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RESEARCH ARTICLE

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Long-term anticholinergic, benzodiazepine and Z-drug use in community-dwelling older adults: What is the impact on cognitive and neuropsychological performance?

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Abstract

Background: Long-term use of anticholinergics, benzodiazepines and related drugs (or "Z-drugs") have been associated with cognitive impairment and dementia. However, the relationship of these medications with cognitive function and domain-specific neuropsychological performance in older adults without dementia, is unclear.

Methods: 5135 older adults (74.0 ± 8.3 years; 67.4% female) without a diagnosis of dementia were recruited in Ireland to the Trinity-Ulster-Department of Agriculture (TUDA) study. Detailed cognitive and neuropsychological assessment was conducted using the Mini-Mental State Examination (MMSE), Frontal Assessment Battery (FAB) and Repeatable Battery for Assessment of Neuropsychological Status (RBANS).

Results: A total of 44% (2259 of 5153) used either a potential or definite anticholinergic medication. Overall, 9.7% (n = 500) used a definite anticholinergic medication. Regular benzodiazepine use was reported by 7% (n = 363), whilst 7.5% (n = 387) used a "Z-drug". Use of definite, but not potential anticholinergic medication was associated with poorer performance on all three assessments (β: −0.09; 95% CI: −0.14, −0.03, p = 0.002 for MMSE; β: −0.04; 95% CI: −0.06, −0.02; $p < 0.001$ for FAB; β: −4.15; 95% CI: −5.64, −2.66; $p < 0.001$ for RBANS) in addition to all domains of the RBANS. Regular benzodiazepine use was also associated with poorer neuropsychological test performance, especially in Immediate Memory (β: −4.98; 95% CI: −6.81, −3.15; $p < 0.001$) and Attention (β: −6.81; 95% CI: −8.60, −5.03; $p < 0.001$) RBANS domains.

Conclusions: Regular use of definite anticholinergic medications and benzodiazepines, but not potential anticholinergics or "Z-drugs", was associated with poorer overall and domain-specific neuropsychological performance in older adults.

KEYWORDS
anticholinergic medication, benzodiazepine, cognition, older adults

Key points

- Use of both anticholinergic medication and benzodiazepines have been associated with dementia in older adults.
- Use of these medications and domain-specific cognitive performance in those without dementia, is less well-understood.
- In >5000 older adults, use of these medications was associated with poorer overall and domain-specific cognitive performance.
- These findings have important implications for risk vs benefit decisions of prescribing these medications in older adults.

1 | INTRODUCTION

The use of medications with anticholinergic properties have been associated with the later development of dementia in older adults.[1–5] Medications with such anticholinergic properties, either as an intended/potent side effect, are used to treat a wide range of urological, psychiatric and cardiovascular conditions and are used by significant proportions of older adults.[6,7] Several longitudinal studies have demonstrated a significantly increased risk of incident Mild Cognitive Impairment (MCI) and dementia in those regularly using these medications.[2,8] Less well explored is the specific relationship between these medications and detailed cognitive and neuropsychological performance in community-dwelling older adults, free from a diagnosis of dementia.

One of the most convincing longitudinal studies on anticholinergic medication use and incident dementia, involving just-under 300,000 individuals, demonstrated significant associations between the use of several types of strong anticholinergic drugs (those with an anticholinergic cognitive burden score of 2 or 3) and the later risk of dementia.[9] This study follows earlier studies that demonstrated an effect of strong anticholinergic medication use on cognitive impairment and dementia diagnosis, in addition to accelerated cognitive decline in those with established dementia using anticholinergic medications.[10] Comparatively fewer studies have focused on specific domains of cognitive function and the studies that do exist have typically focused on a relatively small number of general cognitive tests.[11,12] The impact of anticholinergic medication use on specific domains of detailed neuropsychological and cognitive function has been less well evaluated.

Regular benzodiazepine use has also been linked to an increased risk of cognitive impairment. Despite recommendations against their use in older adults, benzodiazepines and related medications (BDZRs: Bendoziazepine and Related Medications) are commonly used as anxiolytics, sedatives, hypnotics and anticonvulsants.[13] BDZRs consist of benzodiazepine and non-benzodiazepine sedative hypnotics (also termed "Z-drugs"). Several published studies have examined the impact of BDZRs on dementia diagnosis but, whilst a number of studies support an association, other studies do not.[14–17] Some studies examining BDZRs have demonstrated an association with poorer cognitive function and/or with the rate of cognitive decline.[18,19] Again, the evidence is somewhat limited in the range of cognitive tests used and studies examining the association between these medication classes and detailed tests of neuropsychological function are lacking.

The Trinity-Ulster-Department of Agriculture (TUDA) study enrolled over five-thousand adults of >60 years, and free from a diagnosis of dementia, from two separate jurisdictions on the island of Ireland. The purpose of the current study was to explore the TUDA data to investigate the relationship of anticholinergic and BDZR medication use with neuropsychological performance in this cohort, based on global cognition and detailed assessments of specific cognitive domains.

2 | METHODS

2.1 | Study setting and background

The current study was embedded within the TUDA study, which recruited community-dwelling older people (aged >60 years), free from a formal diagnosis of dementia, for detailed health and cognitive assessment from 2008–2012 (ClinicalTrials.gov identifier: NCT02664584).[20–22] Participants were recruited as part of three predefined cohorts: (i) hypertensive cohort: from general practices in the Western and Northern Health and Social Care trusts catchment area in Northern Ireland; (ii) bone cohort: individuals with a diagnosis of osteopaenia/osteoporosis, from a specialist tertiary referral bone clinic at St James's Hospital Dublin and; (iii) cognitive cohort: from general geriatric clinics/day hospital service at St James's Hospital Dublin. All participants were free from an established diagnosis of dementia. All participants provided written informed consent and underwent identical assessment at all recruitment sites by centrally trained researchers. Ethical approval was granted from the Research Ethics Committee in St James's Hospital, Dublin, Ireland and the Office for Research Ethics Committees Northern Ireland (ORECNI; ref: 08/NIR03/113).

2.2 | Medication use

Participants were asked to provide a list of current medications and information about duration of use. Medications were coded using the Anatomic Therapeutic Classification (ATC) System. For the current study, we only included medications which were taken daily (not on an "as needed"/"prn" basis) and had been used continuously for at least six months at the time of assessment.

In order to characterise anticholinergic medication use, we used the Anticholinergic Cognitive Burden (ACB) score.[23] The ACB score assigns a score of 1 (potential anticholinergic medication), two or three (definite evidence of clinically significant anticholinergic effect) and the total score for each participant was calculated by combining an arithmetic sum of the potential/definite anticholinergic medications used. Further, a binary variable for potential and definite anticholinergic medications were used in order to assess the association of these medication classes individually with cognitive impairment. Use of benzodiazepines and related drugs (BDZR) was identified using the ATC codes: N03AE, N05BA, N05CD and N05CF relating to benzodiazepine drugs and benzodiazepine-related sedative hypnotics ("Z-Drugs").

2.3 | Covariate assessment

Routine demographic information was collected as part of the study visit. Body Mass Index (BMI) was assessed in a standardised fashion. Participants underwent detailed medical interview which in particular identified a history of cerebrovascular disease (stroke or transient ischaemic attack), diabetes, hypertension and cardiovascular disease (ischaemic heart disease, congestive cardiac failure, myocardial infarction, atrial fibrillation). Participants also underwent detailed screening for anxiety (using the Hospital Anxiety and Depression Scale: HADS) and depressive symptoms (Centre for Epidemiological Studies Depression Scale: CES-D).[24,25] Further, assessment of personal activities of daily living was made using the Physical Self-Maintenance Scale (PSMS). The component of the PSMS connected to toileting and related incontinence symptoms was used in order to adjust for potential urinary incontinence, given that urological agents are one of the commonest definite anticholinergics prescribed. Finally, self-identified visual impairment was extracted in order to control for indication for ophthalmological anticholinergic medications.

2.4 | Cognitive assessment

The Mini-Mental State Examination (MMSE) was used as an assessment of general cognitive function in the current study.[26] To assess frontal lobe function/executive function, the Frontal Assessment Battery (FAB) was used which assesses conceptualization (assessing similarities), mental flexibility (verbal fluency), motor programming ('Luria' test), resistance to interference (conflicting instructions), inhibitory control (via a go-no go paradigm) and environmental autonomy (prehension behaviour).[27] The Repeatable Battery for Assessment of Neuropsychological Status (RBANS) was used to measure performance overall and on specific domains including immediate memory (Index I), visual-spatial (Index II), language (Index III), attention (Index IV) and delayed memory (Index V), to provide a comprehensive neuropsychological assessment.[28]

2.5 | Statistical analysis

All analysis was carried out using STATA v15.0. Descriptive statistics are provided as means with standard deviations and proportions with percentages as appropriate. Between group differences were analysed using ANOVA and chi-square tests as appropriate. After examining data for normality (using Q-q plots and histograms), data which did not conform to a normal distribution was log-transformed prior to analysis.

In order to assess the relationship between anticholinergic medication/BDZR use and cognitive function, mixed effects linear regression was used, with study cohort (cognitive, hypertensive, bone) considered a random effect and cognitive function (MMSE, log transformed FAB, RBANS) as the dependent variable. Associations were tested unadjusted in the first instance (model 1) with adjustment made for age, sex, BMI, family history of dementia and educational attainment in the second model (model 2). Further adjustment was made for medical comorbidity (diabetes, hypertension, ischaemic heart disease, myocardial infarction, cerebrovascular disease, congestive cardiac failure and total number of regular medications), alcohol use (current) and smoking (current) under model 3. Finally, model 4 adjusted for screened anxiety/depressive symptoms, the presence of visual impairment and symptoms of incontinence (toileting section of the PSMS) in order to further control for confounding by indication and protopathic bias.

Analyses were performed in the first instance using total ACB score as the predictor variable. Given that studies have demonstrated that it may only be definite anticholinergic medications that are linked to potential adverse cognitive effects, we repeated analysis estimating effects for definite and potential anticholinergic medication use separately (with no regular anticholinergic use as the reference group in both instances). Analysis were then repeated using both regular benzodiazepine and finally with regular Z-drug use as the independent variable of interest.

Sensitivity analyses were conducted in order to further evaluate observed associations. In the first instance, we excluded individuals with intermittent use ("as required"/"prn") of either anticholinergic or BDZR medication from both the exposure and reference group, in order to only assess the impact of regular use vs non-use. Analyses were also repeated excluding individuals using both anticholinergic and BDZR medication, in order to avoid potential interactions between these medication classes and to estimate the effect of each medication class individually. In order to evaluate the association in those without cognitive impairment, given that these medications may be prescribed in some instances for early symptoms of cognitive

impairment and that established cognitive impairment may bias results, we used a MMSE score cut-off of 24, consistent with the population under study to define potential cognitive impairment.[29] This was carried out in order to assess those with MMSE scores within the normal range.

Finally, in order to further evaluate the association between definite anticholinergic medication use and cognitive function, we divided definite anticholinergics into: (i) antipsychotics; (ii) urologicals and; (iii) antidepressants which accounted for the majority of definite anticholinergic use in order to examine if any observed effects were specific to a particular subclass of anticholinergic medication or represent an overall class effect. Results of mixed-effects models are reported as beta coefficients and 95% confidence intervals (CIs). For all analysis $p < 0.05$ was considered the threshold for statistical significance.

3 | RESULTS

3.1 | Study participants and medication usage

In total, of 5186 recruited to TUDA, 5153 participants were included in the current study (aged 74.0 ± 8.3 years; 67.4% female) following exclusion of those with missing data for all three cognitive assessments ($n = 33$). Use of any anticholinergic medication (potential or definite) was reported by 44.0% (2259/5153) of participants whilst 9.7% (500/5,153) regularly used a definite anticholinergic medication. Of those using any anticholinergic medication, the median ACB score was 2.[1–3] A minority, 7.1% (363/5135) were regular users of a benzodiazepine medication whilst 7.5% (387/5135) regularly used a "Z-drug". Baseline characteristics by medication use are presented in tabular format below (See Table 1).

The most common definite anticholinergic medications used were tolterodine ($n = 126$), amitriptyline ($n = 119$), solnifenacin ($n = 50$), paroxetine ($n = 47$), olanzapine ($n = 33$), oxybutynin ($n = 32$) and quetiapine ($n = 28$). The most common benzodiazepines used were diazepam ($n = 104$), temazepam ($n = 95$), alprazolam ($n = 63$), bromazepam ($n = 34$) and lormatazepam ($n = 25$). In total, 83 (1.6%) participants used both a definite anticholinergic medication and a regular benzodiazepine.

3.2 | Anticholinergic use and neuropsychological performance

Under unadjusted models, increasing ACB score in addition to both potential and definite anticholinergic medication use was associated with significantly poorer cognitive performance on the MMSE, FAB and RBANS in addition to all RBANS indices (Table 2). Associations for potential anticholinergics were attenuated under all adjusted models. Associations between both increasing ACB score and definite anticholinergic use and poorer performance on the MMSE, FAB, RBANS and all RBANS indices persisted following robust covariate adjustment (Table 2).

3.3 | Benzodiazepine and related drug use and neuropsychological performance

Regular benzodiazepine use was associated with significantly poorer performance on the MMSE, FAB and RBANS. Under robust covariate adjustment, associations for poorer performance on total MMSE, FAB, RBANS in addition to RBANS domains I, III, IV and V with regular benzodiazepine use persisted (Table 2). Associations between regular Z-drug use and poorer cognitive performance were seen under unadjusted models for total RBANS in addition to RBANS domain II and III. The associations between regular Z-drug use and poorer cognitive performance were attenuated on covariate adjustment.

3.4 | Anticholinergic medication subclass and cognitive performance

We divided definite anticholinergic use into regular (i) antipsychotic; (ii) urological and; (iii) antidepressant use. Associations for antipsychotic use and poorer performance on all total cognitive scores and RBANS indices were observed and persisted following adjustment. Regular use of urologicals was associated with poorer performance on the MMSE and RBANS indices I and III after adjustment. Associations for anticholinergic antidepressant use were somewhat weaker, with poorer performance on the total RBANS score persisting following robust covariate adjustment in addition to indices I, II and V (See Table 3).

3.5 | Sensitivity analysis

Associations for increasing ACB, definite anticholinergic and benzodiazepine use and poorer scores on the MMSE, FAB and RBANS persisted after excluding individuals with intermittent usage of these medication classes. Associations for benzodiazepine use and poorer performance on RBANS index I were attenuated whilst all other associations between ACB, definite anticholinergic usage and benzodiazepine use persisted (Table S1).

On excluding those using both anticholinergic and benzodiazepines, associations for total ACB score, definite anticholinergics and benzodiazepine use and poorer MMSE score were attenuated. Associations for definite anticholinergic use and poorer performance on the FAB persisted. Finally, associations for total ACB score, definite anticholinergic use and benzodiazepine use persisted on the total RBANS and RBANS index I and RBANS index IV whilst associations for poorer performance on index II, III and V were seen for ACB score and definite anticholinergic use only (Table S2).

TABLE 1 Characteristics of the TUDA cohort by use of anticholinergic, benzodiazepine and related drug use

Characteristic	Any anticholinergic (Potential or definite)			Definite anti-cholinergic			Benzodiazepine			Z-drug		
	Non-user (*n = 2876*)	User (*n = 2259*)	*p*	Non-user (*n = 4635*)	User (*n = 500*)	*p*	Non-user (*n = 4772*)	User (*n = 363*)	*p*	Non-user (*n = 4748*)	User (*n = 387*)	*p*
Age (years)	72.3 (7.8)	76.3 (8.3)	<0.001	73.9 (8.2)	75.4 (8.5)	<0.001	73.8 (8.2)	76.9 (8.3)	<0.001	73.8 (8.2)	77.4 (8.2)	<0.001
Sex (female)	1942 (67.5%)	1517 (67.2%)	0.78	3089 (66.7%)	370 (74%)	0.001	3164 (66.3%)	295 (81.3%)	<0.001	3.165 (66.7)	294 (75.6)	<0.001
Body Mass index	27.6 (5.1)	28.4 (5.8)	<0.001	27.8 (5.3)	28.8 (5.9)	<0.001	27.9 (5.4)	27.7 (5.5)	0.20	28.0 (5.4)	27.4 (5.1)	0.02
Age finished education (y)	16.3 (3.1)	15.6 (2.7)	<0.001	16.1 (3.0)	15.8 (2.9)	0.56	16.1 (3.0)	15.3 (2.3)	<0.001	16.1 (3.0)	15.7 (3.0)	0.01
Family history of dementia	442 (15.4%)	255 (11.3%)	<0.001	632 (13.6%)	65 (13%)	0.76	659 (13.8%)	38 (10.5%)	0.09	658 (13.9%)	39 (10.1%)	0.18
Smoking (current)	326 (11.3%)	290 (12.8%)	0.005	539 (11.6%)	77 (15.4%)	0.04	545 (11.4%)	71 (19.6%)	<0.001	560 (11.9%)	56 (14.47%)	0.29
Alcohol (current)	1781 (61.9%)	1165 (51.6%)	<0.001	2710 (58.5%)	236 (47.2%)	<0.001	2785 (58.4%)	161 (44.4%)	<0.001	2738 (57.7%)	208 (53.8%)	<0.001
Diabetes mellitus	303 (10.5%)	353 (15.6%)	<0.001	569 (12.3%)	87 (17.4%)	<0.001	607 (12.7%)	49 (13.5%)	0.95	610 (12.9%)	46 (11.9%)	0.92
Hypertension	1968 (68.4%)	1717 (76.0%)	<0.001	3340 (72.1%)	345 (69.0%)	0.31	3432 (71.9%)	253 (69.7%)	0.47	3428 (72.2%)	257 (66.4%)	0.05
Myocardial infarction	183 (6.4%)	327 (14.5%)	<0.001	455 (9.8%)	55 (11.0%)	0.70	456 (9.6%)	54 (14.9%)	0.003	465 (9.8%)	45 (11.6%)	0.51
Atrial fibrillation	155 (5.4%)	516 (22.8%)	<0.001	607 (13.1%)	64 (12.8%)	0.96	617 (12.9%)	54 (14.9%)	0.41	611 (12.9%)	60 (15.5%)	0.40
Ischaemic heart disease	277 (9.6%)	548 (24.3%)	<0.001	739 (15.9%)	86 (17.2%)	0.79	739 (15.5%)	86 (23.7%)	<0.001	740 (15.6%)	85 (21.1%)	0.009
Cerebrovascular disease	275 (9.6%)	495 (21.9%)	<0.001	654 (14.1%)	116 (23.2%)	<0.001	695 (14.6%)	75 (20.1%)	0.008	690 (14.5%)	80 (20.7%)	0.006
Congestive cardiac failure	46 (1.6%)	264 (11.7%)	<0.001	260 (5.6%)	50 (10%)	0.001	271 (5.7%)	39 (10.7%)	0.002	266 (5.6%)	44 (11.4%)	<0.001
Total no. of medications	4.9 (2.8)	8.3 (3.5)	<0.001	6.1 (3.4)	9.2 (2.7)	<0.001	6.2 (3.4)	9.6 (3.6)	<0.001	6.2 (3.4)	9.3 (3.5)	<0.001
Probable depression	219 (7.6%)	327 (14.5%)	<0.001	453 (9.8%)	93 (18.6%)	<0.001	460 (9.6%)	86 (23.7%)	<0.001	475 (10.0%)	71 (18.4%)	<0.001
Probable anxiety	126 (4.4%)	132 (5.9%)	0.02	229 (4.9%)	29 (5.8%)	0.39	217 (4.6%)	41 (11.3%)	<0.001	227 (4.8%)	31 (8.0%)	0.005
MMSE	27.4 (2.4)	26.7 (2.7)	<0.001	27.2 (2.6)	26.4 (2.6)	<0.001	27.2 (2.5)	26.0 (2.8)	<0.001	27.1 (2.6)	26.5 (2.8)	<0.001
Frontal assessment battery	15.6 (2.6)	14.7 (2.9)	<0.001	15.3 (2.7)	14.4 (3.0)	<0.001	15.3 (2.7)	14.1 (3.1)	<0.001	15.3 (2.8)	14.5 (3.1)	<0.001
RBANS (total)	88.3 (16.7)	81.6 (16.5)	<0.001	86.1 (16.9)	79.1 (16.5)	<0.001	86.1 (16.9)	80.0 (15.7)	<0.001	85.8 (16.9)	80.3 (16.7)	<0.001
RBANS index I (immediate Memory)	91.6 (17.6)	86.7 (17.4)	<0.001	89.9 (17.7)	84.3 (17.1)	<0.001	89.9 (17.6)	83.5 (18.1)	<0.001	89.6 (17.7)	87.2 (17.7)	0.005
RBANS index II (Visuo-Spatial)	91.0 (19.6)	84.6 (19.8)	<0.001	88.9 (19.9)	81.9 (19.2)	<0.001	88.9 (19.9)	79.4 (17.6)	<0.001	88.8 (19.9)	80.4 (19.2)	<0.001
RBANS index III (Language)	92.0 (12.4)	87.9 (13.9)	<0.001	90.6 (13.1)	86.5 (14.4)	<0.001	90.5 (13.2)	85.6 (13.8)	<0.001	90.5 (13.1)	86.6 (14.7)	<0.001
RBANS index IV (Attention)	91.1 (17.3)	84.3 (17.0)	<0.001	88.8 (17.5)	82.3 (16.7)	<0.001	88.8 (17.4)	79.0 (15.8)	<0.001	88.5 (17.6)	83.8 (16.1)	<0.001
RBANS index V (delayed Memory)	88.8 (18.1)	83.5 (18.6)	<0.001	87.0 (18.4)	81.8 (18.3)	<0.001	86.9 (18.4)	80.6 (18.8)	<0.001	86.8 (18.4)	82.8 (18.9)	<0.001

Characteristics of TUDA participants are presented by use vs non-use of four different medication categories. Data are presented either as means (with standard deviations) or proportions (with percentages). Statistical analysis was conducted using ANOVA and chi-square tests as appropriate.

Abbreviations: MMSE: Mini-Mental State Examination; RBANS: Repeatable Battery for Assessment of Neuropsychological Status.

TABLE 2 Effect of anticholinergic, benzodiazepine and related medication use on cognitive function in older adults

	Model 1 β (CI)	*p*	Model 2 β (CI)	*p*	Model 3 β (CI)	*p*	Model 4 β (CI)	*p*
MMSE								
ACB score (total)	−0.15 (−0.20, −0.09)	<0.001	−0.11 (−0.16, −0.06)	<0.001	−0.10 (−0.15, −0.04)	0.001	−0.09 (−0.14, −0.03)	0.002
Definite anticholinergic use	−0.39 (−0.62, −0.16)	0.001	−0.42 (−0.65, −0.20)	<0.001	−0.36 (−0.59, −0.13)	0.002	−0.32 (−0.55, −0.09)	0.007
Potential anticholinergic use	−0.28 (−0.43, −0.13)	<0.001	−0.06 (−0.22, 0.08)	0.38	−0.07 (−0.22, 0.09)	0.39	−0.05 (−0.21, 0.10)	0.49
Benzodiazepine use	−0.81 (−1.08, −0.54)	<0.001	−0.63 (−0.89, −0.37)	<0.001	−0.56 (−0.38, −0.39)	<0.001	−0.49 (0.76, −0.23)	<0.001
Z-drug use	−0.18 (−0.44, 0.09)	0.19	−0.10 (−0.35, 0.16)	0.47	−0.03 (−0.29, 0.23)	0.81	0.03 (−0.23, 0.29)	0.86
$_{ln}$FAB								
ACB score (total)	−0.01 (−0.02, −0.01)	<0.001	−0.01 (−0.01, −0.00)	0.007	−0.01 (−0.01, −0.00)	0.01	−0.01 (−0.01, −0.00)	0.02
Definite anticholinergic use	−0.04 (−0.06, −0.02)	<0.001	−0.04 (−0.06, −0.01)	0.001	−0.03 (−0.06, −0.01)	0.001	−0.03 (−0.05, −0.01)	0.004
Potential anticholinergic use	−0.03 (−0.04, −0.00)	<0.001	−0.00 (−0.02, 0.01)	0.82	−0.00 (−0.02, 0.01)	0.86	−0.01 (−0.01, 0.01)	0.94
Benzodiazepine use	−0.06 (−0.09, −0.04)	<0.001	−0.04 (−0.06, −0.01)	0.002	−0.04 (−0.06, −0.01)	0.002	−0.03 (−0.05, −0.00)	0.02
Z-drug use	−0.02 (−0.04, 0.00)	0.054	−0.01 (−0.03, 0.02)	0.50	−0.01 (−0.03, 0.01)	0.43	−0.00 (−0.03, 0.20)	0.78
RBANS total								
ACB score (total)	−1.39 (−1.72, −1.07)	<0.001	−0.88 (−1.23, −0.54)	<0.001	−0.84 (−1.18, −0.50)	<0.001	−0.77 (−1.11, −0.43)	<0.001
Definite anticholinergic use	−4.15 (−5.64, −2.66)	<0.001	−3.60 (−5.03, 2.17)	<0.001	−3.46 (−4.88, −2.03)	<0.001	−3.15 (−4.56, −1.74)	<0.001
Potential anticholinergic use	−3.13 (−4.04, −2.21)	<0.001	−0.69 (−1.64, 0.25)	0.15	−0.63 (−1.57, 0.31)	0.19	−0.53 (−1.46, 0.40)	0.26
Benzodiazepine use	−6.14 (−7.87, −4.41)	<0.001	−3.69 (−5.33, −2.04)	<0.001	−3.49 (−5.13, −1.84)	<0.001	−2.83 (−4.47, −1.20)	0.001
Z-drug use	−2.45 (−4.16, −0.75)	0.005	−1.17 (−2.78, 0.43)	0.15	−1.29 (−2.89, 0.31)	0.11	−0.89 (−2.476, 0.69)	0.27
RBANS index I (immediate memory)								
ACB score (total)	−1.27 (−1.62, −0.92)	<0.001	−1.04 (−1.42, −0.67)	<0.001	−1.00 (−1.38, −0.63)	<0.001	−0.91 (−1.29, −0.54)	<0.001
Definite anticholinergic use	−4.23 (−5.81, −2.64)	<0.001	−4.17 (−5.74, 2.61)	<0.001	−4.05 (−5.62, −2.49)	<0.001	−3.76 (−5.32, −2.21)	<0.001
Potential anticholinergic use	−2.48 (−3.46, −1.50)	<0.001	−0.83 (−1.87, 0.21)	0.12	−0.78 (−1.81, 0.26)	0.14	−0.68 (−1.71, 0.36)	0.20
Benzodiazepine use	−4.98 (−6.81, −3.15)	<0.001	−3.55 (−5.35, −1.75)	<0.001	−3.40 (−5.20, −1.60)	<0.001	−2.63 (−4.43, −0.83)	0.004
Z-drug use	−1.08 (−2.87, 0.71)	0.24	−0.32 (−2.06, 1.42)	0.72	−0.47 (−2.21, 1.27)	0.60	−0.01 (−1.74, 1.72)	0.99
RBANS index II (Visuo-spatial)								
ACB score (total)	−1.36 (−1.75, −0.98)	<0.001	−0.69 (−1.10, −0.28)	0.001	−0.65 (−1.06, −0.24)	0.002	−0.59 (−1.00, −0.18)	0.005
Definite anticholinergic use	−3.98 (−5.74, −2.22)	<0.001	−2.64 (−4.34, −0.94)	0.002	−2.54 (−4.24, −0.85)	0.003	−2.18 (−3.87, −0.50)	0.01
Potential anticholinergic use	−2.92 (−4.00, −1.83)	<0.001	−0.45 (−1.58, 0.68)	0.44	−0.35 (−1.48, 0.78)	0.54	−0.30 (−1.41, 0.82)	0.61
Benzodiazepine use	−6.01 (−8.05, −3.97)	<0.001	−2.32 (−4.29, −0.35)	0.02	−2.05 (−4.01, −0.08)	0.04	−1.39 (−3.35, 0.57)	0.16
Z-drug use	−4.48 (−6.48, −2.48)	<0.001	−2.62 (−4.53, −0.71)	0.01	−2.70 (−4.60, −0.80)	0.01	−2.36 (−4.25, −0.47)	0.01

TABLE 2 (Continued)

	Model 1 β (CI)	*p*	Model 2 β (CI)	*p*	Model 3 β (CI)	*p*	Model 4 β (CI)	*p*
RBANS index III (language)								
ACB score (total)	−0.64 (−0.90, −0.40)	<0.001	−0.51 (−0.79, −0.23)	<0.001	−0.48 (−0.77, −0.20)	0.001	−0.45 (−0.73, −0.17)	0.002
Definite anticholinergic use	−2.03 (−3.19, −0.88)	0.001	−2.16 (−3.34, −0.99)	<0.001	−2.08 (−3.26, −0.91)	0.001	−1.91 (−3.09, −0.73)	<0.001
Potential anticholinergic use	−1.55 (−2.27, −0.84)	<0.001	−0.58 (−1.36, 0.20)	0.14	−0.58 (−1.35, 0.21)	0.15	−0.54 (−1.32, 0.24)	0.17
Benzodiazepine use	−2.82 (−4.15, −1.48)	<0.001	−2.13 (−3.49, −0.78)	0.002	−2.10 (−3.45, −0.74)	0.002	−1.80 (−3.17, −0.44)	0.009
Z-drug use	−1.43 (−2.73, −0.12)	0.03	−0.90 (−2.21, 0.41)	0.18	−1.01 (−2.31, 0.30)	0.13	−0.79 (−2.10, 0.52)	0.24
RBANS index IV (attention)								
ACB score (total)	−1.44 (−1.78, −1.10)	<0.001	−0.82 (−1.18, −0.46)	<0.001	−0.79 (−1.15, −0.43)	<0.001	−0.73 (−1.09, −0.38)	<0.001
Definite anticholinergic use	−3.63 (−5.18, −2.09)	<0.001	−2.86 (−4.36, −1.36)	<0.001	−2.78 (−4.27, −1.28)	<0.001	−2.50 (−3.98, −1.02)	0.001
Potential anticholinergic use	−3.60 (−4.54, −2.65)	<0.001	−0.95 (−1.93, 0.04)	0.06	−0.86 (−1.85, 0.12)	0.09	−0.74 (−1.71, 0.23)	0.14
Benzodiazepine use	−6.81 (−8.60, −5.03)	<0.001	−4.28 (−.600, −2.56)	<0.001	−4.04 (−5.75, −2.32)	<0.001	−3.52 (−5.23, −1.81)	<0.001
Z-drug use	−1.32 (−3.08, 0.45)	0.14	0.16 (−1.52, 1.84)	0.85	0.14 (−1.54, 1.81)	0.87	0.50 (−1.15, 2.17)	0.55
RBANS index V (delayed memory)								
ACB score (total)	−0.92 (−1.28, −0.55)	<0.001	−0.79 (−1.19, −0.39)	<0.001	−0.74 (−1.15, −0.35)	<0.001	−0.69 (−1.09, −0.30)	0.001
Definite anticholinergic use	−2.81 (−4.46, −1.16)	0.001	−3.28 (−4.94, −1.63)	<0.001	−3.16 (−4.81, −1.51)	<0.001	−2.88 (−4.52, −1.23)	0.001
Potential anticholinergic use	−2.15 (−3.17, −1.13)	<0.001	−0.63 (−1.73, 0.47)	0.26	−0.60 (−1.70, 0.49)	0.28	−0.54 (−1.63, 0.55)	0.33
Benzodiazepine use	−4.03 (−5.95, −2.12)	<0.001	−3.00 (−4.90, −1.08)	0.002	−2.91 (−4.82, −1.00)	0.003	−2.32 (−4.24, −0.41)	0.02
Z-drug use	−1.62 (−3.49, 0.24)	0.09	−1.11 (−2.96, 0.73)	0.24	−1.26 (−3.11, 0.58)	0.18	−0.89 (−2.73, 0.95)	0.34

Mixed-effects linear regression was used to assess the effect between medication use (independent variable) and cognitive/neuropsychological performance (dependent variable). Model 1 was performed unadjusted. Model 2 adjusts for age, sex, education, body mass index and family history of dementia. Model 3 adjusts additionally for medical history of cardiovascular and cerebrovascular disease, alcohol and smoking use in addition to medication burden (total number of medications). Model 4 additionally controls for symptoms of urinary incontinence, anxiety (Hospital Anxiety and Depression Scale), depression (Centre for Epidemiological Studies Depression Scale) and visual impairment. Results are presented as beta-coefficients and corresponding 95% confidence intervals. Frontal Assessment Battery (FAB) scores were log transformed prior to analysis.

Abbreviations: MMSE: Mini-Mental State Examination; FAB: Frontal Assessment Battery; RBANS: Repeatable Battery for Assessment of Neuropsychological Status.

TABLE 3 Effect of definite anticholinergic medication use on cognition by subclass

	Model 1 β (CI)	*p*	Model 2 β (CI)	*p*	Model 3 β (CI)	*p*	Model 4 β (CI)	*p*
MMSE								
Antipsychotic	−1.15 (−1.80, −0.49)	0.001	−1.44 (−2.07, −0.81)	<0.001	−1.35 (−1.98, −0.72)	<0.001	−1.03 (−1.67, −0.39)	0.002
Urological	−0.38 (−0.70, −0.05)	0.022	−0.40 (−0.72, −0.09)	0.012	−0.33 (−0.65, −0.01)	0.041	−0.40 (−0.72, −0.08)	0.013
Antidepressant	−0.18 (−0.55, 0.19)	0.344	−0.23 (−0.59, 0.12)	0.198	−0.16 (−0.52, 0.20)	0.376	−0.08 (−0.44, 0.29)	0.671
$_{In}$FAB								
Antipsychotic	−0.08 (−0.14, −0.03)	0.004	−0.11 (−0.16, −0.05)	<0.001	−0.10 (−0.15, −0.04)	0.001	−0.07 (−0.13, −0.01)	0.016
Urological	−0.02 (−0.05, 0.01)	0.164	−0.02 (−0.05, 0.00)	0.092	−0.01 (−0.04, 0.01)	0.325	−0.02 (−0.05, 0.01)	0.185
Antidepressant	−0.03 (−0.07, 0.00)	0.060	−0.04 (−0.07, −0.01)	0.023	−0.03 (−0.06, 0.00)	0.078	−0.02 (−0.05, 0.01)	0.271
RBANS total								
Antipsychotic	−9.63 (−13.94, −5.32)	<0.001	−11.19 (−15.2, −7.22)	<0.001	−10.13 (−14.09, −6.17)	<0.001	−8.29 (−12.2, −4.36)	<0.001
Urological	−1.99 (−4.07, 0.09)	0.061	−2.50 (−4.42, −0.57)	0.011	−1.63 (−3.56, 0.31)	0.100	−1.98 (−3.89, −0.06)	0.04
Antidepressant	−4.43 (−6.84, −2.02)	<0.001	−4.46 (−6.70, −2.20)	<0.001	−3.58 (−5.83, −1.33)	0.002	−2.85 (−5.10, −0.60)	0.013
RBANS index I (immediate memory)								
Antipsychotic	−11.30 (−15.64, −6.96)	<0.001	−12.10 (−16.22, −7.97)	<0.001	−11.34 (−15.47, −7.21)	<0.001	−6.56 (−13.56, −5.33)	<0.001
Urological	−2.02 (−4.25, 0.22)	0.077	−2.83 (−4.96, −0.70)	0.009	−2.15 (−4.30, 0.01)	0.051	−2.48 (−4.62, −0.35)	0.023
Antidepressant	−4.56 (−7.10, −2.02)	<0.001	−4.95 (−7.39, −2.51)	<0.001	−4.41 (−6.87, −1.96)	<0.001	−3.65 (−6.11, −1.19)	0.004
RBANS index II (Visuo-spatial)								
Antipsychotic	−6.40 (−11.37, −1.42)	0.012	−7.91 (−12.52, −3.29)	0.001	−6.87 (−11.49, −2.25)	0.004	−5.04 (−9.63, −0.45)	0.031
Urological	−1.26 (−3.74, 1.23)	0.322	−1.09 (−3.41, 1.23)	0.357	−0.15 (−2.49, 2.19)	0.902	−0.67 (−2.99, 1.64)	0.570
Antidepressant	−5.65 (−8.43, −2.87)	<0.001	−4.55 (−7.18, −1.93)	0.001	−3.66 (−6.30, −1.02)	0.007	−2.69 (−5.32, −0.05)	0.046
RBANS index III (executive function)								
Antipsychotic	−6.20 (−9.39, −3.01)	<0.001	−7.03 (−10.15, −3.91)	<0.001	−6.56 (−9.59, −3.43)	<0.001	−5.43 (−8.56, −2.30)	0.001
Urological	−1.56 (−3.18, 0.07)	0.060	−2.07 (−3.67, −0.47)	0.011	−1.69 (−3.30, −0.07)	0.041	−1.88 (−3.50, −0.27)	0.022
Antidepressant	−1.09 (−2.93, 0.76)	0.249	−1.60 (−3.43, 0.23)	0.09	−1.13 (−2.98, 0.72)	0.230	−0.75 (−2.61, 1.12)	0.431
RBANS index IV (attention)								
Antipsychotic	−6.12 (−10.56, −1.68)	0.007	−7.46 (−11.61, −3.32)	<0.001	−6.42 (−10.55, −2.29)	0.002	−4.60 (−8.69, −0.51)	0.03
Urological	−1.91 (−4.07, 0.25)	0.083	−2.37 (−4.39, −0.35)	0.022	−1.44 (−3.48, 0.59)	0.165	−1.77 (−3.78, 0.24)	0.09
Antidepressant	−3.77 (−6.26, −1.27)	0.003	−3.68 (−6.04, −1.32)	0.002	−2.64 (−5.00, −0.27)	0.029	−2.09 (−4.45, 0.27)	0.08

TABLE 3 (Continued)

	Model 1 β (CI)	p	Model 2 β (CI)	p	Model 3 β (CI)	p	Model 4 β (CI)	p
RBANS index V (delayed memory)								
Antipsychotic	−9.58 (−14.21, −4.95)	<0.001	−11.23 (−15.69, −6.77)	<0.001	−10.77 (−15.24, −6.30)	<0.001	−9.08 (−13.54, −4.62)	<0.001
Urological	−0.87 (−3.19, 1.46)	0.47	−1.48 (−3.73, 0.77)	0.198	−1.13 (−3.41, 1.14)	0.328	−1.47 (−3.73, 0.79)	0.203
Antidepressant	−2.64 (−5.27, −0.00)	0.05	−3.48 (−6.05, −0.91)	0.008	−3.21 (−5.81, −0.62)	0.015	−2.62 (−5.23, −0.02)	0.048

Mixed-effects linear regression was used to assess the effect between medication use (independent variable) and cognitive/neuropsychological performance (dependent variable). Model 1 was performed unadjusted. Model 2 adjusts for age, sex, education, body mass index and family history of dementia. Model 3 adjusts additionally for medical history of cardiovascular and cerebrovascular disease, alcohol and smoking use in addition to medication burden (total number of medications). Model 4 additionally controls for symptoms of urinary incontinence, anxiety (Hospital Anxiety and Depression Scale), depression (Centre for Epidemiological Studies Depression Scale) and visual impairment. Results are presented as beta-coefficients and corresponding 95% confidence intervals. Frontal Assessment Battery (FAB) scores were log transformed prior to analysis.

Abbreviations: MMSE: Mini-Mental State Examination; FAB: Frontal Assessment Battery; RBANS: Repeatable Battery for Assessment of Neuropsychological Status.

In order to analyse the association of anticholinergic/benzodiazepine and related medication usage with poorer cognitive function, we re-ran analysis excluding those with a MMSE score < 24. Using this analysis, associations for ACB score and definite anticholinergics, but not benzodiazepines persisted for the FAB whilst associations for ACB score, definite anticholinergic and benzodiazepine persisted for total RBANS score. Additionally, associations between benzodiazepine use and poorer performance on RBANS domains I and V were not observed on excluding those with probable cognitive impairment based on MMSE score (Table S3).

4 | DISCUSSION

In the current study of over 5000 community-dwelling older adults, we demonstrated a significant association between the regular use of strong anticholinergic medications (for the preceding 6 months) and benzodiazepines and poorer neuropsychological performance. These effects were observed for strong anticholinergic use across all domains of cognitive function, and for immediate memory and attention were most pronounced for benzodiazepine use. This is one of the first studies to characterise in detail the association between use of these medications and neuropsychological performance in older adults.

In the current study, associations between definite (but not potential) anticholinergic medication use and cognitive function persisted after robust adjustment for a range of clinical covariates. We controlled for several factors known to influence cognitive performance in older adults (including background medical history, demographic and lifestyle factors). Importantly, by having a comprehensive assessment of mood and anxiety symptoms, we were able to control for confounding by indication in individuals prescribed these medications for management of mood/anxiety symptoms. Furthermore, we were also able to control for the presence of urological symptoms and other factors which may result in confounding-by-indication. The issue of confounding-by-indication is one of the consistent issues in the literature examining medication use and cognition, and we were able to control for this by virtue of the comprehensive medical assessment performed as part of TUDA.

Importantly, our findings for each persisted on excluding those with concomitant use of benzodiazepine and strong anticholinergic medications in addition to excluding those with intermittent use. The results in this regard hint that the associations observed may be due to long term use of both medication classes independently and not simply reflective of overall medication burden. Further, we controlled for the total number of medications in all of our models and it did not appear that the associations were simply an effect of overall medication burden. Finally, by excluding individuals with low MMSE scores, we reduced the potential for bias owing to established cognitive impairment. It is also notable that to be included in the current study, participants were required to be free from a pre-existing diagnosis of dementia. By excluding those with a MMSE score below the population-based cut-off for normative Irish data, we were able to assess the neuropsychological associations of

anticholinergic and benzodiazepine use in those with no objective signs of established cognitive impairment on the MMSE.

In line with preceding studies, the effect sizes observed in the current study are relatively small. Whilst our findings highlight potential adverse cognitive effects of strong anticholinergic medications and benzodiazepines, the risk vs benefit of prescribing these medications in day-to-day practice should be assessed on an individual basis. It is also worth bearing in mind that to date, there is limited evidence that decreasing anticholinergic burden in high risk individuals may not improve cognitive function.[30] However, it must be noted that many studies in this regard have examined this in individuals with established cognitive impairment with typically short follow-up period.[30] Trials aimed at reducing overall anticholinergic burden are needed in older adults without established cognitive impairment to examine the impact of discontinuation on cognitive and neuropsychological performance. Not least, our findings would encourage prescribers to consider less-anticholinergic alternatives where available (for instance with antidepressant medications). Further, the other potential effects of medications in older adults must be taken into account. For instance, benzodiazepines and Z-drugs have been associated with increased risk of both falls and delirium, which may be greatest in those with established cognitive impairment.[31]

A notable strength of the current study is the large sample size of community-dwelling older adults and the detailed cognitive and neuropsychological assessments used. An important limitation however is its cross-sectional design which precludes inference about causality. Further longitudinal studies will be required to replicate and further characterise the specific findings in relation to medication use and neuropsychological performance in older adults. Like any study examining the links between medication use and cognition, we are also unable to exclude confounding by indication/protopathic bias. Whilst we were able to perform a detailed assessment of screened anxiety and depressive symptoms in addition to other important confounders, it is important to reflect that anticholinergic/benzodiazepines may be used for prodromal symptoms of cognitive impairment/dementia such as anxiety and sleep disturbance.

5 | CONCLUSIONS AND IMPLICATIONS

In conclusion, we demonstrated an association between strong anticholinergic medication/benzodiazepine use and cognitive/neuropsychological performance in older adults free from a diagnosis of dementia. Further longitudinal studies will be required to establish the longitudinal effects of anticholinergic medications and benzodiazepine use on specific domains of neuropsychological performance, in order to identify potential targets for the promotion of brain health in older adults at risk of cognitive impairment.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data from this study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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