapeutic drug classes in descending order and classified by anticholinergic or sedative status. Overall, 44% (n = 298) of participants were exposed to one or more antipsychotic medications with risperidone being most common (15.7%, n = 106). The most commonly reported sedative class was the ATC class N05C (Hypnotics and Sedatives), and the most commonly reported drug within this class was zopiclone, which 2.8% (n = 19) of the

participants reported taking on a regular basis. Valproic acid was the most commonly reported drug overall, with 19.4% (n = 131) of participants exposed to this medication. Other therapeutic classes reported by <5% in decreasing prevalence included in Supporting Information Table S4.

Supporting Information Table S5 displays the univariate analysis of DBI score and specific population parameters.

Multivariate regression analysis of the relationship between DBI scores and potential adverse effects (Table 4), adjusted for gender, age, type of residence, level of ID, behaviours that challenge, comorbidities (FCI) and number of non-DBI medicines, revealed that daytime dozing, chronic constipation and history of falls were not significantly associated with DBI score > 0 ($p = 0.764$ & 0.094; $p = 0.486$ & 0.102; $p = 0.168$ & 0.731, respectively).

Figure 3 displays adjusted means for Barthel Index activities of daily living.

Significantly lower scores in Barthel Index activities of daily living were identified for those with a DBI score of ≥1 ($p = 0.002$; mean score 12.4, 95% CI 11.7 – 13.0) compared to those with DBI 0 (mean score 14.5, 95% CI 13.4 – 15.6) after adjusting for cofounders (gender, age, level of ID, comorbidities (FCI), behaviours that challenge and history of falls). There was also significant difference in performance for those with a DBI score of 0 > 1 ($p < 0.001$; mean score 14.6, 95% CI 13.6 – 15.6) compared to those with no DBI exposure.

Discussion

Principal findings

To our knowledge this is the first study to describe Drug Burden Index in a representative population of older adults with an intellectual disability. Our findings reveal that in contrast to existing studies on older adults without ID, older people with ID had higher cumulative exposure to both sedative and anticholinergic medicines; over three-quarters of the study population were exposed to at least one anticholinergic or sedative medication (DBI Score > 0) (Table 2). This reflects the higher levels of multimorbidity in this population, in particular mental health and neurological morbidity [4]. After adjusting for confounders, multivariate analysis identified that daytime dozing, chronic constipation and history of falls were not significantly associated with DBI score ($p > 0.05$, Table 4). Analysis of covariance identified higher levels of dependence in Barthel Index activities of daily living as DBI scores increased ($p < 0.05$, Figure 3).

Comparison with other studies

The magnitude of the DBI scores were much higher in our study than in published studies of older adults in the general population (Supporting Information Table S6). Patterns of mutimorbidity in people with ID differ substantially from those in people without ID [3, 64]. In particular, depression rates varied between 9 – 22% in older adults without ID in preceding DBI studies, while lifetime prevalence was reported at 28% in IDS-TILDA participants. Patterns of neurological disease were also different. Epilepsy was the predominant neurological condition in IDS-TILDA (36%) [33], levels of epilepsy are higher in people with ID compared to those in the general population [65]. Other DBI studies most commonly reported dementia

or cognitive impairment [24, 26, 27, 46, 48, 53, 60, 66] both of which are difficult to assess in people with ID (Supporting Information Table S6).

As a result, there is a noticeable contrast in exposure and contributing therapeutic classes observed in those with ID compared to older adults without ID. Antipsychotic and antiepileptic medicines are most prevalent in our cohort (44% and 42%, respectively, Table 3) and are frequently associated with anticholinergic effects [1], while only between 1 – 10% of participants in previous DBI studies of older adults have reported exposure to antipsychotics and 2% reported exposure to antiepileptics. [24, 27]. In the population without ID, sedative exposure was higher in two of the five studies while anticholinergic exposure was substantially lower compared to the anticholinergic burden (51%) in this population (Supporting Information Table S6).

Prevalence of therapeutic drug classes

Antiepileptic medications (ATC N03A) accounted for over one-quarter of the overall burden (Table 3), in contrast to studies of drug burden in the existing literature which do not report antiepileptic medication as a significant contributor to drug burden [21, 23-28, 42, 48, 49]. In addition to causing anticholinergic and sedative effects, antiepileptic medications also require careful monitoring and have the potential to introduce other clinical implications, including drug-drug interactions [67]. Multiple antipsychotic use is prevalent in this population and anticholinergics such as biperiden are often co-prescribed for movement disorders [1] and these add significantly to the anticholinergic burden along with antidepressants and anxiolytics (Table 3). The concurrent use of antipsychotics and anticholinergics requires caution [68] and has been associated with constipation and laxative use [1] in an earlier wave of this cohort. Hypnotics and sedatives were the dominant component of the sedative burden

(7.1% of population exposed) while anti-dementia drugs were less prevalent (3.4%). However, with drugs from 38 therapeutic classes (Table 3 and Supporting Information Table S4) contributing to the DBI scores of the participants, the sources of the burden reflect the diverse range of drugs used in people with ID [64].

Potential adverse effects and drug burden

Although levels of daytime dozing were high (35%), it was not significantly associated with DBI score after adjusting for confounding factors (DBI 0 > 1, p = 0.764; DBI ≥1, p = 0.094, Table 4). The effect of medications on sleep in adults with ID not clear cut. It has been reported that the circadian sleep-wake rhythm in older adults with ID is less stable and more fragmented than older adults without ID. Higher age, dementia, depression and epilepsy have been associated with this disturbed sleep cycle, while no independent association was found with taking antiepileptic, antidepressant, antipsychotic or benzodiazepine medications [69]. In contrast, a systematic review of sleep disturbance in ID identified a number of studies which found associations between medication use and sleep problems [70]. These studies, however, examined early morning waking, broken sleep, snoring and nocturnal incontinence rather than daytime dozing. As sleep patterns are different in this population and a number of different factors may be influencing levels of daytime sedation, and since the DBI combines sedative and anticholinergic measures, it is not surprising that a conclusive association was not found. Further investigation is required to examine associations between DBI, its sedative and anticholinergic components and other measures of sleep quality in this population.

After adjusting for confounders, we identified no association between chronic constipation and higher DBI scores (DBI 0 > 1, p = 0.486; DBI ≥1, p = 0.102, Table 4). However, it is noteworthy that almost nine in ten of those reporting constipation were exposed to anticholinergic and/or sedative medication, and almost two-thirds had a DBI score of ≥ 1 (Supporting Information Table S5). Overall there is a high prevalence of constipation among the population with ID (38%). Although the cause of constipation is multifactorial, it is acknowledged that medications with anticholinergic action contribute to constipation in older people [71]. It has been found that medications are strongly associated with the presence of constipation in older adults with ID, in particular antiepileptic medications and antipsychotic medications, due to slowing down the transit times of the large bowel as a result of their anticholinergic activity [1, 72]. People reporting constipation generally also report lower health-related Quality of Life [73-75], thus the impact of the anticholinergic medication component of the DBI should not be underestimated in this area.

History of falls was not significant after multivariate regression in our population of older adults with ID (DBI 0 > 1, p = 0.168; DBI ≥ 1, p = 0.731, Table 4), which is in contrast to the findings of DBI studies in older adults without ID [27, 49]. It is possible that the susceptibility to falls from anticholinergic and sedative medications may be different in older adults with ID as the long-term use of these medications in this population may result in the absence of the "starting effect" which has been associated with falls in adults who commence these types of medications later in life [76]. The susceptibility to anticholinergic and/or sedative effects may vary with age and with the cause of ID and pattern of multimorbidity in this cohort. In addition, seizure disorders have been identified as one of the major risk factors for falls in adults with ID [77, 78], thus antiepileptic medications, despite being anticholinergic and

sedative in nature, may provide seizure control which could affect the relationship between DBI and rate of falls differently to that observed in the general population. Individuals with higher dependency and/or multimorbidity may be monitored more closely for falls and risk of falls, or may be immobile due to factors such as poor health and level of disability.

It is worth noting that confidence intervals across all the categories were quite wide, thereby indicating there was still wide variation remaining after adjusting for confounding factors.

Factors associated with drug burden and physical function measures

Higher Drug Burden Index scores were significantly associated with higher levels of dependency in Barthel Index activities of daily living after adjusting for relevant confounders including level of ID in this study ($p < 0.05$, Figure 3). This is similar to the findings of a study of DBI and instrumental activities of daily living in older Australian men [24]. Compared to older adults without ID, people with ID may have lower scores in the Barthel Index which in turn may further be affected by Drug Burden Index. However as this is a cross-sectional study it is not possible to establish causality, but with repeated assessments over several waves of the cohort further analysis will be possible.

Impact of findings on practice

Difficulties in patient assessment, including, but not limited to, problems with communication, staff shortages and time constraints, can hinder care and leave individuals with ID vulnerable to prescribing that is not regularly reviewed, the “prescribing cascade” or initiation of inappropriate drugs [31]. Devolving responsibility and fragmentation of care have been identified as barriers to de-prescribing anticholinergic and sedative medications in older

adults without ID [79]. This is particularly relevant to older people with ID, due to the variety of medical conditions experienced. Higher rates of epilepsy, as outlined above, require the attention of specialist care, but unless there is adequate multidisciplinary involvement in review, de-prescribing cannot take place, as general practitioners feel specialist prescribers must conduct the de-prescribing and vice versa [79, 80].

People with ID in older age profile may experience different susceptibility to certain adverse effects of anticholinergic and sedative medications compared to the general population. A recent study in the United Kingdom found people with ID are more likely to experience movement-related side effects from antipsychotic medications [81]. The effect of the drug burden itself may compromise individuals who have difficulties expressing their symptoms and whose expression of adverse drug effects may be limited. This may make it more challenging for carers and clinicians to assess and monitor these patients effectively. Therefore, the DBI tool offers a valuable tool to review these medications regimens [82].

The association of drug burden with poor performance in Barthel Index activities of daily living indicates the potential impact this burden has on the quality of life of older adults with intellectual disabilities. Further longitudinal examination of this burden is necessary. Evidence here should encourage greater attention to reducing polypharmacy, selection of alternative treatment options and finding means to systematically reduce sedative and anticholinergic drug burden.

Recognition of the impact of anticholinergic and sedative medications on physical and cognitive function, collaboration between patients, carers and healthcare professionals and reaction to de-prescribing “triggers” have all been acknowledged as facilitators for optimising

medication use in people without ID [79]. Indeed, targeted de-prescribing of drugs with anticholinergic and sedative effects is already underway in the older age population without ID, guided by the DBI [83].

While regular medication reviews are part of good case management, this is a population for whom review is often inhibited by difficulties in communication, high levels of morbidity and polypharmacy and utilisation of numerous specialist and non-specialist prescribers. The DBI could be a screening tool to trigger medication review for older adults with ID. It can alert the prescriber to the existing status of the individual, make them mindful of the current burden, trigger a more frequent review of medications, allow for possible rationalisation of therapy, and inform further prescribing.

The potential of the DBI tool as a trigger for de-prescribing, and an enabler for medication review of people with ID, who often cannot speak for themselves, should be investigated. Dissemination of the findings of this study, education of professionals, patients and carers in optimising the use of anticholinergics and sedatives, encouraging the identification of adverse effects from these medicines and recognising the absence of symptoms can contribute to the optimising of medication use in this population. Longitudinal follow-up is required to fully establish the association of DBI with this population, as this study provides only baseline data which may be further investigated in future waves of the study.

Strengths and limitations

Our study has five important strengths. First, the use of a large, nationally representative sample of older adults with intellectual disabilities which was selected at random in Ireland allowed sufficient power for multivariate analysis and is representative of the older

population with ID in Ireland. Second, comprehensive medication data was recorded for the majority of Wave 2 participants (95.6%) and this medication data was cross-checked by interviewers. While collection of medication data was carried out by non-pharmacists, the training provided by a pharmacist (MO'D) and design of the medication data section facilitated high quality data capture. Participants and/or their proxies received the medication data section in advance of the face-to-face interview, allowing time to consult medical files to accurately capture this information. Third, detailed assessment of health characteristics provided data on potential confounding factors for our analysis. Fourth, we used the Drug Burden Index, which is a score that has been validated across a number of studies internationally and is a robust measure of anticholinergic and sedative drug effects. It also takes into account the dose each participant is exposed to, which is useful as adverse effects may often be dose-related. A comprehensive approach was utilised to create the Drug Burden Index inventory for use in an Irish population, and this list was both developed and approved by consensus of three pharmacists. Fifth, objective measures of physical performance were selected for examining physical function outcomes.

There are a number of limitations; as this is a cross-sectional observational study, we can only describe the associations between Drug Burden Index scores, potential adverse effects and physical function outcomes. This correlation does not imply causality, particularly with respect to physical function. While it is not possible to establish the effect of DBI scores on functional decline at present, this study offers the scope for further longitudinal analysis of data from IDS-TILDA by identifying the baseline levels of exposure and function in this population.

Although bias was removed where possible in our multivariate analysis by making adjustment for confounders, residual confounding factors may remain.

With respect to the multivariate regression and Barthel Index measure of dependency, it should be noted that the numbers of participants with all information available is restricted to 70% of the overall population due to missing data of participants who were unable to complete these elements of the interview. Thus, interpretation of this data should be conservative as it may not be fully representative of the entire population. The highest rates of missing data were observed in those with mild/moderate level of ID and those living independently or in community group homes.

In conclusion, this study has highlighted extensive use of medications with both anticholinergic and sedative properties in older adults with intellectual disabilities. This is the first time a study has examined the combined anticholinergic and sedative exposure of a cohort of people with ID. In addition, this high burden has been shown to have an association with higher dependency in Barthel Index activities of daily living. Use of the Drug Burden Index as a tool for clinicians could help guide prescribing practice and multidisciplinary involvement would be essential for the development of optimal medicine regimens and improvement of health outcomes for older adults with ID.

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Conflicts of Interest

None declared.

Contributors

JOC, EB, NM, COD, CD, PM, MM, MCH and MOD contributed to the overall conception and design of the study. JOC and CD undertook the data extraction. JOC and MOD carried out the statistical analyses of the study; JOC wrote the first draft of this manuscript. MOD, PM, MM, COD, CD, NM, EB and MCH revised the manuscript. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the interpretation of results and drafting of this manuscript. All authors read and approved the final manuscript. JOC and MM are the guarantors.

References:

1. O'Dwyer M, Maidment ID, Bennett K, Peklar J, Mulryan N, McCallion P, McCarron M, Henman MC. Association of anticholinergic burden with adverse effects in older people with intellectual disabilities: an observational cross-sectional study. Br J Psychiatry 2016; 209: 1 - 7.

2. O'Dwyer M, Peklar J, McCallion P, McCarron M, Henman M. Factors associated with polypharmacy and excessive polypharmacy in older people with intellectual disability differ from the general population: a cross-sectional observational nationwide study. BMJ Open 2016; 6.

3. Santosh PJ, Baird G. Psychopharmacotherapy in children and adults with intellectual disability. Lancet 1999; 354: 233-42.

4. McCarron M, Swinburne J, Burke E, McGlinchey E, Carroll R, McCallion P. Patterns of multimorbidity in an older population of persons with an intellectual disability: results from the intellectual disability supplement to the Irish longitudinal study on aging (IDS-TILDA). Res Dev Disabil 2013; 34: 521-7.

5. Glass J, Lanctôt KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ 2005; 331.

6. Weiner DK, Hanlon JT, Studenski SA. Effects of Central Nervous System Polypharmacy on Falls Liability in Community-Dwelling Elderly. Gerontology 1998; 44: 217-21.

7. Rubenstein LZ. Falls in older people: epidemiology, risk factors and strategies for prevention. Age Ageing 2006; 35-S2: ii37-ii41.

8. Johnell K, Fastbom J. Gender and use of hypnotics or sedatives in old age: a nationwide register-based study. Int J Clin Pharm 2011; 33: 788-93.

9. Levy HB. Non-benzodiazepine hypnotics and older adults: what are we learning about zolpidem? Expert Rev Clin Pharmacol 2014; 7: 5-8.

10. Vestergaard P, Prieto-Alhambra D, Javaid MK, Cooper C. Fractures in users of antidepressants and anxiolytics and sedatives: effects of age and dose. Osteoporos Int 2013; 24: 671-80.

11. Gnjidic D, Le Couteur DG, Hilmer SN, Cumming RG, Blyth FM, Naganathan V, Waite L, Handelsman DJ, Bell JS. Sedative load and functional outcomes in community-dwelling older Australian men: the CHAMP study. Fundam Clin Pharmacol 2014; 28: 10-9.

12. Peklar J, O'Halloran AM, Maidment ID, Henman MC, Kenny RA, Kos M. Sedative Load and Frailty Among Community-Dwelling Population Aged ≥65 Years. J Am Med Dir Assoc 2015; 16: 282-89.

13. Mintzer J, Burns A. Anticholinergic side-effects of drugs in elderly people. J R Soc Med 2000; 93: 457-62.

14. Feinberg M. The Problems of Anticholinergic Adverse Effects in Older Patients. Drugs & Aging 1993; 3: 335-48.

15. Molyneux P, Emerson E, Caine A. Prescription of Psychotropic Medication to People with Intellectual Disabilities in Primary Health-care Settings. J Appl Res Intellect Disabil 1999; 12: 46-57.

16. de Kuijper G, Hoekstra P, Visser F, Scholte FA, Penning C, Evenhuis H. Use of antipsychotic drugs in individuals with intellectual disability (ID) in the Netherlands: prevalence and reasons for prescription. J Intellect Disabil Res 2010; 54: 659-67.

17. Stolker JJ, Koedoot PJ, Heerdink ER, Leufkens HG, Nolen WA. Psychotropic drug use in intellectually disabled group-home residents with behavioural problems. Pharmacopsychiatry 2002; 35: 19-23.

18. Robertson J, Emerson E, Gregory N, Hatton C, Kessissoglou S, Hallam A. Receipt of psychotropic medication by people with intellectual disability in residential settings. J Intellect Disabil Res 2000; 44: 666-76.

19. Chitty KM, Evans E, Torr JJ, Iacono T, Brodaty H, Sachdev P, Trollor JN. Central nervous system medication use in older adults with intellectual disability: Results from the successful ageing in intellectual disability study. Aust N Z J Psychiatry 2016; 50: 352-62.

20. Linjakumpu T, Hartikainen S, Klaukka T, Koponen H, Kivelä S-L, Isoaho R. A model to classify the sedative load of drugs. Int J Geriatr Psychiatry 2003; 18: 542-45.

21. Hilmer SN, Mager DE, Simonsick EM, Cao Y, Ling SM, Windham G, Harris TB, Hanlon JT, Rubin SM, Shorr RI, Bauer DC, Abernethy DR. A Drug Burden Index to Define the Functional Burden of Medications in Older People. Arch Intern Med 2007; 167: 781-87.

22. Kouladjian L, Gnjidic D, Chen TF, Mangoni AA. Drug Burden Index in older adults: theoretical and practical issues. Clin Interv Aging 2014; 9: 1503-15.

23. Hilmer SN, Mager DE, Simonsick EM, Ling SM, Windham BG, Harris TB, Shorr RI, Bauer DC, Abernethy DR. Drug burden index score and functional decline in older people. Am J Med 2009; 122: 1142-49.e1-2.

24. Gnjidic D, Cumming RG, Le Couteur DG, Handelsman DJ, Naganathan V, Abernethy DR, Hilmer SN. Drug Burden Index and physical function in older Australian men. Br J Clin Pharmacol 2009; 68: 97-105.

25. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Cumming RG, Handelsman DJ, McLachlan AJ, Abernethy DR, Banks E, Le Couteur DG. High-Risk Prescribing and Incidence of Frailty Among Older Community-Dwelling Men. Clin Pharmacol Ther 2012; 91: 521-28.

26. Gnjidic D, Le Couteur DG, Naganathan V, Cumming RG, Creasey H, Waite LM, Sharma A, Blyth FM, Hilmer SN. Effects of drug burden index on cognitive function in older men. J Clin Psychopharmacol 2012; 32: 273-77.

27. Wilson NM, Hilmer SN, March LM, Cameron ID, Lord SR, Seibel MJ, Mason RS, Chen JS, Cumming RG, Sambrook PN. Associations Between Drug Burden Index and Falls in Older People in Residential Aged Care. J Am Geriatr Soc 2011; 59: 875-80.

28. Gnjidic D, Hilmer SN, Hartikainen S, Tolppanen A-M, Taipale H, Koponen M, Bell JS. Impact of High Risk Drug Use on Hospitalization and Mortality in Older People with and without Alzheimer's Disease: A National Population Cohort Study. PLoS ONE 2014; 9: e83224.

29. Salahudeen MS, Hilmer SN, Nishtala PS. Comparison of anticholinergic risk scales and associations with adverse health outcomes in older people. J Am Geriatr Soc 2015; 63: 85-90.

30. Cardwell K, Hughes CM, Ryan C. The Association Between Anticholinergic Medication Burden and Health Related Outcomes in the 'Oldest Old': A Systematic Review of the Literature. Drugs Aging 2015; 32: 835-48.

31. Krahn GL, Hammond L, Turner A. A cascade of disparities: Health and health care access for people with intellectual disabilities. Dev Dis Res Rev 2006; 12: 70-82.

32. O'Dwyer M, Mestrovic A, Henman M. Pharmacists' medicines-related interventions for people with intellectual disabilities: a narrative review. Int J Clin Pharm 2015; 37: 566-78.

33. Burke E, McCarron M, McCallion P. Advancing Years, Different Challenges: Wave 2 IDS-TILDA Findings of the ageing of people with Intellectual Disability. In, Dublin: School of Nursing and Midwifery, Trinity College, Dublin, 2014: 1 - 178.

34. McCarron M, Swinburne J, Burke E, McGlinchey E, Mulryan N, Andrews V, Foran S, McCallion P. Growing Older with an Intellectual Disability in Ireland 2011: First Results from

the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing. In, Dublin: School of Nursing, Trinity College, 2011.

35. Coppus AMW. People with intellectual disability: What do we know about adulthood and life expectancy? Dev Dis Res Rev 2013; 18: 6-16.

36. Burke E. Bone health in older adults with intellectual disability. Dublin, Ireland: Trinity College, 2016.

37. Burke E, Walsh J, McCallion P, McCarron M. One Size Does Not Fit All, Making Reasonable Adjustment to Facilitate the Engagement of People with Intellectual Disability in Objective Health Assessment. In: IASSIDD Congress, Melbourne, Australia, 2016.

38. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, Initiative S. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg 2014; 12: 1495-9.

39. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M, Initiative S. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg 2014; 12: 1500-24.

40. WHO Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical Classification System [Internet]. In: ATC/DDD Index, 2016 [cited January - June 2016]. Available from: http://www.whocc.no/atc_ddd_index/.

41. Nishtala PS, Hilmer SN, McLachlan AJ, Hannan PJ, Chen TF. Impact of residential medication management reviews on drug burden index in aged-care homes: a retrospective analysis. Drugs Aging 2009; 26: 677-86.

42. Castelino RL, Hilmer SN, Bajorek BV, Nishtala P, Chen TF. Drug Burden Index and potentially inappropriate medications in community-dwelling older people: the impact of Home Medicines Review. Drugs Aging 2010; 27: 135-48.

43. Indiana University of Aging Research. The Anticolinergic Cognitive Burden Scale (2012 Update). In, 2012 [cited January - June 2016]. Available from: http://www.agingbraincare.org/uploads/products/ACB_scale_-_legal_size.pdf.

44. Health Products Regulatory Authority. Health Products Regulatory Authority [Internet]. In: Medicines, 2016 [cited January - June 2016]. Available from: http://www.hpra.ie.

45. Gnjidic D, Le Couteur DG, Abernethy DR, Hilmer SN. Drug burden index and beers criteria: impact on functional outcomes in older people living in self-care retirement villages. J Clin Pharmacol 2012; 52: 258-65.

46. Gnjidic D, Bell JS, Hilmer SN, Lonnroos E, Sulkava R, Hartikainen S. Drug Burden Index associated with function in community-dwelling older people in Finland: a cross-sectional study. Ann Med 2012; 44: 458-67.

47. Kaila T, Korte JM, Saari KM. Systemic bioavailability of ocularly applied 1% atropine eyedrops. Acta Ophthalmol Scand 1999; 77: 193-6.

48. Best O, Gnjidic D, Hilmer SN, Naganathan V, McLachlan AJ. Investigating polypharmacy and drug burden index in hospitalised older people. Intern Med J 2013; 43: 912-8.

49. Nishtala PS, Narayan SW, Wang T, Hilmer SN. Associations of drug burden index with falls, general practitioner visits, and mortality in older people. Pharmacoepidemiol Drug Saf 2014; 23: 753-8.

50. Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: A reliability study. Int Disabil Stud 1988; 10.

51. Sainsbury A, Seebass G, Bansal A, Young JB. Reliability of the Barthel Index when used with older people. Age Ageing 2005; 34: 228-32.

52. Wade D, Collin C. The Barthel ADL index: a standard measure of physical disability? Int Disabil Stud 1988; 10: 64-67.

53. Jamsen KM, Bell JS, Hilmer SN, Kirkpatrick CM, Ilomaki J, Le Couteur D, Blyth FM, Handelsman DJ, Waite L, Naganathan V, Cumming RG, Gnjidic D. Effects of Changes in Number of Medications and Drug Burden Index Exposure on Transitions Between Frailty States and Death: The Concord Health and Ageing in Men Project Cohort Study. J Am Geriatr Soc 2016; 64: 89-95.

54. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th Editon. Arlington, VA: American Psychiatric Publishing, 2013.

55. McVilly KR, Bristow S, Foreman P, Goddard L, Australian Society for the Study of Intellectual Disability. Positive behaviour support for people with intellectual disability : evidence-based practice, promoting quality of life. Putney, N.S.W.: Australian Society for the Study of Intellectual Disability, 2002.

56. Matson JL, Neal D. Psychotropic medication use for challenging behaviors in persons with intellectual disabilities: an overview. Res Dev Disabil 2009; 30: 572-86.

57. McGillivray JA, McCabe MP. Pharmacological management of challenging behavior of individuals with intellectual disability. Research in Developmental Disabilities 2004; 25: 523-37.

58. McGillivray JA, McCabe MP. Emerging Trends in the Use of Drugs to Manage the Challenging Behaviour of People with Intellectual Disability. Journal of Applied Research in Intellectual Disabilities 2005; 19: 163 - 72.

59. Mulryan N, Reilly E, Carroll R, O'Dwyer M, Lawlor B, McCallion P, McCarron M. Sleep problems and associated health variables in an older Irish population with Down syndrome:

Results from the Intellectual Disability Supplement to The Irish Longitudinal study on Ageing (IDS-TILDA). J Intellect Disabil Res 2016; 60: 711.

60. Lonnroos E, Gnjidic D, Hilmer SN, Bell JS, Kautiainen H, Sulkava R, Hartikainen S. Drug Burden Index and hospitalization among community-dwelling older people. Drugs Aging 2012; 29: 395-404.

61. Kutner MH, Nachtsheim C, Neter J. Applied linear regression models. , 2004.: McGraw-Hill/Irwin, 2004.

62. Dancy C, Reidy J. Statistics without maths for psychology. Harlow: Pearson Education Limited, 2004.

63. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996; 49: 1373-9.

64. Peklar J, Kos M, O'Dwyer M, McCarron M, McCallion P, Kenny RA, Henman MC. Medication and supplement use in older people with and without intellectual disability: An observational, cross-sectional study. PLoS One 2017; 12: e0184390.

65. McCarron M, O'Dwyer M, Burke E, McGlinchey E, McCallion P. Epidemiology of epilepsy in older adults with an intellectual disability in Ireland: associations and service implications. Am J Intellect Dev Disabil 2014; 119: 253-60.

66. Dauphinot V, Faure R, Bourguignon L, Goutelle S, Krolak-Salmon P, Mouchoux C. Factors associated with changes in exposure to anticholinergic and sedative medications in elderly hospitalized patients: multicentre longitudinal study. Eur J Neurol 2016.

67. Perucca E. The new generation of antiepileptic drugs: advantages and disadvantages. Br J Clin Pharmacol 1996; 42: 531-43.

68. Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines in Psychiatry. 12th Editon: John Wiley & Sons, 2015.

69. Maaskant M, van de Wouw E, van Wijck R, Evenhuis HM, Echteld MA. Circadian sleep-wake rhythm of older adults with intellectual disabilities. Res Dev Disabil 2013; 34: 1144-51.

70. van de Wouw E, Evenhuis HM, Echteld MA. Prevalence, associated factors and treatment of sleep problems in adults with intellectual disability: a systematic review. Res Dev Disabil 2012; 33: 1310-32.

71. Collamati A, Martone AM, Poscia A, Brandi V, Celi M, Marzetti E, Cherubini A, Landi F. Anticholinergic drugs and negative outcomes in the older population: from biological plausibility to clinical evidence. Aging Clin Exp Res 2016; 28: 25-35.

72. McDermott A. A descriptive quantitative study examining the prevalence of constipation in older adults with intellectual disabilities in Ireland. Dublin, Ireland: Trinity College, 2016.

73. Irvine EJ, Ferrazzi S, Pare P, Thompson WG, Rance L. Health-related quality of life in functional GI disorders: focus on constipation and resource utilization. Am J Gastroenterol 2002; 97: 1986-93.

74. Dennison C, Prasad M, Lloyd A, Bhattacharyya SK, Dhawan R, Coyne K. The health-related quality of life and economic burden of constipation. PharmacoEconomics 2012; 23: 467-76.

75. Gliav A, Lindberg G. Quality of Life in Patients with Different Types of Functional Constipation. Scand J Gastroenterol 1997; 32: 1083-89.

76. Chiba Y, Shimada A, Yoshida F, Keino H, Hasegawa M, Ikari H, Miyake S, Hosokawa M. Risk of Fall for Individuals With Intellectual Disability. Am J Intellect Dev Disabil 2009; 114: 225 - 36.

77. Hsieh K, Rimmer J, Heller T. Prevalence of Falls and Risk Factors in Adults with Intellectual Disability. Am J Intellect Dev Disabil 2012; 117: 442 - 54.

78. Cox C, Clemson L, Stancliffe R, Durvasula S, Sherrington C. Incidence of and risk factors for falls among adults with an intellectual disability. J Intellect Disabil Res 2010; 54: 1045-57.

79. Kouladjian L, Gnjidic D, Reeve E, Chen TF, Hilmer SN. Health Care Practitioners' Perspectives on Deprescribing Anticholinergic and Sedative Medications in Older Adults. Ann Pharmacother 2016; 50: 625-36.

80. Jansen DE, Krol B, Groothoff JW, Post D. Towards Improving Medical Care for People with Intellectual Disability Living in the Community: Possibilities of Integrated Care. J Appl Res Intellect Disabil 2005; 19: 214-18.

81. Sheehan R, Horsfall L, Strydom A, Osborn D, Walters K, Hassiotis A. Movement side effects of antipsychotic drugs in adults with and without intellectual disability: UK population-based cohort study. BMJ Open 2017; 7.

82. Kouladjian L, Gnjidic D, Chen TF, Hilmer SN. Development, validation and evaluation of an electronic pharmacological tool: The Drug Burden Index Calculator(c). Res Social Adm Pharm 2016; 12: 865-75.

83. Ailabouni N, Mangin D, Nishtala PS. Deprescribing anticholinergic and sedative medicines: protocol for a Feasibility Trial (DEFEAT-polypharmacy) in residential aged care facilities. BMJ Open 2017; 7: e013800.

Table 1: Sedative Search Terms

Sedative Search Terms	Clinically Significant Adverse Effect Frequency
• Fatigue • Asthenia • Somnolence • Sedation • Drowsiness	• Very Common: Occurring in >1/10 users • Common: Occurring in >1/100 and <1/10 users

Table 2: Baseline characteristics of the study population.

	Number of Participants % (95% CI)
Gender (n = 677)	
Male (n = 297)	43.9 (40.16 – 47.64)
Female (n = 380)	56.1 (52.36 – 59.84)
Age (n = 676)	
44 – 49 years (n = 187)	27.6 (24.23 – 30.97)
50 – 64 years (n = 347)	51.3 (47.53 – 55.07)
65 years + (n = 142)	21.0 (17.93 – 24.07)
Level of ID (n = 624)	
Mild (n = 149)	23.9 (20.55 – 27.25)
Moderate (n = 287)	44.0 (40.11 – 47.89)
Severe/Profound (n = 188)	30.1 (26.5 – 33.7)
Type of Residence (n = 676)	
Independent (n = 102)	15.0 (12.31 – 17.69)
Community Group Home (n = 298)	44.1 (40.36 – 47.84)
Residential Care (n = 276)	40.8 (37.1 – 44.5)
Barthel Index (n = 635)	
Total Independence (n = 113)	17.8 (14.9 – 21.0)
Mild Dependence (n = 50)	7.9 (5.9 – 10.2)
Moderate Dependence (n = 274)	43.1 (39.3 – 47.1)
Severe Dependence (n = 112)	17.6 (14.8 – 20.8)
Total Dependence (n = 86)	13.5 (11.0 – 16.5)
Median (IQR) FCI Score (n = 532)	3.00 (2.00)
Neurological Disease (n = 641)	41.2 (37.3 – 45.1) (n = 264)
Depression (n = 673)	28.4 (25.0 – 32.0) (n = 191)
Anxiety (n = 673)	19.2 (16.3 – 22.3) (n = 129)
Daytime Dozing (n = 665)	34.9 (31.3 – 38.6) (n = 232)
Chronic Constipation (n = 669)	38.4 (34.7 – 42.2) (n = 257)
Fall in previous 12 months (n = 667)	28.5 (25.07 – 31.93) (n = 190)
Behaviours that Challenge (n = 677)	52.0 (48.2 – 55.8) (n = 352)
Polypharmacy (n = 677)	
No polypharmacy (n = 256)	37.8 (34.1 – 41.6)
Polypharmacy (n = 258)	38.1 (34.4 – 41.9)
Excessive polypharmacy (n = 163)	24.1 (20.9 – 27.5)
Exposure to any Medications (n = 677)	95.1 (93.47 – 96.73) (n = 644)
Median (IQR) no. of Medications	6.00 (6.00)
Median (IQR) no. of DBI Medications	2.00 (3.00)
Median (IQR) no. of non-DBI Medications	4.00 (5.00)
Exposure to DBI Medications	
Anticholinergic only (n = 347)	51.3 (47.5 – 55.1)
Sedative only (n = 217)	32.1 (28.6 – 35.6)
Total (anticholinergic and/or sedative) (n = 532)	78.6 (75.3 – 81.6)

DBI Score	
0 (n = 145)	21.4 (18.31 – 24.49)
0 > 1 (n = 165)	24.4 (21.16 – 27.64)
≥ 1 (n = 367)	54.2 (50.45 – 57.95)
Median (IQR) DBI Score	1.10 (±1.73)
Median (IQR) DBA Score	1.00 (±1.13)
Median (IQR) DBS Score	0.69 (±0.79)
Range (min-max)	0 – 5.47

Table 3: Prevalence of exposure to drug classes with anticholinergic and sedative activity

Therapeutic DBI Drug Class and Most Frequently Reported Medicine within Each Class	ATC Code	% of Population Exposed, (95% CI) (n)
Anticholinergic		
Antipsychotics	N05A	44.0 (40.26 – 47.74) (n = 298)
Risperidone	N05AX08	15.7 (12.9 – 18.4) (n = 106)
Antiepileptics	N03A	42.4 (38.68 – 46.12) (n = 287)
Valproic Acid	N03AG01	19.4 (16.4 – 22.3) (n = 131)
Antidepressants	N06A	27.8 (24.43 – 31.17) (n = 188)
Escitalopram	N06AB10	5.8 (4.0 – 7.5) (n = 39)
Anticholinergic Agents	N04A	13.0 (10.47 – 15.52) (n = 88)
Biperiden	N04AA02	8.7 (6.6 – 10.8) (n = 59)
Anxiolytics	N05B	11.5 (9.1 – 13.9) (n = 78)
Diazepam	N05BA01	6.1 (4.3 – 7.9) (n = 41)
Diuretics	C03(A, C, D)	7.4 (5.43 – 9.37) (n = 55)
Furosemide	C03CA01	5.0 (3.4 – 6.7) (n = 34)
Antihistamines	R06A	5.5 (3.78 – 7.22) (n = 37)
Cetirizine	R06AE07	1.6 (0.7 – 2.6) (n = 11)
Sedative		
Hypnotics & Sedatives	N05C	7.1 (5.17 – 9.03) (n = 48)
Zopiclone	N05CF01	2.8 (1.6 – 4.1) (n = 19)
Anti-Dementia Drugs	N06D	3.4 (2.03 – 4.77) (n = 23)
Donepezil	N06DA02	2.2 (1.1 – 3.3) (n = 15)
Drugs for Benign Prostate Hypertrophy	G04C	1.8 (0.8 – 2.8) (n = 12)
Tamsulosin	G04CA02	1.8 (0.8 – 2.8) (n = 12)
Other therapeutic classes reported by <5% listed in Supporting Information Table S4.		

Table 4: Multivariate Analysis of DBI Scores and Potential Adverse Effects (n = 484) [a]

	DBI 0 > 1		DBI ≥1	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Daytime Dozing				
No	1 (reference)		1 (reference)	
Yes	1.108 (0.568;2.162)	*0.764*	1.670 (0.916;3.044)	*0.094*
Chronic Constipation				
No	1 (reference)		1 (reference)	
Yes	1.276 (0.643;2.532)	*0.486*	1.679 (0.902;3.123)	*0.102*
Fall in the Previous 12 Months				
No	1 (reference)		1 (reference)	
Yes	0.611 (0.303;1.231)	*0.168*	1.113 (0.605;2.046)	*0.731*

a. Reference category: DBI 0. P<0.05 is significant, all significant factors in bold. Cox and Snell r^2 = 0.245, Nagelkerke r^2 = 0.284. Data are adjusted odds ratio (OR). Model adjusted for gender, age, level of ID, type of residence, behaviours that challenge, comorbidities (FCI) and number of non-DBI medicines.

Figure 1: Flow Chart of IDS-TILDA Study

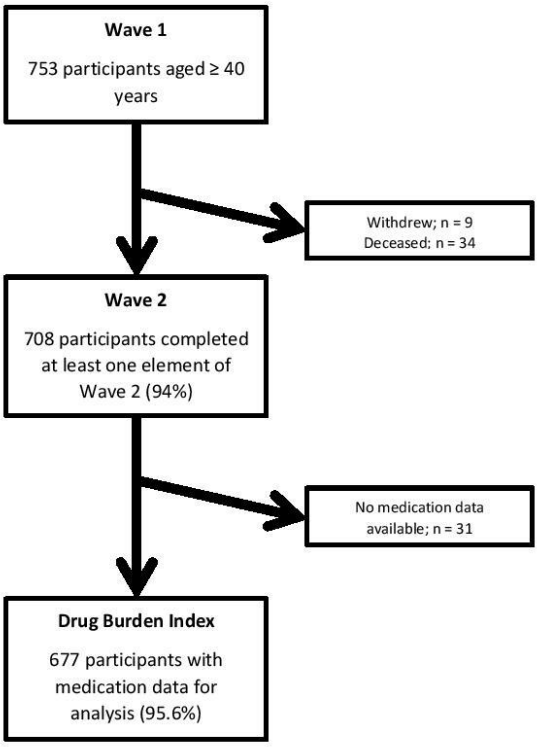
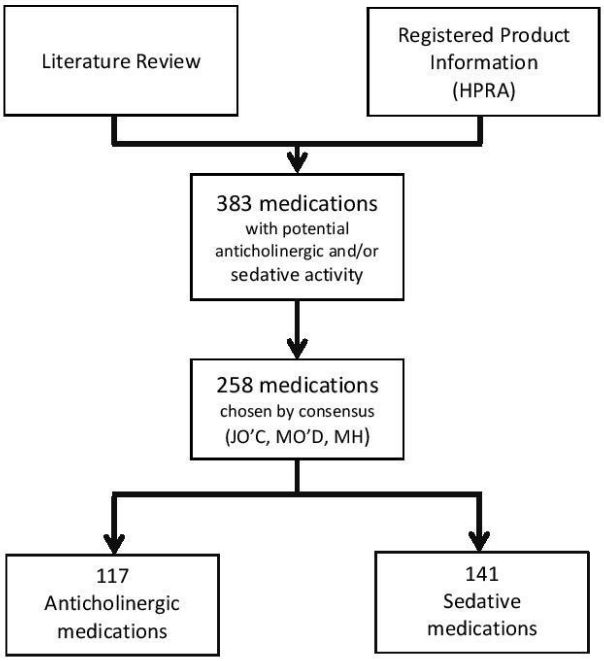


Figure 2: Development of Medication Inventory



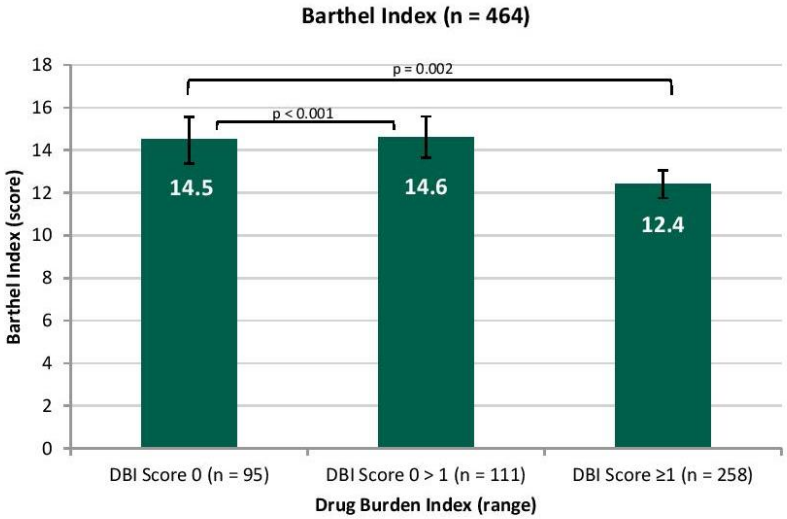


Figure 3: Analysis of covariance for the association of adjusted means of Barthel Index with increasing Drug Burden Index. Means are adjusted for gender, age, level of ID, comorbidities (FCI), behaviours that challenge and history of falls. Drug Burden Index is grouped into three intervals (0, 0 > 1 and ≥1). Error bars show 95% confidence interval (CI). Barthel Index instrumental activities of daily living – lower score indicates worse function.