Title: Association of Anticholinergic Burden with Adverse Effects in Older People with Intellectual Disabilities in Ireland: an observational cross-sectional study

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Table 2,3,6 and Figure 1 may be included as online supplementary (figure 2 may be also included as supplementary).

Background Older people with intellectual disabilities (ID) receive anticholinergic drugs but no studies to date have investigated cumulative anticholinergic exposure and its effects in adults with ID.

Aim: To determine the cumulative exposure to anticholinergics and the factors associated with high exposure.

Methods A modified anticholinergic burden score (ACB) was calculated for a representative cohort (2009/2010) of 736 people over 40 years with ID and associations with demographic and clinical factors assessed.

Results Age over 65 years was associated with higher exposure (ACB 1-4- OR 3·28; 95% CI 1·49-7·25, ACB 5+- OR 3·08; 95% CI 1·21-7·63), as was a mental health condition (ACB 1-4- OR 9·79; 95% CI 5·63-17·02, ACB 5+- OR 23·74; 95% CI 1·29-45·83). Day time drowsiness was associated with higher ACB ($p<0·001$) and chronic constipation reported more frequently (26·6% ACB 5+ vs 7·5% ACB 0) ($p<0·001$).

Conclusions Older people with ID and with mental health conditions were exposed to high anticholinergic burden. This was associated with daytime dozing and constipation.

Declaration of Interests All authors declare there are no conflicts of interest

Introduction

Many medicines used to treat conditions prevalent in older people possess anticholinergic (AC) activity and they may produce central and peripheral side effects - sedation, confusion, dry mouth, adverse dental outcomes and constipation (1). The risk of adverse outcomes including hospitalisation and falls increases with increasing anticholinergic exposure. (1, 2) Frail, older people are particularly vulnerable to anticholinergic adverse effects due to high probability of exposure to treat multiple conditions, and increased age-related sensitivity to anticholinergic-related cognitive adverse effects (3). Furthermore, medical problems prevalent in older people such as constipation, sleep difficulties and dementia may be worsened by use of anticholinergics.(4) Consequently, anticholinergic medications are considered potentially inappropriate in older populations, particularly those with dementia who have limited cognitive reserve. (3, 5) A systematic review examining associations between drugs with anticholinergic effects and adverse outcomes in older adults carried out by Ruxton and colleagues concluded that exposure to individual medicines with AC effects or increased overall AC exposure may increase risk of falls, cognitive impairment and all cause mortality. (6) In those over 65 years of age one recent study has shown associations with dementia and cognitive impairment. (7)

People with intellectual disabilities (ID) continue to have a shorter life expectancy compared to the general population, are at increased risk of mortality from preventable or treatable illnesses,(8) and experience health inequities, including barriers to accessing primary care.(9) They experience up to 2.5 times the health problems (10) and higher incidence of morbidities such as dental disease, eye disease, epilepsy and dementia. (11, 12) Dual diagnosis is common, with one study reporting 41% of adults with ID with mental illness, (13) which increases the likelihood of polypharmacy. Higher use of antipsychotics and other psychotropics prescribed to manage mental health conditions and challenging behaviours is a concern (14-16) and may confer additional risk as organic brain dysfunction may lead to idiosyncratic responses to drugs. (17) Drug-induced anticholinergic activity is thought to be additive; the overall burden of anticholinergic drugs determining the risk of adverse effects. (18) People with ID may be at additional risk of experiencing the "prescribing cascade" as for example, the high prevalence of antipsychotic use may lead to the prescribing of anticholinergics for movement disorders (extrapyramidal symptoms; ATC N04A), a practice no longer recommended in older people (5). (6) Anticholinergic (AC) effects may be misattributed to a consequence of the normal ageing process and drugs with AC properties may be a cause of unrecognised adverse drug reactions (ADRs). (19)

People with ID receive a variety of different medicines with anticholinergic activity and scales which capture cumulative burden are needed to stratify risk. The Anticholinergic Cognitive Burden (ACB) scale is one such scale that computes a total score of drugs to determine individual anticholinergic burden. (1) The ACB scale identifies the burden of anticholinergic negative effects on cognition of medications (prescribed and over the counter)-; drugs with no AC effects score 0, drugs with possible AC effects score 1, drugs with definite cognitive anticholinergic effects score 2 or 3. (1) In one study an ACB score of 5 or more was associated with an Mini Mental State Examination (MMSE) score of 1 point lower compared to an ACB score of 0.(20) It also found the largest effect on cognitive decline was observed in people with mild dementia (MMSE 26 to 30). The ACB scale has been demonstrated to have predictive validity, with higher ACB scores associated with adverse clinical outcomes.(21)

Given evidence in the general older population of the risks associated with anticholinergic exposure and of frailty, cognitive decline and adverse effects we hypothesised that adverse effects would be associated with exposure to a high anticholinergic load in older people with ID.

Our objectives were;

(i) to determine each individual's cumulative exposure to anticholinergic medications by using the ACB scale;

(ii) to describe the pattern of anticholinergic medication use in relation to demographic and clinical characteristics and the most frequently reported therapeutic classes contributing to the anticholinergic burden;

(iii) to examine factors associated with higher anticholinergic burden exposure;

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

Methods

Study Design

Medication data for this study was drawn from Wave 1 (2009/2010) of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA), which contains a nationally representative sample of 753 persons with an ID, aged between 41 and 90 years *(figure 1).*(22) IDS-TILDA is a longitudinal study of older adults with ID and has been described in detail elsewhere.(22, 23) Age 40 years and over was selected to reflect the lower longevity of people with ID and their earlier onset of chronic disease, for example dementia (24). (25).

This would also ensure that there would be sufficient subjects for future waves of data collection and provide opportunities to offer insights into ageing for those who may age prematurely. Everyone included in the study was registered on the NIDD, and therefore had an intellectual disability. The person's level of ID was checked and confirmed from case notes at the time of the face-to face interview. The STROBE (The Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for cross-sectional studies was utilised.(26) Ethical approval for the study was received from the Faculty of Health Sciences Trinity College Dublin and 138 Intellectual Disability Service Providers, and all participants and/or proxies as appropriate provided informed consent to partake in the study.

ADD FIGURE 1 HERE

Medication Exposure Measures

Participants/proxies were asked "Can you tell me what medications (including prescribed and over the counter, herbal medicines) you take on a regular basis – like every day or every week?" in the pre-interview questionnaire. (22) The pre-interview questionnaire was sent to participants and/or proxies one week in advance of the face to face interview to give them time to check patient records or charts to record the medicines they were taking. This information was then cross-checked by interviewers at the time of interview, by asking if the list they had provided in the pre-interview questionnaire included all of their medicines, and where necessary checking patient files if they had permission.

Medicines were recorded by brand or generic name, including prescription and non-prescription and over the counter, and all data was anonymised. Medications were coded using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system. (27) Two pharmacists (MO'D, JP) independently reviewed and confirmed medication entries.

Measuring Exposure to Anticholinergic Medications

The dependent variable was participants' Anticholinergic Burden Score calculated using the updated 2012 Anticholinergic Cognitive Burden (ACB) Scale.(28)

In addition, the ACB list was assessed and modified to include drugs with anticholinergic properties taken by participants, available in Ireland, but not included in the ACB scale. (20) Two pharmacists (MO'D, IM- who developed the original scale) independently consulted standard reference sources, the product characteristics (SmPC) information, and the other validated anticholinergic rating scales, to assign a score to other drugs with anticholinergic properties available in Ireland but not included in the ACB list; this was based on the approach used to develop the original scale The 22 medicines not included in the original ACB list with respective scoring are listed in *Suppl Table1*. Medications with anticholinergic properties which were not available in Ireland and/or not present in the dataset were excluded (42 medications).

We categorised exposure to anticholinergics in three ways; (i) The total Anticholinergic Cognitive Burden (ACB) score of each individual, created by summing the score of each possible (ACB1) or definite (ACB2 or 3) anticholinergic, (ii) a binary variable; those exposed to any anticholinergic medicine, (ACB score $\geq$1), and no anticholinergic exposure (ACB 0), and (iii) a categorical variable; no exposure to anticholinergic medications (ACB 0), ACB score of 1-4 , and ACB score of $\geq$5), as in previous studies. (20)

Covariates

Covariates included; gender, age (a categorical variable; 40-49 years, 50-64 years, 65+ years) , level of intellectual disability, place of residence (independent, community group home or residential setting), 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. Community group homes are in community setting with staff support for small groups (<10) of people with ID. Other covariates included any dementia (doctor's diagnosis of dementia, organic brain dysfunction, senility or serious memory impairment), polypharmacy (no polypharmacy=0-4 medicines), polypharmacy=$\geq$5 medicines). Participants/ proxies reported if the participant had ever received a doctor's diagnosis of 12 chronic health conditions. (23) Dementia, lung disease, stroke, cancer and liver disease had insufficient numbers (<5% prevalence) and were excluded from further multivariate analysis.

The relationship between anticholinergic exposure and indicators of anticholinergic adverse effects was examined; if the participant had reported fall(s) in the previous year, day-time dozing, constipation or physician diagnosed chronic constipation and laxative use. Participants were also divided into those who were dentate or edentulous. (29)

Statistical Analyses

Descriptive statistics (percentages, medians (as the data was not normally distributed), and 95% confidence intervals (C.I.s)) described the characteristics of the eligible study population.

We used univariate analysis to examine the associations between the dependant (anticholinergic exposure (ACB ≥1) versus no exposure) and clinical and demographic variables. Here, for categorical variables chi-squared (χ^2) tests for independence was used to test for a significant association between the three ACB groupings. For continuous variables, a one-way Analysis of Variance (ANOVA) was used to test for a significant difference.
Multinomial logistic regression identified factors associated with an ACB of 1-4 and an ACB of 5+, with those with no AC exposure (ACB 0) as the reference category. All demographic variables were included in the model (age, gender, and level of ID). Those with unverified level of ID (n=54) were excluded from regression analyses. Those who lived independently or in community group homes were combined as a single group, as the numbers in the independent setting with AC exposure were small (n=11).
Variables with a p value <0·10 in univariate analysis were included in our multivariable model (this p value was selected to ensure that important or influential factors were not omitted)(30). All variables were entered into the model simultaneously. The model is adjusted for polypharmacy status (polypharmacy versus no polypharmacy), with results presented as adjusted Odds Ratios with corresponding 95% CIs.
Sample size calculation for the logistic regression was based on the guideline of Peduzzi et al. (1996); for a minimum number of cases (N) needed for the study; N=10 k/p, where **p** is the smallest of the proportions of negative or positive cases in the population, **k** the number of covariates (independent variables). (31) For the regression model there were 10 covariates and the proportion of negative cases (ACB 0) was 0·284, therefore a minimum sample size (N) of 352 was needed. There were 658 cases available for regression analyses, so sample size was sufficient.
The ACB score and anticholinergic adverse effects were explored at univariate level. To control for problems of Type I error associated with multiple comparisons a Bonferroni correction was applied,(32) testing six associations, with a desired α of 0·05, resulting in α=0·05/6 =0·008.
Statistical Analyses were carried out using the Statistical Package for Social Sciences, Version 20 (SPSS Inc.).

Role of the Funding Source and Access to Data
The IDS-TILDA study is funded by the Health Research Board and the Department of Health and Children. The lead author (MO'D) received funding for a PhD from the Trinity College Dublin Studentship. The funding body did not play a role in the study design, writing of the manuscript. The corresponding author (MO'D) had full access to the study data, and had final responsibility to submit for publication.

Results
Of 753 participants, 736 (98%) provided medication use data. Baseline characteristics of our sample are presented in *Table 1.* Mean age of participants was 54·1 years (S.D·8.8, range 41-90 years), with almost half (45·7%) aged between 50-64 years. Almost half (46%) of the sample with recorded level of ID (n= 682) reported moderate ID. Overall, participants reported a mean (±SD) of 5.7(±4.4) medicines, with 53.7% exposed to polypharmacy (5+ medicines).
In the total sample of 736, no exposure was reported by 214 (29·1%; ACB = 0, while 308 (41·8%) had a score of ACB 1-4 and 214 (29·1%) ACB score 5+ *(Table 2).* Of those reporting medications with ACB ≥1 score (522) half (370) received medicines with an ACB score of 2 or 3, and of those (n=370), 42·9% (159) reported concurrent use of two or more ACB 2 or 3 drugs. The median (±S·D) total ACB score was 4·0 (±3·0) (range 1-16; N=522).
There was a significant association between ACB score and reporting mental health conditions (n=706) (p<0·001); 46·6% had ACB 5+, and a further 46·7% had a score of 1-4 (p<0·001).
Similarly level of ID was associated with AC exposure; 36·5% of those with severe/ profound ID had an ACB score of 5+, compared to just 19·9% of those with mild ID (n=682, p<0·001) (*Table 2*).

INSERT TABLE 1 HERE, TABLE 2

In total, 72 different AC medicines were reported in 1266 instances (*Table 3*); most were ACB 1 medications (52·1%) with 36·3% ACB3 drugs.

Antipsychotics comprised 35.4% of the total cumulative ACB score, followed by anticholinergics (16%) (ATC N04A e.g. biperiden) (*figure 1).* Of those with antipsychotics (319), 25% (n=82) received two or more concurrently.

Medications with ACB score 2 were reported by 26·6% of those with exposure, with carbamazepine being the most frequent (n=127). ACB score 3 medicines were reported by 59·1% (n=309), with olanzapine the most frequent (n=101). Antipsychotics accounted for 46% of ACB 3 medicines, N04A anticholinergics (27·6%) and antidepressants (9·4%).

Of those who reported N04A anticholinergics (n=121), 91·7% reported concurrent use of antipsychotics with anticholinergic properties and of those receiving antipsychotics (319), 35·2% also received N04A anticholinergic agents, and of those with antipsychotic polytherapy (n=82), over half (58·5%, n=48) received a N04A anticholinergic.

INSERT TABLE 3, FIGURE 2 HERE

Those aged over 65 years were more likely to report an ACB score of 1-4 (odds ratio [OR] 3·28, 95% CI 1·49-7·28) and ACB of 5+ ([OR] 3·08, 95% CI 1·20-7·63), after controlling for other factors (*Table 4).* Having a mental health condition was associated with having a score of ACB 1-4 ([OR] 9·79, 95% CI 5·63-17·02), and ACB 5+ ([OR] 23·74, 95% CI 12·29-45·83). Levels of ID, gender or place of residence were not significant with either level of AC exposure, nor were the other clinical conditions.

INSERT TABLE 4 HERE

Day time drowsiness was significantly associated with a higher ACB score at univariate level ($p<0·001$), with 43·3% of those with an ACB score of 5+ reporting a moderate/high likelihood of daytime drowsiness, compared to 23·4% of those with no anticholinergic exposure (*Table 5).* A greater proportion of those with higher anticholinergic burden reported a doctor's diagnosis of chronic constipation; 26·6% of those with an ACB score of 5+ compared to 7·5% of those with no AC exposure ($p<0·001$). Furthermore, 29·0% of those with an ACB 5+ used two or more concurrent laxatives, compared to 4·7% of those with no exposure ($p<0·001$).

INSERT TABLE 5 HERE

Discussion

Principal Findings

As the first study in a representative population of older adults with ID, our findings reveal high levels of cumulative anticholinergic exposure, with 30% exposed to an ACB score of 5+. Multivariable regression analysis showed that those over 65 years and those with mental health conditions were much more likely to have high anticholinergic exposure. Antipsychotics, N04A anticholinergics, antiepileptics and antidepressants were the most frequent classes contributing to the ACB. Antipsychotics accounted for over one-third of the cumulative burden, with a notably high prevalence of typical antipsychotics and with one in four of these taking two or more antipsychotics. Our findings revealed that higher anticholinergic burden was associated with greater likelihood of reporting daytime dozing, constipation and use of multiple laxatives.

Comparison with other studies

There are no equivalent studies with other cohorts with ID. In studies that used the ACB scale with cohorts of older adults without ID, the degree of the anticholinergic burden found in our study was much greater and the types of anticholinergic drugs were different. (20, 33, 34) (*Table 6*).

Factors associated with Anticholinergic Burden and Adverse effects

Our analysis showed no association between higher anticholinergic burden scores and gender, but age over 65 years was a significant factor both for exposure to a score of 1-4 and exposure to an ACB score of 5 or more (*Table 4*). After adjusting for relevant confounders, we did not find an association between the level of ID and anticholinergic burden, however it was notable that 85% of those with severe or profound ID were exposed to anticholinergic medications, and over one-third to an ACB score of 5+. The confidence intervals across all the categories were quite wide indicating the scale of variation remaining after adjusting for confounding factors, including polypharmacy. Other studies have only examined psychotropic polypharmacy (35, 36) or polypharmacy (37) and have reported varying associations with age, gender and level of ID, but in contrast to the general elderly population, where women are identified as being more likely to be exposed to psychotropic polypharmacy. (38). It may be that many of the conditions that are treated with AC medicines occur earlier in the lives of people with ID than in those without ID so that the use of these medicines has become similar in men and women and is increasing to a lesser extent in these older age groups.

Almost half of those with a mental health condition andfour in ten of those over 65 were exposed to an ACB of 5+. The wide confidence intervals of the association of mental health conditions may reflect variability in reporting of mental health conditions, however, 12 of the 16 highest contributors to the ACB score were drugs for mental health.

We found that 35% of those with antipsychotics had concurrent exposure to N04A anticholinergics, which was higher than previously reported in a UK study (14%) (39), yet Parkinson's disease was reported by only 1% in this cohort. The risks associated with using these medicines in combination in patients who are vulnerable and cognitively impaired are substantial (40). Our findings revealed that over one-fifth of those reporting antipsychotics reported chlorpromazine and 14% reported haloperidol, both agents that carry significant anticholinergic, noradrenergic and antihistamine adverse effects (41). These older agents are associated with more extra-pyramidal side effects (41) and people with ID may be more susceptible to these side effects compared to the general population (17, 41) Risperidone was also the second most commonly antipsychotic, an agent also associated with extra-pyrimidal side effects 41)While our findings are limited by the fact that we did not have information in relation to side effects of medications, it is probable that these anticholinergic agents are being to some extent used to treat or in prophylaxis of extra-pyramidal symptoms associated with antipsychotic agents. There is recent evidence of increased incident dementia associated with higher anticholinergic burden and length of exposure in those over 65 years.(7)

Our univariate findings must be interpreted conservatively; while a higher AC burden was associated with a risk of daytime dozing, falls in the previous year were not significantly associated, in contrast to studies in the general older population.(6, 42) Constipation is common in older people, and increases with age.(43) People with ID are at risk of constipation from several factors,(44) and we found an association between increasing anticholinergic burden and constipation and laxative use, and furthermore, with six times as many of those with ACB 5+ receiving laxative polytherapy as those with no AC exposure. Multiple laxative use poses risks of electrolyte disturbance and dehydration which may exacerbate constipation.(43) The relationship between anticholinergic medications and xerostomia and tooth loss has been previously established (45) but although a higher proportion of the participants with an ACB of 5+ were edentate (30·6%), this was not significant.

Impact of Findings on Practice

Since anticholinergic activity may affect both central and peripheral systems, several factors make managing the anticholinergic burden complex in people with ID;

Multimorbidity combined with complex mental health conditions and epilepsy increases the number and different classes of drugs with anticholinergic activity prescribed for people with ID, and the cumulative burden. The sensitivity of people with ID to the effects of these drugs may be greater, and may increase with age, but is unquantifiable because of lack of evidence. Consequently, the prevalence of anticholinergic side effects may be greater in this population, especially as the oldest age group were exposed to the greatest burden.
Patient assessment is challenging, which may lead to diagnostic overshadowing (14) and initiation of inappropriate drugs. Physical problems, such as constipation, may present as challenging behaviours (41), which could trigger a prescribing cascade with a significant anticholinergic burden, as the association of antipsychotic, anticholinergic and laxative use in this study suggests.

A high proportion of people with ID are prescribed drugs with anticholinergic effects from an early age, and are likely to be exposed for many years(17). Length of exposure may increase as life expectancy of people with ID grows, potentially increasing the risks of chronic use of psychotropics (46).
These factors imply that the extent and burden of anticholinergic side effects in people with ID are greater than in the general older population, and could have an impact on their quality of life. Therefore, assessment of this burden, particularly among the oldest and those with mental health conditions and multiple morbidities, and who receive psychotropic polypharmacy is essential.

The risks of cumulative anticholinergic burden could be reduced through regular, multidisciplinary medication review. Scales such as the ACB scale, allied to review of patients symptoms currently remain useful aids to guide clinical decision making (47). Little is known about the influence of ageing on people with ID and their response to medicines, which reinforces the need for review and education of healthcare professionals. Integrated and co-ordinated care is receiving increased attention in the older population (48), and needs to be further developed when providing care to people with ID. In older people and those with cognitive impairment, anticholinergic-induced cognitive impairment is more likely to occur at therapeutic doses potentially increasing risks of medication errors (49) for people with ID managing their own medicines. Continuing deinstitutionalisation creates challenges for Primary Care professionals who may not have the necessary expertise or experience to provide care for people with ID, nor may they be able to meet the needs of their carers (50). Guidelines are needed to support professionals, people with ID and carers to optimise anticholinergic medicines use. However, since people with ID are often excluded from RCTs (51), additional data may also need to be generated by national audits and longitudinal studies(14).

Strengths and Limitations

Our study has four important strengths. First, use of a large, randomly selected population-representative sample offered sufficient power for multivariate analysis, with findings generalisable to the population with ID in Ireland. Second, the great majority of respondents recorded detailed medication data, including over-the-counter medicines (98%). Third, participants and/or proxy respondents underwent a detailed assessment of health characteristics, providing data on potential confounders for the regression model. The use of the Bonferroni correction addressed the problem of multiplicity. Fourth, we used the ACB scale, which has been widely used, making the assessment of anticholinergic burden robust and relevant to clinical practice (3, 20). We added to its content validity by reviewing other anticholinergic medicines available in Ireland with an independent expert.
There are also limitations; there was no independent confirmation of medicines or conditions, but cross-checking of medicines in the pre-interview questionnaire at the time of interview improved accuracy. Information was also not recorded about disease severity. Data on dose and frequency of medicines were not always available and adverse effects may be dose dependent (47), however the ACB scale does not take dose into account. While a higher dose of an anticholinergic agent would be expected to cause more central effects, the relationship may not be linear(53). The ACB scale has not been validated against measures of *in vitro* anticholinergic activity. However, assays are difficult to interpret, not readily available in practice and due to variations in blood-brain barrier permeability may not reflect levels in the CNS. It is currently accepted, that allied to a careful review of the patients' symptoms and medicines, scales and lists such as the ACB scale remain the best aid to guide clinical decision making (47).The ACB scale does not take into account influences of patient variability in drug response associated with older age, frailty, multimorbidity, cognitive reserve and individual pharmacokinetic factors.
As an observational study, we could only describe associations between anticholinergic burden and clinical and demographic factors. In our multivariate analysis, potential bias was reduced by adjusting for known confounders; however, residual confounding may remain. Although potential adverse effects associated with anticholinergic exposure were examined at univariate level, other factors such as functional status, or baseline cognitive status which could influence the prescription of anticholinergics were not measured in this study, and this analysis was descriptive and not adjusted for confounders.

In conclusion, the use of medications with anticholinergic activity is commonplace among older adults with ID, with psychotropic agents accounting for much of the burden. For the first time in people with ID a high anticholinergic burden has been shown to be associated with daytime dozing, constipation and multiple laxative use. The possible impact that anticholinergics may have on cognitive and executive function should be evaluated and more attention should be paid to the assessment of peripheral anticholinergic effects, such as constipation. People with ID are amongst the most vulnerable members of society and regular, multidisciplinary review of medications to decrease the use of anticholinergic medicines is likely to reduce morbidity and improve quality of life in this population.

Acknowledgements: We would like to thank the people with ID who participated in this study, their families, the services involved, the IDS-TILDA Scientific Advisory Committee, and the Intellectual Disability Consultative Groups for their support. We would like to acknowledge the contributions of Dr Caoimhin MacGiolla Phadraig, Anne Belton, Professor John Haslett and Dr Rachael Carroll.

Contributors

MO'D, IM, MH, KB, JP, NM, PMcm, MMcM contributed to the overall conception and design of this study.
MO'D and JP undertook the data extraction. MO'D, MH and IM drew up, agreed and revised the ACB scale. MO'D and KB carried out the statistical analyses of the study. MO'D wrote the first draft of this manuscript. MO'D and MH 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.
The views expressed are those of the authors and are not necessarily those of the Department of Health, the Health Research Board or Trinity College Dublin. MO'D and MMcC are the guarantors.

Declaration of Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org and declare: no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical Approval: Ethical approval for the IDS-TILDA study was granted by the Faculty of Health Sciences Ethics Committee, and 138 Intellectual Disability Service Providers.

Transparency: The lead author (MO'D) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies as planned have been explained.

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Table 1 Anticholinergic exposure binary table

	Total Population (n=736)	**Anticholinergic Use (n=522)**	**No anticholinergic use (n=214)**	**p-value†**
Sex				
Male	330(44·8)	225 (68·2)	105 (31·8)	0·08
Female	406(55·2)	297 (73·2)	109 (26·8)	
Age				
40-49 years	266 (36·1)	171 (64·3)	95 (35·7)	<0·001
50-64 years	336 (45·6)	234 (69·6)	102 (30·4)	
65+ years	134 (18·2)	117 (87·3)	17 (12·7)	
Level of ID (n=682)*				
Mild	163 (23·9)	107 (65·6)	56 (34·4)	
Moderate	316 (42·9)	207 (65·5)	106 (34·5)	<0·001
Severe/ profound	203 (27·6)	173 (85·2)	30 (14·8)	
Residential Setting				
Independent	122 (16·6)	47 (38·5)	75 (61·5)	<0·001
Community Group Home	265 (36·0)	183 (69·1)	82 (30·9)	
Residential	349 (47·4)	292 (83·7)	57 (16·3)	
Polypharmacy Status				
No- polypharmacy	341 (46·3)	160 (46·9)	181 (53·1)	<0.001
Polypharmacy	395 (53·7)	362 (91·6)	33 (8·4)	
Number of co-morbidities				
0	51	27 (52·9)	24 (47·1)	<0·001
1	157	84 (53·5)	73 (46·5)	
2	192	137 (71·4)	55 (28·6)	
3+	336	279 (83·0)	57 (17·0)	
Data are n(%) * 54 Level of ID not verified **p<0·05 is significant**				

Table 2 Demographic and Clinical Characteristics by ACB Score Categories

Characteristic	Total Population (n=736)	No-anticholinergic exposure (n=214)	ACB 1-4 (n=308)	ACB 5+ (n=214)	p-value*
Demographics					
Gender					
Male	330 (44·8)	105 (31·8)	119 (36·1)	106 (32·1)	0·013
Female	406 (55·2)	109 (26·8)	189 (46·6)	108 (26·6)	
Age group					
40-49 years	266 (36·1)	95 (35·7)	103 (38·7)	68 (25·6)	<0·001
50-64 years	336 (45·6)	102 (30·4)	143 (42·6)	91 (27·1)	
65+ years	134 (18·2)	17 (12·7)	62 (45·5)	55 (41·8)	
Level of ID †					
Mild	163 (23·9)	56 (34·4)	66 (23·2)	41 (19·9)	<0·001
Moderate	316 (42·9)	109 (34·5)	118 (37·3)	89 (28·2)	
Severe/profound	203 (27·6)	30 (14·8)	99 (48·8)	74 (36·5)	
Residential setting					
Independent	122 (16·6)	75 (61·5)	36 (29·5)	11 (9·0)	<0·001
Community Group Home	265 (36·0)	82 (30·9)	124 (46·4)	59 (22·6)	
Residential	349 (47·4)	57 (16·3)	148 (42·4)	144 (41·3)	
Polypharmacy Status					
No-polypharmacy	341 (46·3)	181 (53·1)	138 (38·1)	22 (6·7)	<0·001
Polypharmacy (5+ medicines)	395 (53·7)	33 (8·4)	170 (43·0)	192 (48·6)	
Conditions					
Eye disease	380 (51·6)	128 (33·7)	157 (41·3)	95 (25·0)	<0·001
Mental Health‡	356 (50·4)	22 (6·2)	168 (47·2)	166 (46·6)	<0·001
Neurological **	268 (36·4)	53 (19·8)	132 (49·3)	83 (31·0)	<0·001
Gastrointestinal	198 (26·9)	32 (16·2)	88 (44·4)	78 (39·4)	<0·001
Endocrine	162 (22·0)	49 (30·3)	67 (40·7)	46 (28·4)	0·94
Joint Disease	153 (20·8)	36 (23·5)	71 (46k4)	47 (29·0)	0·21
Hypertension	112 (15·2)	26 (12·4)	43 (38·4)	46 (30·1)	0·06
Heart Disease	89 (12·1)	22 (24·7)	42 (47·2)	21 (38·9)	0·49

Data are n(%). *From $\chi 2$ test. †54 Level of ID not verified. ‡ 30 Don't know/missing data.
****Neurological disease includes epilepsy, cerebral palsy,multiple sclerosis,Parkinson's disease, Spina bifida,muscular dystrophy, Alzheimer's disease, dementia, organic brain syndrome or senility and serious memory impairment**
p<0·10 is significant for entry into multinomial logistic regression

Table 3 Frequently Reported ACB Medicines by those with AC exposure (N=522)

Medicine (ATC Code)	Type	N (%)	Rank
ACB 3			
Olanzapine (N05AH03)	Atypical antipsychotic	101 (19·3)	3
Biperiden (N04AA02)	Anticholinergic	85(16·3)	4
Chlorpromazine (N05AA01)	Typical antipsychotic	70 (13·4)	6
Haloperidol (N05AD01)	Typical antipsychotic	44 (8·4)	8
Procyclidine (N04AA04)	Anticholinergic	37(7·0)	9
Quetiapine (N05AH05)	Atypical antipsychotic	27 (5·1)	12
Paroxetine (N06AB05)	SSRI antidepressant	25 (4·8)	14
ACB 2			
Carbamazepine (N03AF01)	Mood-stabilising antiepileptic	127(24·3)	1
ACB 1			
Risperidone (N05AX08)	Atypical antipsychotic	111(21·4)	2
Diazepam* (N05BA01)	Benzodiazepine anxiolytic	82(15·7)	5
Loperamide (A07DA03)	Anti-diarrhoeal	56(10·7)	7
Escitalopram (N06AB10)	SSRI antidepressant	35(6·8)	9
Furosemide (CA03CA01/ C03DB01)	Diuretic	33(6·3)	10
Ipatropium (R03BB01)	Inhaled anticholinergic	31(5·9)	11
Citalopram (N06AB04)	SSRI antidepressant	25(4·8)	13
Alprazolam (N05BA12)	Benzodiazepine anxiolytic	22(4·2)	15

Table 4 Multivariate Analysis of Factors associated with ACB score 1-4 and ACB score 5+ (n=658)

	ACB Categories			
	ACB score 1-4		**ACB score 5+**	
Characteristic	**OR (95% CI)**	**P-Value**	**OR (95% CI)**	**P-Value**
Gender				
Male	1 (reference)	0·22	1 (reference)	0·31
Female	1·34 (0·84-2·15)		0·74 (0·41-1·31)	
Age				
40-49 years	1 (reference)		1 (reference)	
50-64 years	1·13 (0·69-1·85)	0·64	0·97 (0·52-1·79)	0·91
65+ years	**3·28 (1·49-7·25)**	**0·003**	**3·08 (1·2-7·63)**	**0·02**
Level of ID*				
Mild	1 (reference)		1 (reference)	
Moderate	0·78(0·45-1·37)	0·39	0·66 (0·33-1·36)	0·26
Severe/ profound	1·44 (0·67-3·09)	0·35	0·83 (0·33-2·07)	0·68
Residence				
Independent/Community Group				
Home	1 (reference)		1 (reference)	
Residential	0·92 (0·53-1·58)	0·75	1·56 (0·82-2·97)	0·18
Conditions				
Mental Health†				
No	**1 (reference)**		**1 (reference)**	
Yes	**9·79(5·63-17·02)**	**<0·001**	**23·74(12·29-45·83)**	**<0·001**
Neurological				
No	1 (reference)		1 (reference)	
Yes	1·30 (0·76-2·20)	0·34	0·73 (0·39-1·37)	0·33
Gastrointestinal				
No	1 (reference)		1 (reference)	
Yes	1·21 (0·66-2·22)	0·54	1·27 (0·64-2·53)	0·52
Eye				
No	1 (reference)		1 (reference)	
Yes	0·81 (0·50-1·32)	0·41	0·68 (0·37-1·24)	0·21
Hypertension				
No	1 (reference)		1 (reference)	
Yes	0·66 (0·32-1·35)	0·25	0·74 (0·32-1·70)	0·48

Reference category = ACB 0, p<0·05 is significant, all significant factors in bold
Cox and Snell R^2 = 0.46 Nagelkirke R^2 = 0·52
Data are adjusted odds ratio (OR). Model is adjusted for polypharmacy status.
***54 no verified level of ID. †30 missing data/ don't know**

Table 5 ACB Scores and Adverse Effects

Characteristic	Total Population (n=736)	No AC Exposure (n=214)	ACB 1-4 (n=308)	ACB 5+ (n=214)	p-value*
Central Anticholinergic Adverse Effects					
Likelihood of Daytime Dozing					
High/ Moderate Likelihood	267 (36·3)	50(23·4)	118(38·3)	99(46·3)	<0·001
Slight/ Would never doze	469 (63·7)	164(76·6)	190(61·7)	115(53·7)	
Have fallen in previous year †	200(27·4)	43(20·3)	95(31·0)	62(29·1)	0·02
Peripheral Adverse Effects					
"Is constipation a problem for you?" ‡	316(43·6)	60(28·7)	139(45·7)	117(55·2)	<0·001
Doctor's Diagnosis of Chronic Constipation	128(17·4)	16(7·5)	55(17·9)	57(26·6)	<0·001
Any Laxative Use	276(37·5)	41(19·2)	119(38·6)	116(53·5)	<0·001
1 Laxative	146(19·8)	31 (14·5)	61(19·8)	54(25·2)	
2+ Laxatives	130(17·7)	10 (4·7)	58(18·8)	62(29·0)	
Dentate Status¥					
Dentate	547(74·5)	169(80·5)	228(74·0)	150(69·4)	0·03
Edentulous	187(25·5)	41(18·5)	80(26·0)	66(30·6)	

Data are n(%) * From $\chi 2$ test (and applying Bonferroni correction), p <0·008 for significance. †5 missing data ‡ 11 missing data. ¥2 missing data

Table 6: Study Comparisons

Study	Population	ACB 1 medicines	ACB 2-3 medicines	ACB score 5+	Rank order of most frequent AC medicines (with corresponding ACB scores)
Present Study (2015)	736 people with ID aged 41-90 years	70% had an ACB score of 1+	50% had a definite AC medicine	29% had an ACB score 5+	1.Carbamazepine(2) 2.Risperidone(1) 3.Olanzapine(3) 4.Biperiden(3)
***Use of medications with anti-cholinergic activity and injurious falls in community-dwelling adults aged 50 years and older Richardson et al.* (2015)**	6,666 Irish community dwelling adults over 50 years	26% had an ACB 1 medicine	4% had a definite AC medicine	Not reported	1.Hydrochlorothiazide(1) 2.Atenolol(1) 3.Bendroflumethiazide(1)
***Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study* Fox et al.(2011)**	12,423 community and institutional dwelling adults aged 65 years and older in England and Wales	48% had an ACB score of 1+	4% had medicines with definite AC activity	2% had an ACB score 5+	1.Furosemide(1) 2.Dextroproxyphene(1) 3.Atenolol(1), 4.Nifedipine(1)
***Total anticholinergic burden and risk of mortality and cardiovascular disease over 10 years in 21,636 middle-aged and older men and women of EPIC-Norfolk prospective population study* Myint et al (2014)**	21, 636 adults aged 40-79 years from general practice registers in England	12.5% had an ACB score of 1	6.1% of the population had a score of 2-3	1.3% had a score of ACB 3+	Not reported

Figure 1 Flow Chart

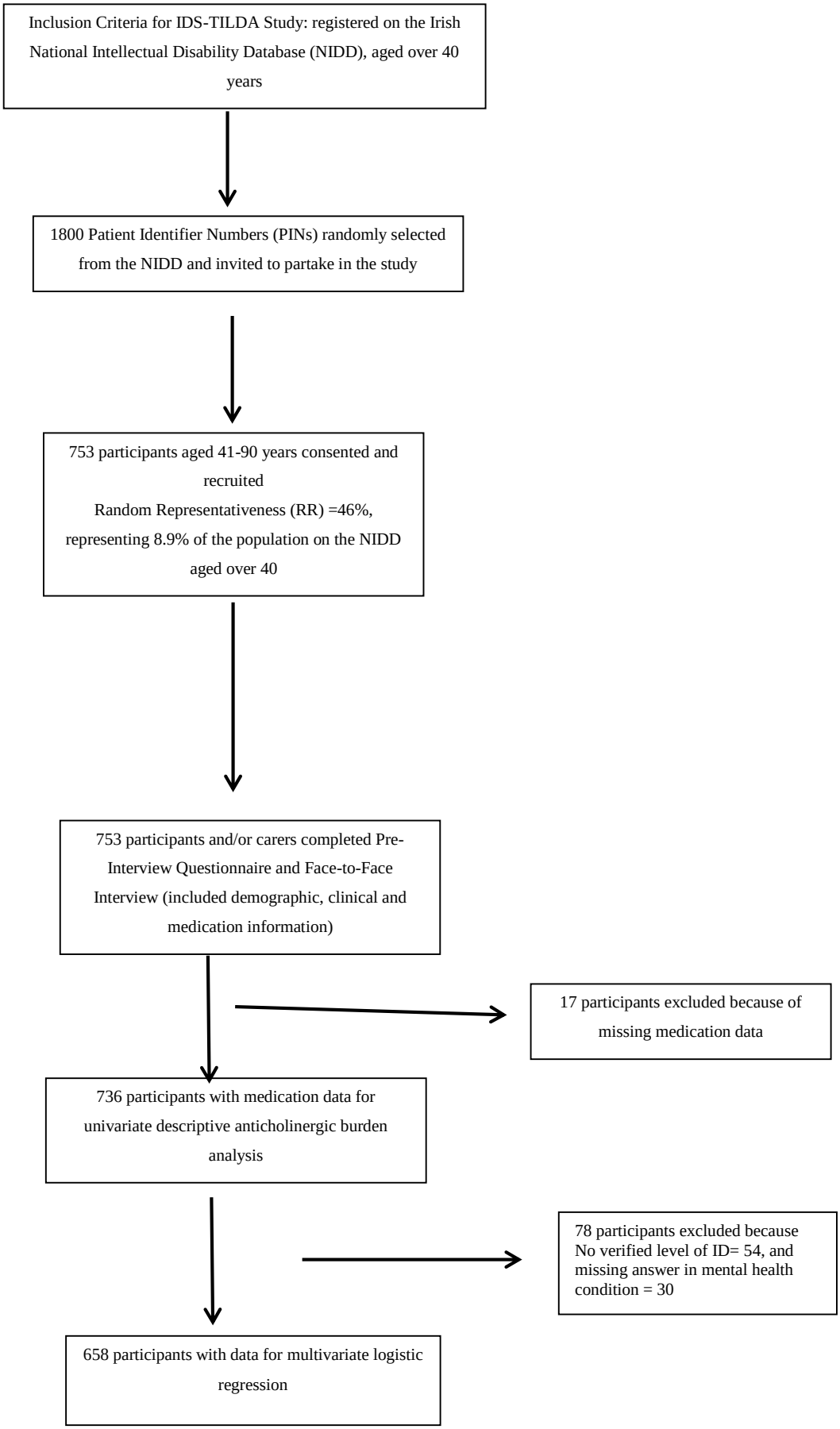
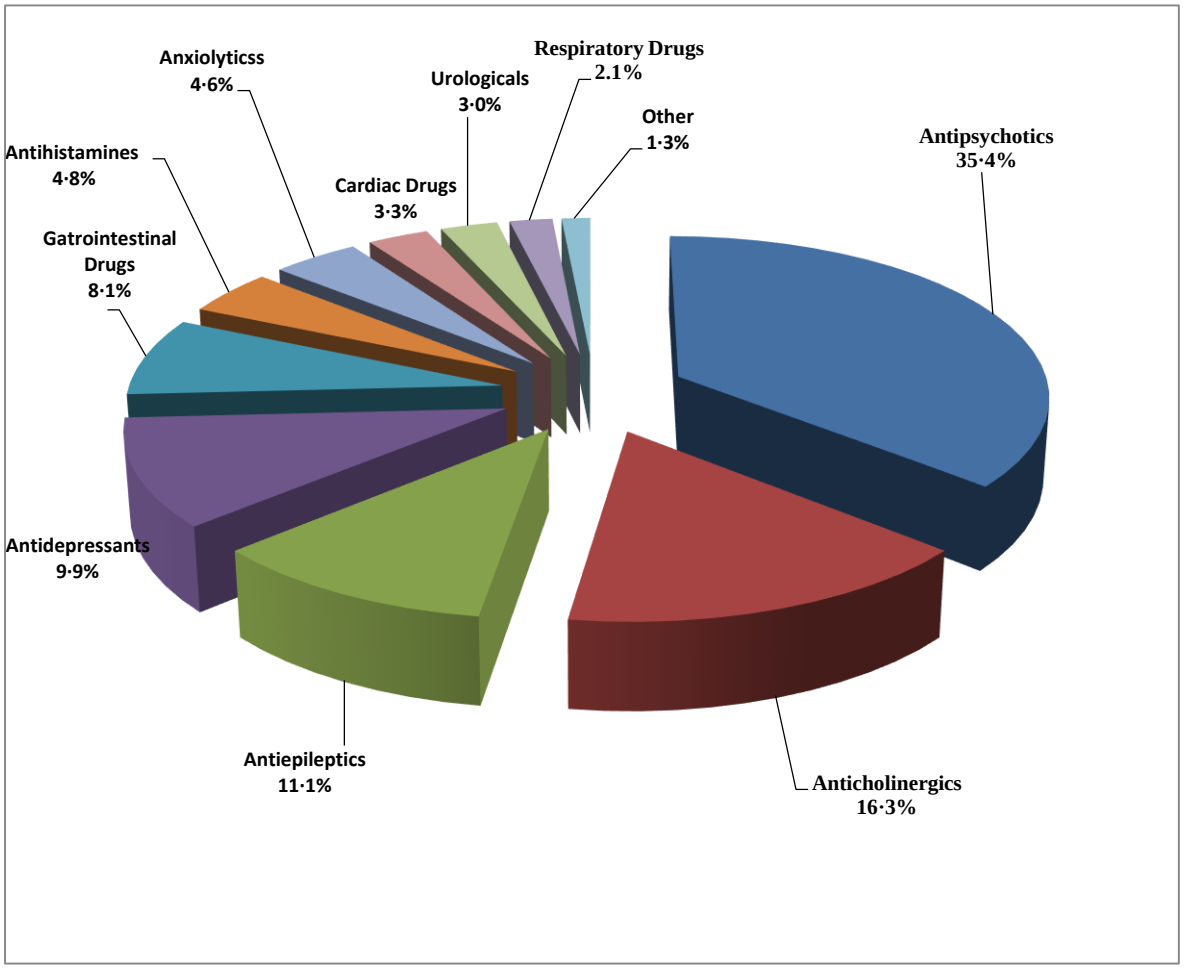


Figure 2 Contribution of therapeutic classes to Total ACB Score in the Population

Figure adapted from Lancot et al. (55)



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