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Complete List of Authors:	Byrne, Catherine; Royal College of Surgeons in Ireland Division of Population Health Sciences, Walsh, Caroline; Royal College of Surgeons in Ireland Division of Population Health Sciences Cahir, Caitriona; Royal College of Surgeons in Ireland Division of Population Health Sciences Ryan, Cristín; University of Dublin Trinity College, School of Pharmacy and Pharmaceutical Sciences Williams, David; Royal College of Surgeons in Ireland and Beaumont Hospital, Geriatric and Stroke Medicine Bennett, Kathleen; Royal College of Surgeons in Ireland Division of Population Health Sciences
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Anticholinergic and sedative drug burden in community-dwelling older people: a cross-sectional national database study

Catherine J Byrne[1], Caroline Walsh[1], Caitriona Cahir[1], Cristin Ryan[2], David J Williams[3], Kathleen Bennett[1]

[1]Division of Population Health Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland; [2]School of Pharmacy and Pharmaceutical Sciences, Trinity College, Dublin, Ireland; [3]Department of Geriatric and Stroke Medicine, Royal College of Surgeons in Ireland and Beaumont Hospital, Dublin, Ireland

Correspondence to: Dr. Catherine Byrne; catherinebyrne@rcsi.com

Abstract

Objectives: The Drug Burden Index (DBI) tool quantifies individual exposure to anticholinergic and sedative medications. The DBI has been internationally validated against adverse health outcomes in older people. DBI exposure has not been reported in the Irish older population. This study aimed to: (i) develop a list of drugs with clinically significant anticholinergic and/or sedative effects (DBI medications) relevant to Ireland; (ii) examine, using the DBI formula, the prevalence of exposure to DBI medications in Irish older people; and (iii) explore patient factors associated DBI exposure.

Design: A cross-sectional national pharmacy claims database study.

Setting: Community setting using the General Medical Services (GMS) scheme pharmacy claims database maintained by the Health Service Executive Primary Care Reimbursement Services.

Participants: Irish older individuals (aged ≥65 years), enrolled in the GMS scheme, and dispensed at least one prescription item in 2016 (*n*=428,516).

Main outcome measures: Prevalence of exposure to DBI medications and patient factors associated with DBI exposure.

Results: 282,874 (66%) of the GMS population aged ≥65 years were exposed to at least one DBI medication in 2016. Prevalence of exposure to DBI medications was significantly higher in females than males (females 71.6% *vs*. males 58.7%, adjusted OR 1.65, 95% CI 1.63-1.68). Prevalence of DBI exposure increased progressively with the number of chronic drugs used, rising from 42.7% of those prescribed 0-4 chronic drugs to 95.4% of those on ≥12 chronic drugs (adjusted OR 27.8, 95% CI 26.7-29.0). The most frequently used DBI medications were codeine/paracetamol combination products (20.1% of patients), tramadol (11.5%), zopiclone (9.5%), zolpidem (8.5%), pregabalin (7.9%) and alprazolam (7.8%).

Conclusions: The majority of older people in Ireland are exposed to medications with anticholinergic and/or sedative effects, particularly females and those with multiple comorbidities. The high use of low-dose codeine/paracetamol combination products, Z-drugs and benzodiazepines suggests there are opportunities for deprescribing.

Strengths and limitations of this study

- This was a large national cross-sectional study of exposure to medications with anticholinergic or sedative effects (DBI medications) in Irish community-dwelling older people.
- A consensus list of DBI medications available in Ireland was developed and used to establish the prevalence of exposure in a highly representative population.
- The main limitations of this study result from the constraints of using pharmacy claims data, which do not include information about the clinical indication for prescriptions, and therefore it is not possible to assess the appropriateness of DBI medications.
- All medications dispensed were included in the analyses but it is not possible to confirm whether the medications were consumed.

Introduction

Medications with anticholinergic and sedative effects carry significant risks of adverse events in older people.[1] However, these medications are used to treat a range of conditions that occur commonly in later life such as mental illness, sleep disturbances, nausea, pain and urinary incontinence.[2] In older patients, particularly those with comorbidities, this may result in an additive anticholinergic and sedative burden.[3] Anticholinergic medications have a range of adverse effects including dry mouth, blurred vision, constipation and urinary retention (peripheral effects), as well as dizziness, confusion, reduced concentration and delirium (central effects).[4] Drugs with sedative effects also cause central nervous system adverse effects, including sedation, memory and psychomotor impairment, and impairment of balance control.[5-7] Older people are more sensitive to these adverse effects due to age-related pharmacokinetic and pharmacodynamic changes.[1] In community-dwelling older people, anticholinergic and sedative drugs have been linked with an increased risk of falls,[8,9] functional impairment,[10,11] and cognitive decline.[12,13] Evidence to support the efficacy of some anticholinergic and sedative medications often does not justify their risks in older people.[14,15] Evidence suggests that deprescribing of some of these medications, such as psychotropic drugs, may result in positive patient health outcomes.[16-18] Therefore, reducing the inappropriate use of these medications in older people is an important public health issue.

Several tools have been developed to evaluate exposure to anticholinergic or sedative medicines. One such tool is the Drug Burden Index (DBI), which is unique when compared with other tools, as it accounts for both cumulative medication exposure and for the patient's dose.[19] The DBI uses the drug monograph to determine whether a drug has clinically significant anticholinergic or sedative effects by considering the pharmacology and side effect profile of the drug. The minimum efficacious dose, which is a key component of the DBI calculation, is determined according to the country-specific approved product information.[2] An accumulating body of evidence supports the validity of the DBI tool in terms of predicting functional impairment in older people, with observational studies from different international settings independently associating DBI exposure with poorer physical function,[7,19,20] frailty,[21] falls,[15,22] healthcare utilisation,[15,23] and, in some studies, mortality.[15,23]

In order to develop strategies to minimise the inappropriate use of anticholinergic and sedative medications in older people, a reliable measure for describing the magnitude of the problem and the identification of targets for improved prescribing of these medications is necessary. However, the prevalence of exposure to anticholinergic and sedative drugs using the DBI tool has not been reported in the Irish older population. Additionally, the list of DBI medications and their minimum effective daily doses needs to be tailored for the specific country of investigation, as the availability of drugs and their minimum recommended daily dose may differ between countries due to regulatory factors as well as factors that may influence drug effects such as genetics, ethnicity, diet and environment.[2] Furthermore, a complete list of DBI medications and minimum effective daily doses to use for screening purposes, which could be adapted to the specific country and periodically updated, has not been published. This study aimed to: (i) develop a list of drugs with clinically significant anticholinergic and/or sedative effects (DBI medications) and their corresponding minimum recommended daily doses in older people relevant

to Ireland; (ii) examine, using the DBI formula, the prevalence of exposure to DBI medications in Irish community-dwelling older people; and (iii) explore patient factors of age, gender and comorbidity associated with increased exposure to DBI medications.

Methods

Study population and design

This was a cross-sectional national pharmacy claims database study in the community setting. Data from the Irish Health Service Executive (HSE) Primary Care Reimbursement Services (PCRS) pharmacy claims database was used to identify the study cohort: older people (aged 65 years and over) enrolled in the General Medical Services (GMS) scheme in Ireland, who had been dispensed at least one prescription in 2016. The HSE-PCRS reimburse pharmacists for the provision of prescription medication in Ireland, through a number of schemes, including the GMS scheme. The GMS database represents the single largest pharmacy claims dataset in Ireland. The GMS scheme provides mainly free health cover (a small co-payment on medicines was introducted in 2010) for those eligible and covers approximately 40% of the general Irish population. Eligibility for the GMS scheme is means tested, with a considerably higher threshold for those over 70 years of age, ensuring approximately 80% of this age group are considered elibible for the scheme.[24,25]

Medicines in the HSE-PCRS pharmacy claims database are coded according to the World Health Organisation Anatomical Therapeutic Chemical (ATC) classification system.[26] Permission to use the anonymised HSE-PCRS data for research purposes was obtained from the HSE-PCRS. Ethics committee approval was not required as all data were anonymised.

Measuring anticholinergic and sedative exposure

The DBI tool was used to calculate cumulative exposure to medications with clinically significant anticholinergic and/or sedative effects (DBI medications) dispensed from 1 January to 31 December 2016. For this analysis, all DBI medications (with the dose information) were identified using relevant ATC codes and subsequently extracted from the pharmacy claims database.

List of DBI medications

Medications with potential anticholinergic and/or sedative effects, available in Ireland, were identified by reviewing several drug monographs,[27-31] and previously published studies.[19,20,32] This list was then refined according to definitions developed by consensus between a pharmacist (CB) and a clinical pharmacologist (DW) as follows: A medication was considered to have clinically significant anticholinergic effects if the pharmacological profile of the drug included anticholinergic activity (blocking activity at muscarinic receptors) as well as a side effect profile consistent with anticholinergic effects listed in the product literature. A medication was considered to have clinically significant sedative effects if drowsiness (or a similar description) was listed as a common (occurring in >1/100 and

<1/10 users) or very common (occurring in >1/10 users) adverse effect in the product literature. Topical preparations without significant systemic effects were excluded as per previous studies.[19,20]

The minimum effective daily dose was decided by consensus between two pharmacists (CB, CW) after independent review of drug monographs.[27-31] The following assumptions were made in determining the minimum effective daily dose:

i) The minimum effective daily dose in older people was used when stated; otherwise, the minimum effective daily adult dose was used.

ii) For drugs initiated at a low dose and titrated to effect, the minimum effective daily maintenance dose was used.

iii) For drugs with several indications, and when doses varied depending on the indication, the minimum effective daily dose across all indications was used, except for opiates where the minimum effective daily dose was based on the analgesic dose.

iv) For drugs available alone and in combination with other drugs, the minimum effective daily dose for the anticholinergic/sedative drug alone was used to define the minimum effective daily dose for the anticholinergic/sedative drug in the combination product.

v) For analgesic drugs with different doses for breakthrough pain and chronic pain, the minimum effective daily dose for chronic pain was used.

vi) For drugs administered on an 'as needed' basis, the minimum effective daily dose was the minimum effective single dose multiplied by the minimum number of times the dose is normally repeated in 24 hours.

vii) For drugs administered by more than one route, the minimum effective daily dose for the oral route (or the most commonly used route if not administered orally) was used as the reference dose. The reference dose was converted to an equivalent dose for other available routes of administration based on reported conversion factors or bioavailability data.[27,28,30,31]

Calculating DBI exposure

Total DBI exposure for each individual was calculated as the sum of exposure to any DBI medication dispensed in 2016 using the following equation:[19]

$$DBI = \sum D/(\delta + D)$$

where D is the daily dose taken by the individual patient, and δ is the minimum effective daily dose for that drug. The daily dose taken by the individual patient for each DBI medication was estimated by multiplying the strength and total quantity dispensed in 2016, and then normalising by dividing by 365 days.[15] DBI exposure was also quantified for each patient over one year including only chronic DBI

medications, defined as at least three prescription items dispensed in the year for the same fourth-level ATC code (e.g. N02AJ).[33]

Statistical Analysis

Exposure to DBI medications was categorized dichotomously as unexposed (DBI=0) and exposed (DBI>0). Prevalence rates and associated 95% CIs for GMS eligible patients aged 65 years and over with at least one prescription dispensed in 2016 (DBI exposure) were calculated. Logistic regression was used to examine the association between DBI exposure and the following patient variables: age at first dispensing in 2016 [categorized into 65-69 (reference), 70-74, 75-79, and ≥80 years], gender [male (reference), female] and number of co-prescribed chronic medications over the year [categorized as 0-4 (reference), 5-7, 8-11, and ≥12 chronic medications]. Chronic medication was defined as receiving at least three prescription items dispensed in the year with the same second-level ATC code (e.g. N02), relating to only the following first-level codes: A (alimentary tract and metabolism), B (blood and blood-forming organs), C (cardiovascular system), G (genito urinary system and sex hormones), H (systemic hormonal preparation, excluding sex hormones and insulins), L (antineoplastic and immunomodulating agents), M (musculo-skeletal system), N (nervous system), R (respiratory system) and S (sensory organs), and excluding those on the denominator of the DBI exposure.[33,34] Adjusted odds ratios (ORs) and 95% CIs were computed. Statistical significance at $P<0.05$ was assumed. Statistical analyses were conducted using SAS® v 9.4 (SAS Institute Inc., Cary, NC, USA).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

The final list of DBI medications, and their minimum effective daily doses, is provided in Supplementary Table S1. This list included 156 medications (15 with anticholinergic effects only, 87 with sedative effects only, and 54 with both anticholinergic and sedative effects).

In total, 282,874 (66%) of the 428,516 GMS eligible population aged 65 years and over in receipt of any claim during 2016 received at least one claim for a DBI medication. The prevalence of chronic DBI exposure was 54.0%. Median (IQR) DBI score over the year was 0.52 (0.11-1.03).

Table 1 shows the prevalence of patients with DBI exposure in 2016 by a range of patient characteristics. Females were significantly more likely to have DBI exposure compared to males (females 71.6% *vs*. males 58.7%, adjusted OR 1.65, 95% CI 1.63, 1.68). Prevalence of DBI exposure increased noticeably with the number of chronic drugs used, rising progressively from 42.7% of those prescribed 0-4 chronic drugs receiving a DBI prescription to 95.4% of those on ≥12 chronic drugs (adjusted OR 27.81, 95% CI 26.72,

28.96). Those aged 80 years and over had a significantly higher prevalence of DBI exposure than those aged <80 years (≥80 years 71.5% *vs*. <80 years 63.5%). In multivariate analysis, the association between increasing age and DBI exposure was diminished (adjusted OR 0.82, 95% CI 0.81, 0.84).

Table 2 shows the 10 most frequently used DBI medications by Irish older people in 2016. Codeine and tramadol were the most commonly used medications with sedative effects (20.1% and 11.5% of patients, respectively). Of the 383,641 codeine prescriptions dispensed in 2016, 98.9% were for codeine/paracetamol combination products, of which 54.6% were for low-dose codeine products (codeine/paracetamol 8 mg/500 mg per tablet), 6.9% were for medium-dose codeine products (codeine/paracetamol 15 mg/500 mg per tablet), and 38.5% were for high-dose codeine products (codeine/paracetamol 30 mg/500 mg per tablet). Prochlorperazine and hyoscine butylbromide were the most commonly used medications with anticholinergic effects (5.9% and 4.6% of patients, respectively).

Figure 1 shows the frequency of DBI drug classes dispensed to Irish older people in 2016. Anxiolytics/hypnotics and antidepressants were the most frequently prescribed drug classes of DBI medications (25% and 24% of DBI prescriptions dispensed in 2016, respectively). Of the 1,264,078 anxiolytic/hypnotic prescriptions dispensed in 2016, 52.5% were for benzodiazepines, and 47.4% were for Z-drugs (zopiclone, zolpidem and zaleplon). Of the 1,211,319 antidepressant prescriptions, 47.3% were for selective serotonin reuptake inhibitors, 16.8% were for tricyclic antidepressants, 16.7% were for serotonin noradrenaline reuptake inhibitors, and 19.2% were for other antidepressants (mirtazapine, phenelzine, and trazodone).

Discussion

This study found that the majority of older people in Ireland are exposed to medications with anticholinergic and/or sedative effects, particularly females and those with multiple comorbidities. A lower prevalence of exposure to DBI medications of 43% was reported in a previous population study of older people living in New Zealand, of similar size and methodology to the current study.[15] Other studies of DBI exposure conducted in Australia, USA and Europe, with smaller cohorts of older people in various settings, have demonstrated a prevalence ranging from 20% up to 79%.[20,21,35,36] This variability may be related to different definitions used to identify anticholinergic and sedative medications, specific sociodemographic or health status characteristics of participants, and differences in medication access and use across different settings and countries.[2] Further, prevalence rates calculated for the current study included DBI medications dispensed on an 'as needed' basis. There is no consistency in terms of the inclusion or exclusion of 'as needed' medications in previous studies, which may also explain the variability in prevalence rates reported.

This current study found that female patients and patients with high comorbidity burdens, who are more likely to be very old (80+ years), all appear to be particularly vulnerable to exposure to DBI medications, which is consistent with the literature.[15] Numerous studies have reported greater use of psychotropic drugs and analgesics by women compared to men.[37-40] Possible reasons for a greater use amongst women include increased willingness to seek medical care, increased likelihood of women to

perceive and report mental illness or pain, and general practitioner (GP) prescribing bias.[41,42] It has been shown that women are more likely to receive a prescription for a psychotropic drug during a GP consultation compared to men.[37] Targeted efforts to reduce inappropriate prescribing of these medications in vulnerable older women are therefore needed.

Examination of the most frequently used DBI medications (Table 2) suggests there may be opportunities for deprescribing of DBI medications in older Irish people. The high use of low-dose codeine/paracetamol combinations is of particular concern. It is known that codeine doses of at least 30 mg are required for analgesia.[43] At this dose, a small but statistically significant increase in the analgesic effect of codeine/paracetamol combinations compared to paracetamol alone has been shown.[43,44] However, there is a lack of pharmacological evidence to support the analgesic benefit from using low-dose codeine combination analgesics.[45] Combining low-doses of codeine with paracetamol is likely to bring minimal analgesic benefit, but will increase the risk of adverse effects.[46] The most frequently prescribed codeine combination product in our study contained 8 mg of codeine and 500 mg of paracetamol per tablet. Thus, at the maximal dose of two tablets (16 mg/1000 mg codeine/paracetamol), the quantity of codeine would not achieve doses close to the minimum effective dose of codeine required for analgesia. Yet, these products will still induce the adverse effects experienced with codeine, including constipation, nausea, dry mouth, dizziness and drowsiness.[47] Further, the use of codeine in older people has been associated with an increased risk of falls and hip fracture (60% increased risk),[48] which highlights the need to limit its use.[49] Therefore, use of a paracetamol alone product, rather than a combined low-dose codeine/paracetamol product, may be more appropriate for some patients.

The high use of hypnotic Z-drugs and anxiolytic benzodiazepines (alprazolam and diazepam) is also noteworthy. Widespread use of benzodiazepines and Z-drugs has been reported in other European countries.[50,51] These drugs should be used with caution due to their adverse effect profile, such as drowsiness, confusion, impairment of memory, and incoordination, which can be particularly problematic in older people.[52] Both benzodiazepines and Z-drugs have been associated with problems in older people including an increased risk of injurious falls and hip fracture, and cognitive impairment.[14,17] It is therefore recommended that these drugs be avoided in older people and, where appropriate, discontinuation under appropriate supervision is widely advised.[17,53] It has been shown that discontinuation of benzodiazepines and Z-drugs in community-dwelling older people is possible, without adverse events attributable to discontinuation, and may be associated with improved health outcomes, such as a reduction in the risk of falls and improvements in cognitive functioning.[16,54,55] A meta-analysis of interventions to reduce benzodiazepine and Z-drug use in older people demonstrated the beneficial effects of consultations and education of both prescribers and patients, followed by a supervised withdrawal.[56]

Strengths and limitations

The present study was a large national study of DBI exposure in community-dwelling older patients in Ireland. The study design enabled examination of the variation in DBI exposure between patients in a

highly representative population. A consensus list of DBI medications was developed, which may be of use for future studies using the DBI tool.

The authors acknowledge the following limitations. These largely result from the constraints of using pharmacy claims data in this study. Information about the clinical indication for prescriptions is not available in pharmacy claims data and therefore it is not possible to assess the appropriateness of DBI prescriptions. DBI prescribing may not always be inappropriate. The prescription may be justified for clinical reasons, after balancing risk and benefit in conditions of uncertainty. Nevertheless, given that DBI medications have been associated with adverse events in older people, the observed high prevalence of DBI prescribing suggests that a significant amount of prescribing could be improved. In addition, pharmacy claims data does not include medications purchased over-the-counter (OTC). However, there is no incentive for GMS patients to buy medications OTC, as most of these items are available on prescription for a small co-payment, and therefore the risk of bias is expected to be low. All medications dispensed were included in the analyses but it was not possible to confirm whether the dispensed medications were consumed and for how long. Therefore, the DBI calculations may not reflect true exposure. However, the results reflect prescribing practice in terms of intention to prescribe. There is also the possibility of socioeconomic bias, particularly in the 65-69 year age group, as only 40% of this population is covered under the GMS scheme, which over represents more socially deprived individuals. However, approximately 80% of those aged ≥70 years are covered for medications under the GMS scheme and, therefore, socioeconomic bias in these patients would be low. Another notable limitation involves the list of DBI medications used in this analysis, which, although determined by consensus, may be associated with interpretation bias leading to an over- or under-estimation of the prevalence of DBI exposure. There is no gold standard definition to describe medications with clinically significant anticholinergic or sedative effects and therefore the clinical validity of our selection of drugs may be limited by this.

Implications for policy and practice

The results of this present study highlight the need for interventions to reduce the inappropriate use of medications with clinically significant anticholinergic or sedative effects in older people in Ireland. In particular, the high use of low-dose codeine/paracetamol combination products, Z-drugs and benzodiazepines, suggests that interventions to alert prescribers and patients about the risks associated with these drugs in older people should be a priority. Due consideration should also be given to the importance of regular medication reviews, with a particular focus on older females and those with multiple comorbidities.

In practice, the DBI may be useful as a screening tool for older patients, to identify those patients with high exposure, which may compromise their physical and cognitive functioning.[57] Such patients are likely to be eligible for deprescribing interventions such as medication review.[57] A previous intervention study showed that collaborative pharmacist-led medication review with the GP can reduce the prescribing of sedative and anticholinergic medications in older people, resulting in a significant decrease in the DBI

score.[58] At the population level, the DBI tool could be used as a quality indicator to guide policy to improve prescribing and optimise clinical outcomes in older people.[15]

Conclusions

In conclusion, this large population-based study has shown that there is a high prevalence of use of medications with anticholinergic and sedative effects among Irish community-dwelling older people, particularly in females and those with multiple comorbidities. The high use of low-dose codeine/paracetamol combination products, Z-drugs and benzodiazepines, suggests that there are opportunities for deprescribing in this population. The consensus list of DBI medications developed may be of use in future studies using the DBI tool. Future research should focus on examining the impact of DBI on important health outcomes in older Irish patients, and developing interventions to reduce the inappropriate use of DBI medications in this vulnerable patient population.

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Footnotes

Contributors: CB and KB conceived and designed the study. CB, CW, DW and CR contributed to development of the DBI medication list. KB accessed the data (HSE-PCRS). KB and CB performed the analysis and interpreted the results. CB wrote the manuscript. All authors critically revised the manuscript and approved the final version.

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Table 1. Prevalence of patients aged 65 years and over dispensed at least one Drug Burden Index medication prescription in 2016

Patient level fixed effects (*n*)	% dispensed a DBI prescription	Odds ratio (95% CI)	
		Unadjusted	Adjusted
Sex:			
Male (185938)	58.7	1.00	1.00
Female (242578)	71.6	1.78 (1.75-1.80)	1.65 (1.63-1.68)
Number of chronic drugs:			
0-4 (153960)	42.7	1.00	1.00
5-7 (113614)	66.4	2.65 (2.60-2.69)	2.67 (2.63-2.71)
8-11 (102682)	83.9	6.96 (6.82-7.09)	7.03 (6.89-7.17)
≥12 (58260)	95.4	27.63 (26.55-28.76)	27.81 (26.72-28.96)
Age (years):			
65-69 (96804)	63.5	1.00	1.00
70-74 (109118)	62.4	0.95 (0.94-0.97)	0.85 (0.83-0.87)
75-79 (93300)	65.3	1.09 (1.07-1.11)	0.81 (0.80-0.83)
≥80 (129294)	71.5	1.44 (1.42-1.47)	0.82 (0.81-0.84)

n, number of patients; DBI, Drug Burden Index; CI, confidence interval

Table 2. Most frequently used Drug Burden Index medications in Irish older people in 2016[a]

Medication	Anticholinergic/sedative effects	% patients
Codeine	Sedative	20.1
Tramadol	Sedative	11.5
Zopiclone	Sedative	9.5
Zolpidem	Sedative	8.5
Pregabalin	Sedative	7.9
Alprazolam	Sedative	7.8
Diazepam	Sedative	6.5
Escitalopram	Sedative	5.9
Prochlorperazine	Anticholinergic + Sedative	5.9
Mirtazapine	Sedative	4.8

[a]Prevalence calculated by the number of patients dispensed at least one prescription for a Drug Burden Index medication divided by the total number of patients dispensed at least one prescription in 2016.

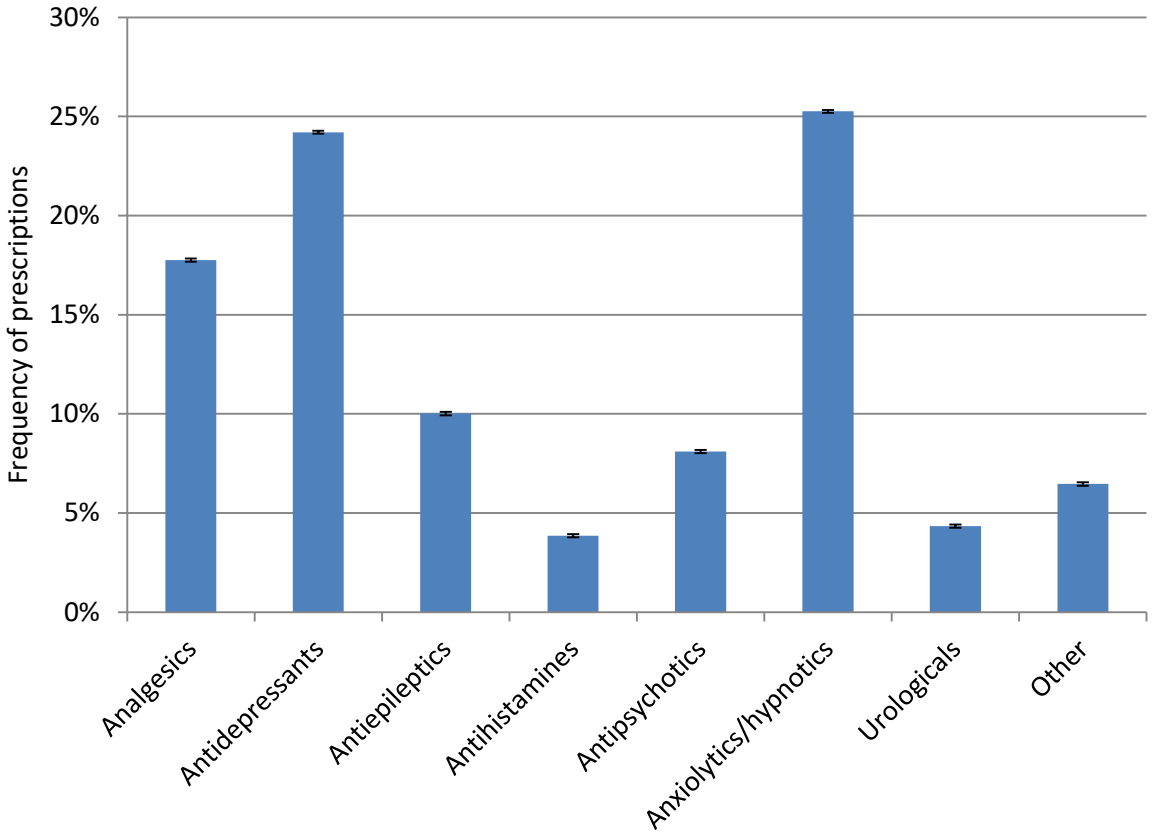

Figure 1. Percentage and 95% confidence intervals of anticholinergic and/or sedative medication prescriptions dispensed by drug class in Irish older patients in 2016. Other=antiparkinson drugs, cardiovascular drugs, gastrointestinal drugs, and muscle relaxants.

SupplementaryTable S1. Medications with anticholinergic and/or sedatives effects for inclusion in the calculation of Drug Burden Index

Drug	WHO ATC Code/s	Anticholinergic effects (AC)	Sedative effects (S)	Minimum effective daily dose by route of administration (mg)					
				Oral	Parenteral	Sublingual/buccal	Transdermal	Rectal	Inhalation
Alimemazine	R06AD01	AC	S	10					
Alprazolam	N05BA12		S	0.5					
Amantadine	N04BB01	AC		100					
Amisulpride	N05AL05		S	50					
Amitriptyline	N06AA09	AC	S	10					
Aripiprazole	N05AX12		S	10	10				
Asenapine	N05AH05		S			10			
Atropine	A03BA01 AO3CB03	AC		0.6	0.3				
Baclofen	M03BX01		S	30	30				
Benperidol	N05AD07		S	0.125					
Benzatropine	N04AC01	AC		0.5	0.5				
Biperiden	N04AA02	AC	S	1					
Brompheniramine	R06AB01 R06AB51	AC	S	16					
Buclizine	R06AE51 R06AE01	AC	S	12.5					
Buprenorphine	N02AE01		S		0.12	0.4	0.12		
Buspirone	N05BE01		S	15					
Carbamazepine	N03AF01	AC	S	400				500	
Cetirizine	R06AE07		S	10					
Cloral Hydrate	N05CC01		S	430					
Chlordiazepoxide	N05BA02		S	5					
Chlorphenamine	R06AB04	AC	S	8	3				
Chlorpromazine	N05AA01	AC	S	30	6				
Cinnarizine	N07CA02	AC	S	60					

	N07CA52								
Citalopram	N06AB04		S	10					
Clemastine	R06AA04 R06AA54	AC	S	2					
Clobazam	N05BA09		S	10					
Clomethiazole	N05CM0 N05CX04		S	192					
Clomipramine	N06AA04	AC	S	30					
Clonazepam	N03AE01		S	0.5	0.5				
Clonidine	N02CX02 C02AC01		S	0.1					
Clozapine	N05AH02	AC	S	25					
Codeine	R05DA04 N02AJ06		S	120					
Cyclizine	R06AE03 N02AA51	AC	S	50	50				
Cyproheptadine	RO6AX02	AC	S	4					
Darifenacin	G04BD10	AC		7.5					
Dexchlorpheniramine	R06AB02 R06AB52	AC	S	8					
Diazepam	N05BA01		S	1	1			1	
Dicycloverine	A03AA07	AC		30					
Dihydrocodeine	N02AA08 N02AJ01		S	40					
Dimenhydrinate	R06AA02 N07CA52	AC	S	150					
Diphenhydramine	N02BE71 N02BE51 R06AA02 R06AA52	AC	S	50					
Diphenoxylate	A07DA01		S	5					

Disopyramide	C01BA03	AC		300	300				
Dosulepin	N06AA16	AC	S	50					
Doxazosin	C02CA04		S	2					
Doxepin	N06AA12	AC	S	25					
Doxylamine	R06AA09 R06AA59 N02BE51	AC	S	25					
Duloxetine	N06AX21		S	30					
Escitalopram	N06AB10		S	5					
Fentanyl	N02AB03		S		0.3	0.6	0.3		
Fesoterodine	G04BD11	AC		4					
Fexofenadine	R06AX26		S	120					
Flavoxate	G04BD02	AC	S	600					
Flunitrazepam	N05CD03		S	0.5					
Fluoxetine	N06AB03		S	20					
Flupentixol	N05AF01	AC	S	0.5	0.3				
Fluphenazine	N05AB02	AC	S		0.36				
Flurazepam	N05CD01		S	15					
Fluvoxamine	N06AB08		S	100					
Gabapentin	N03AX12		S	900					
Glycopyrronium	A03AB02	AC	S	2	0.2				
Haloperidol	N05AD01		S	0.5	0.25				
Hydromorphone	N02AA03		S	7.8	2.6				
Hydroxyzine	N05BB01	AC	S	25					
Hyoscine base	A04AD01	AC	S				0.5		
Hyoscine Butylbromide	A03BB01	AC		30	30				
Hyoscine Hydrobromide	A04AD01	AC	S	0.9			0.5		
Hyoscyamine	A03CB31 A03BA03	AC		0.375					

Imipramine	N06AA02	AC	S	30					
Indoramin	C02CA02		S	20					
Lamotrigine	N03AX09		S	100 200*					
Levetiracetam	N03AX14		S	1000					
Levocetirizine	R06AE09		S	5					
Levomepromazine	N05AA02	AC	S	37.5	37.5				
Lofepramine	N06AA07	AC	S	140					
Loprazolam	N05CD11		S	1					
Loratadine	R06AX13		S	10					
Lorazepam	N05BA06		S	0.5	0.5				
Lormetazepam	N05CD06		S	0.5					
Loxapine	N05AH01	AC	S						4.5
Meclozine	R06AE05 R06AE55	AC	S	25					
Memantine	N06DX01		S	20					
Meptazinol	N02AX05		S	800					
Methadone	N07BC02		S	5					
Methocarbamol	M03BA03	AC	S	2250					
Methyldopa	C02AB01		S	500					
Metoclopramide	A03FA01 N02BE51		S	15	15				
Mianserin	N06AX03		S	30					
Mirtazepine	N06AX11		S	15					
Morphine	N02AA01 N02AA51		S	20	6.7				
Moxonidine	C02AC05		S	0.2					
Nefopam	N02BG06	AC	S	90					
Nitrazepam	N05CD02		S	2.5					
Nortriptyline	N06AA10	AC	S	30					

Olanzapine	N05AH03	AC	S	5	5				
Orphenadrine	N04AB02	AC		100					
Oxazepam	N05BA04		S	15					
Oxcarbazepine	N03AF02		S	600					
Oxybutynin	G04BD04	AC	S	5			1.95		
Oxycodone	N02AA05 N02AA55		S	20	10			20	
Paliperidone	N05AX13		S	3	0.89				
Paroxetine	N06AB05	AC	S	20					
Pentazocine	N02AD01		S	300	180				
Perampanel	N03AX22		S	4					
Pericyazine	N05AC01	AC	S	5					
Perphenazine	N05AB03	AC	S	3					
Pethidine	N02AB02		S	300	150				
Phenelzine	N06AF03		S	7.5					
Phenobarbital	N03AA02		S	60	60				
Phenytoin	N03AB02		S	200	200				
Pimozide	N05AG02	AC	S	2					
Pizotifen	N02CX01	AC	S	1.5					
Pramipexole	N04BC05		S	0.088					
Prazepam	N05BA11		S	10					
Prazosin	C02CA01		S	2					
Pregabalin	N03AX16		S	150					
Primidone	N03AA03		S	750					
Prochlorperazine	N05AB04	AC	S	10	1.25	4			
Procyclidine	N04AA04	AC		7.5					
Promazine	N05AA03	AC	S	100					
Promethazine	R06AD02	AC	S	20	5				
Propantheline	A03AB05	AC		22.5					

Propiverine	G04BD06	AC	S	15					
Quetiapine	N05AH04	AC	S	50					
Retigabine	N03AX21		S	600					
Risperidone	N05AX08		S	1	0.7				
Ropinirole	N04BC04		S	2					
Rotigotine	N04BC09		S				1		
Rufinamide	N03AF03		S	400					
Sertraline	N06AB06		S	50					
Solifenacin	G04BD08 G04CA53	AC		5					
Sulpiride	N05AL01	AC	S	400					
Tapentadol	N02AX06		S	100					
Temazepam	N05CD07		S	5					
Terazosin	G04CA03		S	2					
Tiagabine	N03AG06		S	15 30*					
Tizanidine	M03BX02	AC	S	6					
Tolterodine	G04BD07	AC	S	2					
Topiramate	N03AX11		S	50					
Tramadol	N02AX02 N02AJ13		S	200	200				
Trazodone	N06AX05		S	100					
Triazolam	N05CD05		S	0.125					
Trifluoperazine	N05AB06	AC	S	2					
Trihexyphenidyl	N04AA01	AC		5					
Trimipramine	N06AA06	AC	S	37.5					
Triprolidine	R06AX07	AC	S	10					
Trospium	G04BD09	AC		40					
Valproic Acid	N03AG01		S	1000					

Venlafaxine	N06AX16		S	75					
Vigabatrin	N03AG04		S	2000					
Zaleplon	N05CF03		S	5					
Ziprasidone	N05AE04		S	40					
Zolpidem	N05CF02		S	5					
Zonisamide	N03AX15		S	300					
Zopiclone	N05CF01		S	3.75					
Zuclopenthixol	N05AF05	AC	S	20	11.4				

WHO ATC, World Health Organisation Anatomical Therapeutic Classification

*Minimum effective daily dose if taken concurrently with agents that induce hepatic enzymes including phenytoin, carbamazepine, phenobarbitone, primidone, rifampicin and lopinavir/ritonavir.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4, 5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	5-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	7, 8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7, Table 1
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7, 8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8, 9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10, 11
Generalisability	21	Discuss the generalisability (external validity) of the study results	9, 10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Anticholinergic and sedative drug burden in community-dwelling older people: a national database study

Catherine J Byrne[1], Caroline Walsh[1], Caitriona Cahir[1], Cristin Ryan[2], David J Williams[3], Kathleen Bennett[1]

[1]Division of Population Health Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland; [2]School of Pharmacy and Pharmaceutical Sciences, Trinity College, Dublin, Ireland; [3]Department of Geriatric and Stroke Medicine, Royal College of Surgeons in Ireland and Beaumont Hospital, Dublin, Ireland

Correspondence to: Dr. Catherine Byrne; catherinebyrne@rcsi.com

Abstract

Objectives: The Drug Burden Index (DBI) tool quantifies individual exposure to anticholinergic and sedative medications. The DBI has been internationally validated against adverse health outcomes in older people. DBI exposure has not been reported in the Irish older population. This study aimed to: (i) develop a list of drugs with clinically significant anticholinergic and/or sedative effects (DBI medications) relevant to Ireland; (ii) examine, using the DBI formula, the prevalence of exposure to DBI medications in Irish older people; and (iii) explore patient factors associated DBI exposure.

Design: A cross-sectional national pharmacy claims database study.

Setting: Community setting using the General Medical Services (GMS) scheme pharmacy claims database maintained by the Health Service Executive Primary Care Reimbursement Services.

Participants: Irish older individuals (aged ≥65 years), enrolled in the GMS scheme, and dispensed at least one prescription item in 2016 (*n*=428,516).

Main outcome measures: Prevalence of exposure to DBI medications and patient factors associated with DBI exposure.

Results: 282,874 (66%) of the GMS population aged ≥65 years were exposed to at least one DBI medication in 2016. Prevalence of exposure to DBI medications was significantly higher in females than males (females 71.6% *vs*. males 58.7%, adjusted OR 1.65, 95% CI 1.63-1.68). Prevalence of DBI exposure increased progressively with the number of chronic drugs used, rising from 42.7% of those prescribed 0-4 chronic drugs to 95.4% of those on ≥12 chronic drugs (adjusted OR 27.8, 95% CI 26.7-29.0). The most frequently used DBI medications were codeine/paracetamol combination products (20.1% of patients), tramadol (11.5%), zopiclone (9.5%), zolpidem (8.5%), pregabalin (7.9%) and alprazolam (7.8%).

Conclusions: The majority of older people in Ireland are exposed to medications with anticholinergic and/or sedative effects, particularly females and those with multiple comorbidities. The high use of low-dose codeine/paracetamol combination products, Z-drugs and benzodiazepines suggests there are opportunities for deprescribing.

Strengths and limitations of this study

- This was a large national cross-sectional study of exposure to medications with anticholinergic or sedative effects (DBI medications) in Irish community-dwelling older people.
- A consensus list of DBI medications available in Ireland was developed and used to establish the prevalence of exposure in a highly representative population.
- The main limitations of this study result from the constraints of using pharmacy claims data, which do not include information about the clinical indication for prescriptions, and therefore it is not possible to assess the appropriateness of DBI medications.
- All medications dispensed were included in the analyses but it is not possible to confirm whether the medications were consumed.

Introduction

Medications with anticholinergic and sedative effects carry significant risks of adverse events in older people.[1] However, these medications are used to treat a range of conditions that occur commonly in later life such as mental illness, sleep disturbances, nausea, pain and urinary incontinence.[2] In older patients, particularly those with comorbidities, this may result in an additive anticholinergic and sedative burden.[3] Anticholinergic medications have a range of adverse effects including dry mouth, blurred vision, constipation and urinary retention (peripheral effects), as well as dizziness, confusion, reduced concentration and delirium (central effects).[4] Drugs with sedative effects also cause central nervous system adverse effects, including sedation, memory and psychomotor impairment, and impairment of balance control.[5-7] Older people are more sensitive to these adverse effects due to age-related pharmacokinetic and pharmacodynamic changes.[1] In community-dwelling older people, anticholinergic and sedative drugs have been linked with an increased risk of falls,[8,9] functional impairment,[10,11] and cognitive decline.[12,13] Evidence to support the efficacy of some anticholinergic and sedative medications often does not justify their risks in older people.[14,15] Evidence suggests that deprescribing of some of these medications, such as psychotropic drugs, may result in positive patient health outcomes.[16-18] Therefore, reducing the inappropriate use of these medications in older people is an important public health issue.

Several tools have been developed to evaluate exposure to anticholinergic or sedative medicines. One such tool is the Drug Burden Index (DBI), which is unique when compared with other tools, as it accounts for both cumulative medication exposure and for the patient's dose.[19] The DBI uses the drug monograph to determine whether a drug has clinically significant anticholinergic or sedative effects by considering the pharmacology and side effect profile of the drug. The minimum efficacious dose, which is a key component of the DBI calculation, is determined according to the country-specific approved product information.[2] An accumulating body of evidence supports the validity of the DBI tool in terms of predicting functional impairment in older people, with observational studies from different international settings independently associating DBI exposure with poorer physical function,[7,19,20] frailty,[21] falls,[15,22] healthcare utilisation,[15,23] and, in some studies, mortality.[15,23]

In order to develop strategies to minimise the inappropriate use of anticholinergic and sedative medications in older people, a reliable measure for describing the magnitude of the problem and the identification of targets for improved prescribing of these medications is necessary. However, the prevalence of exposure to anticholinergic and sedative drugs using the DBI tool has not been reported in the Irish older population. Additionally, the list of DBI medications and their minimum effective daily doses needs to be tailored for the specific country of investigation, as the availability of drugs and their minimum recommended daily dose may differ between countries due to regulatory factors as well as factors that may influence drug effects such as genetics, ethnicity, diet and environment.[2] Furthermore, a complete list of DBI medications and minimum effective daily doses to use for screening purposes, which could be adapted to the specific country and periodically updated, has not been published. This study aimed to: (i) develop a list of drugs with clinically significant anticholinergic and/or sedative effects (DBI medications) and their corresponding minimum recommended daily doses in older people relevant

to Ireland; (ii) examine, using the DBI formula, the prevalence of exposure to DBI medications in Irish community-dwelling older people; and (iii) explore patient factors of age, gender and comorbidity associated with increased exposure to DBI medications.

Methods

Study population and design

This was a cross-sectional national pharmacy claims database study in the community setting. Data from the Irish Health Service Executive (HSE) Primary Care Reimbursement Services (PCRS) pharmacy claims database was used to identify the study cohort: older people (aged 65 years and over) enrolled in the General Medical Services (GMS) scheme in Ireland, who had been dispensed at least one prescription in 2016. The HSE-PCRS reimburse pharmacists for the provision of prescription medication in Ireland, through a number of schemes, including the GMS scheme. The GMS database represents the single largest pharmacy claims dataset in Ireland. The GMS scheme provides mainly free health cover (a small co-payment on medicines was introducted in 2010) for those eligible and covers approximately 40% of the general Irish population. Eligibility for the GMS scheme is means tested, with a considerably higher threshold for those over 70 years of age, ensuring approximately 80% of this age group are considered elibible for the scheme.[24,25]

Medicines in the HSE-PCRS pharmacy claims database are coded according to the World Health Organisation Anatomical Therapeutic Chemical (ATC) classification system.[26] Permission to use the anonymised HSE-PCRS data for research purposes was obtained from the HSE-PCRS. Ethics committee approval was not required as all data were anonymised.

Measuring anticholinergic and sedative exposure

The DBI tool was used to calculate cumulative exposure to medications with clinically significant anticholinergic and/or sedative effects (DBI medications) dispensed from 1 January to 31 December 2016. For this analysis, all DBI medications (with the dose information) were identified using relevant ATC codes and subsequently extracted from the pharmacy claims database.

List of DBI medications

Medications with potential anticholinergic and/or sedative effects, available in Ireland, were identified by reviewing several drug monographs,[27-31] and previously published studies.[19,20,32] This list was then refined according to definitions developed by consensus between a pharmacist (CB) and a clinical pharmacologist (DW) as follows: A medication was considered to have clinically significant anticholinergic effects if the pharmacological profile of the drug included anticholinergic activity (blocking activity at muscarinic receptors) as well as a side effect profile consistent with anticholinergic effects listed in the product literature. A medication was considered to have clinically significant sedative effects if drowsiness (or a similar description) was listed as a common (occurring in >1/100 and

<1/10 users) or very common (occurring in >1/10 users) adverse effect in the product literature. Topical preparations without significant systemic effects were excluded as per previous studies.[19,20]

The minimum effective daily dose was decided by consensus between two pharmacists (CB, CW) after independent review of drug monographs.[27-31] The following assumptions were made in determining the minimum effective daily dose:

i) The minimum effective daily dose in older people was used when stated; otherwise, the minimum effective daily adult dose was used.

ii) For drugs initiated at a low dose and titrated to effect, the minimum effective daily maintenance dose was used.

iii) For drugs with several indications, and when doses varied depending on the indication, the minimum effective daily dose across all indications was used, except for opiates where the minimum effective daily dose was based on the analgesic dose.

iv) For drugs available alone and in combination with other drugs, the minimum effective daily dose for the anticholinergic/sedative drug alone was used to define the minimum effective daily dose for the anticholinergic/sedative drug in the combination product.

v) For analgesic drugs with different doses for breakthrough pain and chronic pain, the minimum effective daily dose for chronic pain was used.

vi) For drugs administered on an 'as needed' basis, the minimum effective daily dose was the minimum effective single dose multiplied by the minimum number of times the dose is normally repeated in 24 hours.

vii) For drugs administered by more than one route, the minimum effective daily dose for the oral route (or the most commonly used route if not administered orally) was used as the reference dose. The reference dose was converted to an equivalent dose for other available routes of administration based on reported conversion factors or bioavailability data.[27,28,30,31]

Calculating DBI exposure

Total DBI exposure for each individual was calculated as the sum of exposure to any DBI medication dispensed in 2016 using the following equation:[19]

$$DBI = \sum D/(\delta + D)$$

where D is the daily dose taken by the individual patient, and δ is the minimum effective daily dose for that drug. The daily dose taken by the individual patient for each DBI medication was estimated by multiplying the strength and total quantity dispensed in 2016, and then normalising by dividing by 365 days.[15] DBI exposure was also quantified for each patient over one year including only chronic DBI

medications, defined as at least three prescription items dispensed in the year for the same fourth-level ATC code (e.g. N02AJ).[33]

Statistical Analysis

Exposure to DBI medications was categorized dichotomously as unexposed (DBI=0) and exposed (DBI>0). Prevalence rates and associated 95% CIs for GMS eligible patients aged 65 years and over with at least one prescription dispensed in 2016 (DBI exposure) were calculated. Logistic regression was used to examine the association between DBI exposure and the following patient variables: age at first dispensing in 2016 [categorized into 65-69 (reference), 70-74, 75-79, and ≥80 years], gender [male (reference), female] and number of co-prescribed chronic medications over the year [categorized as 0-4 (reference), 5-7, 8-11, and ≥12 chronic medications]. Chronic medication was defined as receiving at least three prescription items dispensed in the year with the same second-level ATC code (e.g. N02), relating to only the following first-level codes: A (alimentary tract and metabolism), B (blood and blood-forming organs), C (cardiovascular system), G (genito urinary system and sex hormones), H (systemic hormonal preparation, excluding sex hormones and insulins), L (antineoplastic and immunomodulating agents), M (musculo-skeletal system), N (nervous system), R (respiratory system) and S (sensory organs), and excluding those on the denominator of the DBI exposure.[33,34] Adjusted odds ratios (ORs) and 95% CIs were computed. Statistical significance at $P<0.05$ was assumed. Statistical analyses were conducted using SAS® v 9.4 (SAS Institute Inc., Cary, NC, USA).

Patient and public involvement statement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

The final list of DBI medications (master DBI list), and their minimum effective daily doses, is provided in Supplementary Table S1. This list included 156 medications (15 with anticholinergic effects only, 87 with sedative effects only, and 54 with both anticholinergic and sedative effects). Supplementary Table S2 shows the DBI medications listed in one of the original DBI studies in the USA,[20] but not included in the master DBI list. Supplementary Table S3 shows the DBI medications included in the master DBI list but not included in the original DBI study in the USA.[20]

In total, 282,874 (66%) of the 428,516 GMS eligible population aged 65 years and over in receipt of any claim during 2016 received at least one claim for a DBI medication. The prevalence of chronic DBI exposure was 54.0%. Median (IQR) DBI score over the year was 0.52 (0.11-1.03).

Table 1 shows the prevalence of patients with DBI exposure in 2016 by a range of patient characteristics. Females were significantly more likely to have DBI exposure compared to males (females 71.6% *vs*.

males 58.7%, adjusted OR 1.65, 95% CI 1.63, 1.68). Prevalence of DBI exposure increased noticeably with the number of chronic drugs used, rising progressively from 42.7% of those prescribed 0-4 chronic drugs receiving a DBI prescription to 95.4% of those on ≥12 chronic drugs (adjusted OR 27.81, 95% CI 26.72, 28.96). Those aged 80 years and over had a significantly higher prevalence of DBI exposure than those aged <80 years (≥80 years 71.5% *vs*. <80 years 63.5%). In multivariate analysis, the association between increasing age and DBI exposure was diminished (adjusted OR 0.82, 95% CI 0.81, 0.84).

Table 2 shows the 10 most frequently used DBI medications by Irish older people in 2016. Codeine and tramadol were the most commonly used medications with sedative effects (20.1% and 11.5% of patients, respectively). Of the 383,641 codeine prescriptions dispensed in 2016, 98.9% were for codeine/paracetamol combination products, of which 54.6% were for low-dose codeine products (codeine/paracetamol 8 mg/500 mg per tablet), 6.9% were for medium-dose codeine products (codeine/paracetamol 15 mg/500 mg per tablet), and 38.5% were for high-dose codeine products (codeine/paracetamol 30 mg/500 mg per tablet). Prochlorperazine and hyoscine butylbromide were the most commonly used medications with anticholinergic effects (5.9% and 4.6% of patients, respectively).

Figure 1 shows the frequency of DBI drug classes dispensed to Irish older people in 2016. Anxiolytics/hypnotics and antidepressants were the most frequently prescribed drug classes of DBI medications (25% and 24% of DBI prescriptions dispensed in 2016, respectively). Of the 1,264,078 anxiolytic/hypnotic prescriptions dispensed in 2016, 52.5% were for benzodiazepines, and 47.4% were for Z-drugs (zopiclone, zolpidem and zaleplon). Of the 1,211,319 antidepressant prescriptions, 47.3% were for selective serotonin reuptake inhibitors, 16.8% were for tricyclic antidepressants, 16.7% were for serotonin noradrenaline reuptake inhibitors, and 19.2% were for other antidepressants (mirtazapine, phenelzine, and trazodone).

Discussion

This study found that the majority of older people in Ireland are exposed to medications with anticholinergic and/or sedative effects, particularly females and those with multiple comorbidities. A lower prevalence of exposure to DBI medications of 43% was reported in a previous population study of older people living in New Zealand, of similar size and methodology to the current study.[15] Other studies of DBI exposure conducted in Australia, USA and Europe, with smaller cohorts of older people in various settings, have demonstrated a prevalence ranging from 20% up to 79%.[20,21,35,36] This variability may be related to different definitions used to identify anticholinergic and sedative medications, specific sociodemographic or health status characteristics of participants, and differences in medication access and use across different settings and countries.[2] Further, prevalence rates calculated for the current study included DBI medications dispensed on an 'as needed' basis. There is no consistency in terms of the inclusion or exclusion of 'as needed' medications in previous studies, which may also explain the variability in prevalence rates reported.

This current study found that female patients and patients with high comorbidity burdens, who are more likely to be very old (80+ years), all appear to be particularly vulnerable to exposure to DBI

medications, which is consistent with the literature.[15] Numerous studies have reported greater use of psychotropic drugs and analgesics by women compared to men.[37-40] Possible reasons for a greater use amongst women include increased willingness to seek medical care, increased likelihood of women to perceive and report mental illness or pain, and general practitioner (GP) prescribing bias.[41,42] It has been shown that women are more likely to receive a prescription for a psychotropic drug during a GP consultation compared to men.[37] Targeted efforts to reduce inappropriate prescribing of these medications in vulnerable older women are therefore needed.

In the present study, exposure to medications with sedative effects was considerably higher in older people compared to exposure to medications with anticholinergic effects. This is likely to be due to the frequent use of anxiolytic/hypnotic drugs, antidepressants and opioid analgesics. Similar patterns of use have been noted in cohorts of older people living in Finland,[36] Australia,[43,44] and the USA.[45] However, older aged people in Ireland appear have considerably higher rates of use of codeine products and tramadol than their counterparts in Finland, according to a national population study in Finland of similar design to the present study.[23]

Examination of the most frequently used DBI medications (Table 2) suggests there may be opportunities for deprescribing of DBI medications in older Irish people. The high use of low-dose codeine/paracetamol combinations is of particular concern. It is known that codeine doses of at least 30 mg are required for analgesia.[46] At this dose, a small but statistically significant increase in the analgesic effect of codeine/paracetamol combinations compared to paracetamol alone has been shown.[46,47] However, there is a lack of pharmacological evidence to support the analgesic benefit from using low-dose codeine combination analgesics.[48] Combining low-doses of codeine with paracetamol is likely to bring minimal analgesic benefit, but will increase the risk of adverse effects.[49] The most frequently prescribed codeine combination product in our study contained 8 mg of codeine and 500 mg of paracetamol per tablet. Thus, at the maximal dose of two tablets (16 mg/1000 mg codeine/paracetamol), the quantity of codeine would not achieve doses close to the minimum effective dose of codeine required for analgesia. Yet, these products will still induce the adverse effects experienced with codeine, including constipation, nausea, dry mouth, dizziness and drowsiness.[50] Further, the use of codeine in older people has been associated with an increased risk of falls and hip fracture (60% increased risk),[51] which highlights the need to limit its use.[52] Therefore, use of a paracetamol alone product, rather than a combined low-dose codeine/paracetamol product, may be more appropriate for some patients.

The high use of hypnotic Z-drugs and anxiolytic benzodiazepines (alprazolam and diazepam) is also noteworthy. Widespread use of benzodiazepines and Z-drugs has been reported in other European countries.[53,54] These drugs should be used with caution due to their adverse effect profile, such as drowsiness, confusion, impairment of memory, and incoordination, which can be particularly problematic in older people.[55] Both benzodiazepines and Z-drugs have been associated with problems in older people including an increased risk of injurious falls and hip fracture, and cognitive impairment.[14,17] It is therefore recommended that these drugs be avoided in older people and, where appropriate, discontinuation under appropriate supervision is widely advised.[17,56] It has been shown that

discontinuation of benzodiazepines and Z-drugs in community-dwelling older people is possible, without adverse events attributable to discontinuation, and may be associated with improved health outcomes, such as a reduction in the risk of falls and improvements in cognitive functioning.[16,57,58] A meta-analysis of interventions to reduce benzodiazepine and Z-drug use in older people demonstrated the beneficial effects of consultations and education of both prescribers and patients, followed by a supervised withdrawal.[59]

Strengths and limitations

The present study was a large national study of DBI exposure in community-dwelling older patients in Ireland. The study design enabled examination of the variation in DBI exposure between patients in a highly representative population. A consensus list of DBI medications was developed, which may be of use for future studies using the DBI tool.

The authors acknowledge the following limitations. These largely result from the constraints of using pharmacy claims data in this study. Information about the clinical indication for prescriptions is not available in pharmacy claims data and therefore it is not possible to assess the appropriateness of DBI prescriptions. DBI prescribing may not always be inappropriate. The prescription may be justified for clinical reasons, after balancing risk and benefit in conditions of uncertainty. Nevertheless, given that DBI medications have been associated with adverse events in older people, the observed high prevalence of DBI prescribing suggests that a significant amount of prescribing could be improved. In addition, pharmacy claims data does not include medications purchased over-the-counter (OTC). However, there is no incentive for GMS patients to buy medications OTC, as most of these items are available on prescription for a small co-payment, and therefore the risk of bias is expected to be low. All medications dispensed were included in the analyses but it was not possible to confirm whether the dispensed medications were consumed and for how long. Therefore, the DBI calculations may not reflect true exposure. However, the results reflect prescribing practice in terms of intention to prescribe. There is also the possibility of socioeconomic bias, particularly in the 65-69 year age group, as only 40% of this population is covered under the GMS scheme, which over represents more socially deprived individuals. However, approximately 80% of those aged ≥70 years are covered for medications under the GMS scheme and, therefore, socioeconomic bias in these patients would be low. Another notable limitation involves the list of DBI medications used in this analysis, which, although determined by consensus, may be associated with interpretation bias leading to an over- or under-estimation of the prevalence of DBI exposure. There is no gold standard definition to describe medications with clinically significant anticholinergic or sedative effects and therefore the clinical validity of our selection of drugs may be limited by this. Finally, the master DBI list provided in this study (Supplementary Table S1) was based on medications and dosages relevant to prescribing in Ireland. Therefore, there may be medications available in other countries that are not on this list, and there may be medications on this list that are not available in other countries. The minimum effective dosages applied refer to prescribing in Ireland. Therefore, whilst the master DBI list provided could be used as a starting point in other countries, adaption to the local setting in terms of availability of drugs and dosage is necessary.

Implications for policy and practice

The results of this present study highlight the need for interventions to reduce the inappropriate use of medications with clinically significant anticholinergic or sedative effects in older people in Ireland. In particular, the high use of low-dose codeine/paracetamol combination products, Z-drugs and benzodiazepines, suggests that interventions to alert prescribers and patients about the risks associated with these drugs in older people should be a priority. Due consideration should also be given to the importance of regular medication reviews, with a particular focus on older females and those with multiple comorbidities.

In practice, the DBI may be useful as a screening tool for older patients, to identify those patients with high exposure, which may compromise their physical and cognitive functioning.[60] Such patients are likely to be eligible for deprescribing interventions such as medication review.[60] A previous intervention study showed that collaborative pharmacist-led medication review with the GP can reduce the prescribing of sedative and anticholinergic medications in older people, resulting in a significant decrease in the DBI score.[61] At the population level, the DBI tool could be used as a quality indicator to guide policy to improve prescribing and optimise clinical outcomes in older people.[15]

Conclusions

In conclusion, this large population-based study has shown that there is a high prevalence of use of medications with anticholinergic and sedative effects among Irish community-dwelling older people, particularly in females and those with multiple comorbidities. The high use of low-dose codeine/paracetamol combination products, Z-drugs and benzodiazepines, suggests that there are opportunities for deprescribing in this population. The consensus list of DBI medications developed may be of use in future studies using the DBI tool. Future research should focus on examining the impact of DBI on important health outcomes in older Irish patients, and developing interventions to reduce the inappropriate use of DBI medications in this vulnerable patient population.

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Footnotes

Contributors: CB and KB conceived and designed the study. CB, CW, DW and CR contributed to development of the DBI medication list. KB accessed the data (HSE-PCRS). KB, CB and CC performed the analysis and interpreted the results. CB wrote the manuscript. All authors critically revised the manuscript and approved the final version.

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Table 1. Prevalence of patients aged 65 years and over dispensed at least one Drug Burden Index medication prescription in 2016

Patient level fixed effects (*n*)	% dispensed a DBI prescription	Odds ratio (95% CI)	
		Unadjusted	Adjusted
Sex:			
Male (185938)	58.7	1.00	1.00
Female (242578)	71.6	1.78 (1.75-1.80)	1.65 (1.63-1.68)
Number of chronic drugs:			
0-4 (153960)	42.7	1.00	1.00
5-7 (113614)	66.4	2.65 (2.60-2.69)	2.67 (2.63-2.71)
8-11 (102682)	83.9	6.96 (6.82-7.09)	7.03 (6.89-7.17)
≥12 (58260)	95.4	27.63 (26.55-28.76)	27.81 (26.72-28.96)
Age (years):			
65-69 (96804)	63.5	1.00	1.00
70-74 (109118)	62.4	0.95 (0.94-0.97)	0.85 (0.83-0.87)
75-79 (93300)	65.3	1.09 (1.07-1.11)	0.81 (0.80-0.83)
≥80 (129294)	71.5	1.44 (1.42-1.47)	0.82 (0.81-0.84)

n, number of patients; DBI, Drug Burden Index; CI, confidence interval

Table 2. Most frequently used Drug Burden Index medications in Irish older people in 2016[a]

Medication	Anticholinergic/sedative effects	% patients
Codeine	Sedative	20.1
Tramadol	Sedative	11.5
Zopiclone	Sedative	9.5
Zolpidem	Sedative	8.5
Pregabalin	Sedative	7.9
Alprazolam	Sedative	7.8
Diazepam	Sedative	6.5
Escitalopram	Sedative	5.9
Prochlorperazine	Anticholinergic + Sedative	5.9
Mirtazapine	Sedative	4.8

[a]Prevalence calculated by the number of patients dispensed at least one prescription for a Drug Burden Index medication divided by the total number of patients dispensed at least one prescription in 2016.

Figure legends

Figure 1. Percentage and 95% confidence intervals of anticholinergic and/or sedative medication prescriptions dispensed by drug class in Irish older patients in 2016. Other=antiparkinson drugs, cardiovascular drugs, gastrointestinal drugs, and muscle relaxants.

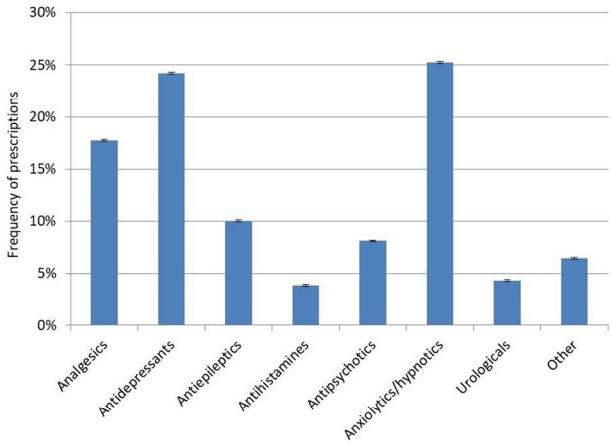

Figure 1. Percentage and 95% confidence intervals of anticholinergic and/or sedative medication prescriptions dispensed by drug class in Irish older patients in 2016. Other=antiparkinson drugs, cardiovascular drugs, gastrointestinal drugs, and muscle relaxants.

125x90mm (300 x 300 DPI)

SupplementaryTable S1. Master Drug Burden Index (DBI) list - medications for inclusion in the calculation of DBI

Drug	WHO ATC Code/s	Anticholinergic effects (AC)	Sedative effects (S)	Minimum effective daily dose by route of administration (mg)					
				Oral	Parenteral	Sublingual/buccal	Transdermal	Rectal	Inhalation
Alimemazine	R06AD01	AC	S	10					
Alprazolam	N05BA12		S	0.5					
Amantadine	N04BB01	AC		100					
Amisulpride	N05AL05		S	50					
Amitriptyline	N06AA09	AC	S	10					
Aripiprazole	N05AX12		S	10	10				
Asenapine	N05AH05		S			10			
Atropine	A03BA01 AO3CB03	AC		0.6	0.3				
Baclofen	M03BX01		S	30	30				
Benperidol	N05AD07		S	0.125					
Benzatropine	N04AC01	AC		0.5	0.5				
Biperiden	N04AA02	AC	S	1					
Brompheniramine	R06AB01 R06AB51	AC	S	16					
Buclizine	R06AE51 R06AE01	AC	S	12.5					
Buprenorphine	N02AE01		S		0.12	0.4	0.12		
Buspirone	N05BE01		S	15					
Carbamazepine	N03AF01	AC	S	400				500	
Cetirizine	R06AE07		S	10					
Cloral Hydrate	N05CC01		S	430					
Chlordiazepoxide	N05BA02		S	5					
Chlorphenamine	R06AB04	AC	S	8	3				
Chlorpromazine	N05AA01	AC	S	30	6				
Cinnarizine	N07CA02	AC	S	60					

	N07CA52								
Citalopram	N06AB04		S	10					
Clemastine	R06AA04 R06AA54	AC	S	2					
Clobazam	N05BA09		S	10					
Clomethiazole	N05CM0 N05CX04		S	192					
Clomipramine	N06AA04	AC	S	30					
Clonazepam	N03AE01		S	0.5	0.5				
Clonidine	N02CX02 C02AC01		S	0.1					
Clozapine	N05AH02	AC	S	25					
Codeine	R05DA04 N02AJ06		S	120					
Cyclizine	R06AE03 N02AA51	AC	S	50	50				
Cyproheptadine	RO6AX02	AC	S	4					
Darifenacin	G04BD10	AC		7.5					
Dexchlorpheniramine	R06AB02 R06AB52	AC	S	8					
Diazepam	N05BA01		S	1	1			1	
Dicycloverine	A03AA07	AC		30					
Dihydrocodeine	N02AA08 N02AJ01		S	40					
Dimenhydrinate	R06AA02 N07CA52	AC	S	150					
Diphenhydramine	N02BE71 N02BE51 R06AA02 R06AA52	AC	S	50					
Diphenoxylate	A07DA01		S	5					

Disopyramide	C01BA03	AC		300	300				
Dosulepin	N06AA16	AC	S	50					
Doxazosin	C02CA04		S	2					
Doxepin	N06AA12	AC	S	25					
Doxylamine	R06AA09 R06AA59 N02BE51	AC	S	25					
Duloxetine	N06AX21		S	30					
Escitalopram	N06AB10		S	5					
Fentanyl	N02AB03		S		0.3	0.6	0.3		
Fesoterodine	G04BD11	AC		4					
Fexofenadine	R06AX26		S	120					
Flavoxate	G04BD02	AC	S	600					
Flunitrazepam	N05CD03		S	0.5					
Fluoxetine	N06AB03		S	20					
Flupentixol	N05AF01	AC	S	0.5	0.3				
Fluphenazine	N05AB02	AC	S		0.36				
Flurazepam	N05CD01		S	15					
Fluvoxamine	N06AB08		S	100					
Gabapentin	N03AX12		S	900					
Glycopyrronium	A03AB02	AC	S	2	0.2				
Haloperidol	N05AD01		S	0.5	0.25				
Hydromorphone	N02AA03		S	7.8	2.6				
Hydroxyzine	N05BB01	AC	S	25					
Hyoscine base	A04AD01	AC	S				0.5		
Hyoscine Butylbromide	A03BB01	AC		30	30				
Hyoscine Hydrobromide	A04AD01	AC	S	0.9			0.5		
Hyoscyamine	A03CB31 A03BA03	AC		0.375					

Imipramine	N06AA02	AC	S	30					
Indoramin	C02CA02		S	20					
Lamotrigine	N03AX09		S	100 200*					
Levetiracetam	N03AX14		S	1000					
Levocetirizine	R06AE09		S	5					
Levomepromazine	N05AA02	AC	S	37.5	37.5				
Lofepramine	N06AA07	AC	S	140					
Loprazolam	N05CD11		S	1					
Loratadine	R06AX13		S	10					
Lorazepam	N05BA06		S	0.5	0.5				
Lormetazepam	N05CD06		S	0.5					
Loxapine	N05AH01	AC	S						4.5
Meclozine	R06AE05 R06AE55	AC	S	25					
Memantine	N06DX01		S	20					
Meptazinol	N02AX05		S	800					
Methadone	N07BC02		S	5					
Methocarbamol	M03BA03	AC	S	2250					
Methyldopa	C02AB01		S	500					
Metoclopramide	A03FA01 N02BE51		S	15	15				
Mianserin	N06AX03		S	30					
Mirtazepine	N06AX11		S	15					
Morphine	N02AA01 N02AA51		S	20	6.7				
Moxonidine	C02AC05		S	0.2					
Nefopam	N02BG06	AC	S	90					
Nitrazepam	N05CD02		S	2.5					
Nortriptyline	N06AA10	AC	S	30					

Olanzapine	N05AH03	AC	S	5	5				
Orphenadrine	N04AB02	AC		100					
Oxazepam	N05BA04		S	15					
Oxcarbazepine	N03AF02		S	600					
Oxybutynin	G04BD04	AC	S	5			1.95		
Oxycodone	N02AA05 N02AA55		S	20	10			20	
Paliperidone	N05AX13		S	3	0.89				
Paroxetine	N06AB05	AC	S	20					
Pentazocine	N02AD01		S	300	180				
Perampanel	N03AX22		S	4					
Pericyazine	N05AC01	AC	S	5					
Perphenazine	N05AB03	AC	S	3					
Pethidine	N02AB02		S	300	150				
Phenelzine	N06AF03		S	7.5					
Phenobarbital	N03AA02		S	60	60				
Phenytoin	N03AB02		S	200	200				
Pimozide	N05AG02	AC	S	2					
Pizotifen	N02CX01	AC	S	1.5					
Pramipexole	N04BC05		S	0.088					
Prazepam	N05BA11		S	10					
Prazosin	C02CA01		S	2					
Pregabalin	N03AX16		S	150					
Primidone	N03AA03		S	750					
Prochlorperazine	N05AB04	AC	S	10	1.25	4			
Procyclidine	N04AA04	AC		7.5					
Promazine	N05AA03	AC	S	100					
Promethazine	R06AD02	AC	S	20	5				
Propantheline	A03AB05	AC		22.5					

Propiverine	G04BD06	AC	S	15					
Quetiapine	N05AH04	AC	S	50					
Retigabine	N03AX21		S	600					
Risperidone	N05AX08		S	1	0.7				
Ropinirole	N04BC04		S	2					
Rotigotine	N04BC09		S				1		
Rufinamide	N03AF03		S	400					
Sertraline	N06AB06		S	50					
Solifenacin	G04BD08 G04CA53	AC		5					
Sulpiride	N05AL01	AC	S	400					
Tapentadol	N02AX06		S	100					
Temazepam	N05CD07		S	5					
Terazosin	G04CA03		S	2					
Tiagabine	N03AG06		S	15 30*					
Tizanidine	M03BX02	AC	S	6					
Tolterodine	G04BD07	AC	S	2					
Topiramate	N03AX11		S	50					
Tramadol	N02AX02 N02AJ13		S	200	200				
Trazodone	N06AX05		S	100					
Triazolam	N05CD05		S	0.125					
Trifluoperazine	N05AB06	AC	S	2					
Trihexyphenidyl	N04AA01	AC		5					
Trimipramine	N06AA06	AC	S	37.5					
Triprolidine	R06AX07	AC	S	10					
Trospium	G04BD09	AC		40					
Valproic Acid	N03AG01		S	1000					

Venlafaxine	N06AX16		S	75					
Vigabatrin	N03AG04		S	2000					
Zaleplon	N05CF03		S	5					
Ziprasidone	N05AE04		S	40					
Zolpidem	N05CF02		S	5					
Zonisamide	N03AX15		S	300					
Zopiclone	N05CF01		S	3.75					
Zuclopenthixol	N05AF05	AC	S	20	11.4				

WHO ATC, World Health Organisation Anatomical Therapeutic Classification

*Minimum effective daily dose if taken concurrently with agents that induce hepatic enzymes including phenytoin, carbamazepine, phenobarbitone, primidone, rifampicin and lopinavir/ritonavir.

Supplementary Table S2. Drug Burden Index (DBI) medications included in a previous study in the USA[20] but not included in the master DBI list

Medications not included in master DBI list	Reason for non-inclusion in master DBI list
Astemizole	Not licensed in Ireland
Azatadine	Not licensed in Ireland
Belladonna	Not licensed in Ireland
Benzonatate	Not licensed in Ireland
Butalbital	Not licensed in Ireland
Carisoprodol	Not licensed in Ireland
Chlorprothixine	Not licensed in Ireland
Chlorzoxazone	Not licensed in Ireland
Clidinium	Not licensed in Ireland
Clorazepate	Not licensed in Ireland
Cyclobenzaprine	Not licensed in Ireland
Desipramine	Not licensed in Ireland
Dexbrompheniramine	Not licensed in Ireland
Dextromethorphan	Does not meet study definitions for DBI medication
Dichloralphenazone	Not licensed in Ireland
Estalozam	Not licensed in Ireland
Guanabenz	Not licensed in Ireland
Guanethidine	Not licensed in Ireland
Guanfacine	Not licensed for use in the elderly in Ireland
Hexobarbital	Not licensed in Ireland
Hydrocodone	Not licensed in Ireland
Loperamide	Does not meet study definitions for DBI medication
Meprobamate	Not licensed in Ireland
Metaxalone	Not licensed in Ireland
Methscopolamine	Not licensed in Ireland
Nefazodone	Not licensed in Ireland
Opium	Not licensed in Ireland
Papaverine	Not licensed in Ireland
Pheniramine	Not licensed in Ireland
Phenyltoloxamine	Not licensed in Ireland
Propoxyphene	Not licensed in Ireland
Reserpine	Not licensed in Ireland
Selegiline	Does not meet study definitions for DBI medication
Tamsulosin	Does not meet study definitions for DBI medication
Thioridazine	Not licensed in Ireland
Tranylcypromine	Does not meet study definitions for DBI medication
Triflupromazine	Not licensed in Ireland
Trimethobenzamide	Not licensed in Ireland
Tripelennamine	Not licensed in Ireland

Supplementary Table S3. Drug Burden Index (DBI) medications included in the master DBI list but not listed as DBI medications taken by participants in a previous USA study[20]

Alimemazine
Amantadine
Amisulpride
Aripiprazole
Asenapine
Atropine
Baclofen
Benperidol
Biperiden
Buclizine
Buprenorphine
Cloral Hydrate
Cinnarizine
Clobazam
Clomethiazole
Clozapine
Cyclizine
Darifenacin
Dicycloverine
Dihydrocodeine
Diphenoxylate
Dosulepin
Duloxetine
Fesoterodine
Fexofenadine
Flunitrazepam
Flupentixol
Fluvoxamine
Glycopyrronium
Hydromorphone
Hyoscine base
Hyoscine Butylbromide
Hyoscine Hydrobromide
Indoramin
Levocetirizine
Levomepromazine
Lofepramine
Loprazolam
Lormetazepam
Memantine
Meptazinol
Mianserin
Moxonidine
Nefopam

Nitrazepam
Paliperidone
Perampanel
Pericyazine
Pethidine
Pimozide
Pizotifen
Prazepam
Pregabalin
Procyclidine
Promazine
Propiverine
Retigabine
Rotigotine
Rufinamide
Solifenacin
Sulpiride
Tapentadol
Tizanidine
Topiramate
Trospium
Vigabatrin
Zonisamide
Zopiclone
Zuclopenthixol

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4, 5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	5-7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	7, 8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7, Table 1
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7, 8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8, 9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10, 11
Generalisability	21	Discuss the generalisability (external validity) of the study results	9, 10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.