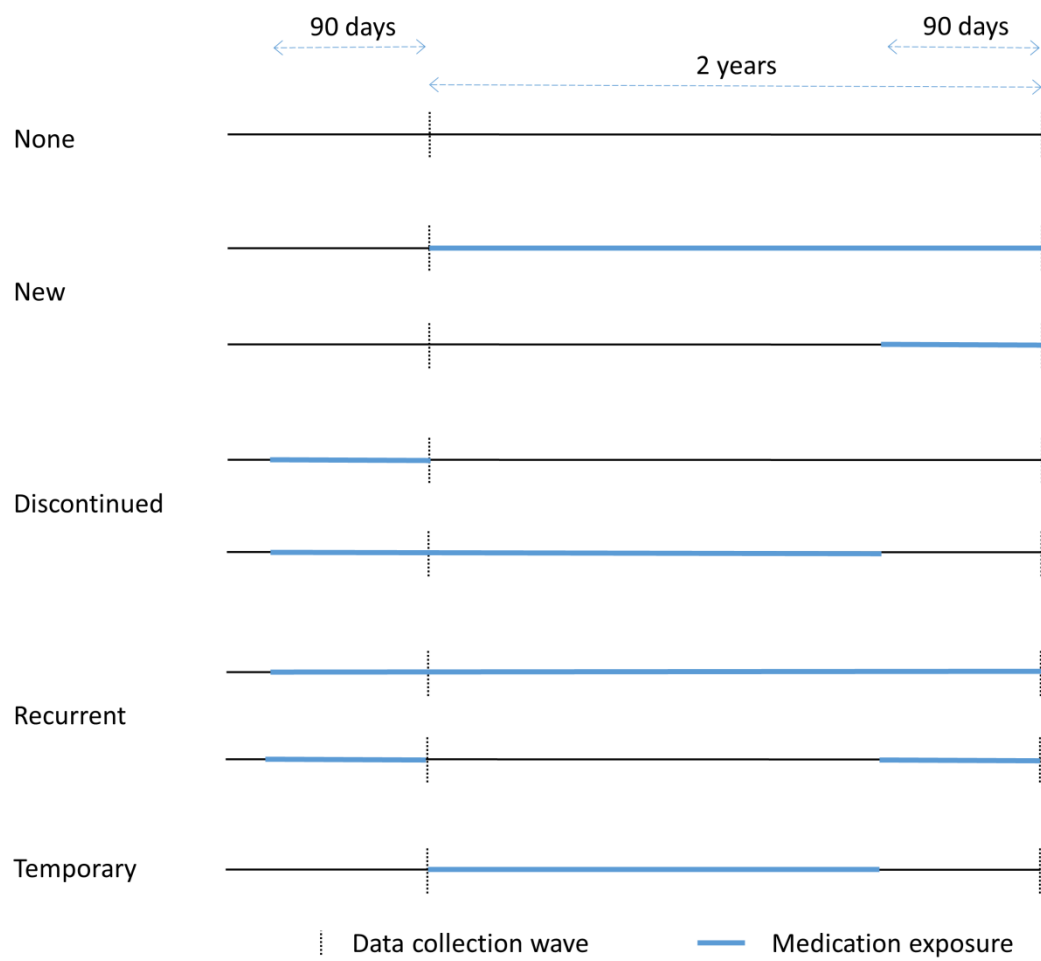


Supplementary figure



eFigure 1. Illustration of categories of exposure defined using administrative pharmacy claims data from the Primary Care Reimbursement Service.

Supplementary tables

eTable 1. World Health Organisation Anatomical Therapeutic Classification (WHO-ATC) codes and drug names for medications included in the analysis.

Medication class	ATC codes	Drug
Anticholinergics		
Antidepressants	N06AA	Non-selective monoamine reuptake inhibitors
	N06AB05	Paroxetine
Urologicals	G04BD02	Flavoxate
	G04BD04	Oxybutynin
	G04BD05	Terodiline
	G04BD06	Propiverine
	G04BD07	Tolterodine
	G04BD08	Solifenacin
	G04BD09	Trospium
	G04BD10	Darifenacin
	G04BD11	Fesoterodine
Antipsychotics	N05AA01	Chlorpromazine
	N05AA03	Promazine
	N05AB03	Perphenazine
	N05AB06	Trifluoperazine
	N05AC02	Thioridazine
	N05AH03	Olanzapine
	N05AH04	Quetiapine
Gastrologicals	A03AA07	Dicycloverine
	A03AB05	Propantheline
	A03BA01	Atropine
	A03BA03	Hyosciamine
	A03BB01	Butylscopolamine
Parkinsonians	N04AA01	Trihexyphenidyl
	N04AA02	Biperiden
	N04AA04	Procyclidine
	N04AB02	Orphenadrine
	N04AC01	Benzatropine
Antihistamines	R06AA02	Diphenhydramine
	R06AA04	Clemastine
	R06AA08	Carbinoxamine
	R06AA09	Doxylamine
	R06AA52	Diphenhydramine and combinations
	R06AB01	Brompheniramine
	R06AB04	Chlorphenamine
	R06AD02	Promethazine
	R06AE05	Meclozine
	N02BE51	Paracetamol and diphenhydramine
Others	M03BA03	Methocarbamol
	M03BC01	Orphenadrine
	N05CM05	Scopolamine
	N05BB01	Hydroxyzine
Benzodiazepines	N05BA	Benzodiazepine anxiolytics
	N05CD	Benzodiazepine hypnotics
	N03AE	Benzodiazepine antiepileptics
Z-drug hypnotics	N05CF	Benzodiazepine-related hypnotics

eTable 2. Description of covariates, data sources, and quantitative coding of variables.

Variable	Data source (question in CAPI unless stated otherwise)	Quantitative coding
Age	In which month and year were you born?	Continuous in years
Sex	Is Respondent male or female?	Binary (male as reference)
Education	What is the highest level of education you have completed?	Categorical: Primary/none (reference), Secondary, Third/higher
Marital status	Are you: Married, Living with a partner as if married, Single (never married), Separated, Divorced, or Widowed	Categorical: Married (reference), Never married, Separated/divorced, Widowed
Employment	Which one of these would you say best describes your current situation? Retired, Employed, Self-employed (including farming), Unemployed, Permanently sick/disabled, Looking after home/family, or In education/training	Categorical: Employed (reference), Retired, Other
Incontinence	During the last 12 months, have you lost any amount of urine beyond your control?	Categorical: No (reference), Yes, Missing
Quintiles of CES-D score#	Completed during SCQ	Categorical: 1 st (reference), 2 nd , 3 rd , 4 th , 5 th , Missing
Pain	Are you often troubled with pain? If yes, How bad is the pain most of the time?	Categorical: None (reference), Mild, Moderate, Severe, Missing
Trouble falling asleep	How often do you have trouble falling asleep?	Categorical: Most of the time (reference), Sometimes, Rarely/never
Disabilities	Because of a health or memory problem, do you have difficulty doing any of the activities on this card (ADLs and IADLs)? Exclude any difficulties you expect to last less than three months.	Categorical: No disability (reference), IADL disability only, Any ADL disability
Smoker	Have you ever smoked cigarettes, cigars, cigarillos or a pipe daily for a period of at least one year? If yes, Do you smoke at the present time?	Categorical: Never (reference), Past, Current
Vision	Is your eyesight (using glasses or contact lens if you use them): excellent, very good, etc.	Categorical: Excellent (reference), Very good, Good, Fair, Poor, Registered Blind
Hearing	Is your hearing (with or without a hearing aid): excellent, very good, etc.	Categorical: Excellent (reference), Very good, Good, Fair, Poor
Self-reported doctor-diagnosed conditions	Has a doctor ever told you that you have any of the conditions on this card?:	Binary: No (reference), Yes (unless otherwise stated)
Eye conditions	Cataracts; Glaucoma; Age-related macular degeneration	Categorical: No (reference), Yes, Missing
Cardiovascular conditions**	High blood pressure or hypertension; Angina; A heart attack (including myocardial infarction or coronary thrombosis); Congestive heart failure; Diabetes or high blood sugar; Ministroke or TIA; High cholesterol; A heart murmur; An abnormal heart rhythm; A stroke (cerebral vascular disease)	Binary: No (reference), Yes
Other health conditions	Chronic lung disease such as chronic bronchitis or emphysema; Asthma; Osteoporosis, sometimes called thin or brittle bones; Cancer or a malignant tumour; Arthritis (including osteoarthritis, or rheumatism); Stomach ulcers; Cirrhosis, or serious liver damage; Varicose ulcers (an ulcer due to varicose veins); Parkinson's disease; Anxiety; Depression; Manic depression; Other psychiatric condition (Hallucinations, Emotional problems, Schizophrenia, Psychosis, Mood swings, or something else)	Binary: No (reference), Yes

All self-reported during computer assisted personal interview, with the exception of CES-D which was included in the self-completion questionnaire.

** For stroke and heart attack, both event at reported at baseline and incident event between baseline and follow-up were adjusted for.

eTable 3. Full descriptive characteristics of all covariates for TILDA participants by self-reported anticholinergic medication, benzodiazepine, and Z-drug use

Characteristic at wave 1	Medication use at wave 1, 2 or 3							
	All (n=7,027)		ACB3 use (n=510)		Benzo use (n=411)		Z-drug use (n=356)	
	n	%	n	%	n	%	n	%
Women	3,906	55.6	333	65.3	286	69.6	247	69.4
Age (years), mean SD	62.4	9.8	65.0	9.9	66.7	10.1	67.0	10.2
Education								
Primary/none	1,899	27.0	171	33.5	167	40.6	149	41.9
Secondary	2,899	41.3	211	41.4	163	39.7	124	34.8
Third/higher	2,229	31.7	128	25.1	81	19.7	83	23.3
Marital status								
Married	5,042	71.8	317	62.2	228	55.5	199	55.9
Never married	639	9.1	54	10.6	51	12.4	27	7.6
Separated/divorced	477	6.8	56	11.0	42	10.2	41	11.5
Widowed	869	12.4	83	16.3	90	21.9	89	25.0
Employment								
Employed	2,742	39.0	92	18.0	65	15.8	50	14.0
Retired	2,397	34.1	220	43.1	170	41.4	177	49.7
Other	1,888	26.9	198	38.8	176	42.8	129	36.2
Incontinence								
Yes	865	12.3	161	31.6	82	20.0	72	20.2
Missing	17	0.24	2	0.4	3	0.7	3	0.8
CES-D, median IQR	3	1-8	6	2-13	9	3-18	7	3-15
Pain								
None	4,564	64.9	223	43.7	171	41.6	146	41.0
Mild	722	10.3	52	10.2	37	9.0	41	11.5
Moderate	1,157	16.5	137	26.9	108	26.3	100	28.1
Severe	576	8.2	98	19.2	94	22.9	69	19.4
Missing	8	0.1	0	0.0	1	0.2	0	0.0
Trouble falling asleep								
Most of the time	742	10.6	84	16.5	109	26.5	126	35.4
Sometimes	1,698	24.2	154	30.2	142	34.5	102	28.7
Rarely or never	4,587	65.3	272	53.3	160	38.9	128	36.0
Disabilities								
Not disabled	6,296	89.6	379	74.3	301	73.2	263	73.9
IADL disability only	203	2.9	32	6.3	27	6.6	27	7.6
Any ADL disability	528	7.5	99	19.4	83	20.2	66	18.5
Smoker								
Never	3,137	44.6	203	39.8	154	37.5	139	39.0
Past	2,669	38.0	211	41.4	141	34.3	132	37.1
Current	1,221	17.4	96	18.8	116	28.2	85	23.9
Vision								
Excellent	1,405	20.0	73	14.3	46	11.2	51	14.3
Very good	2,709	38.6	177	34.7	146	35.5	120	33.7
Good	2,302	32.8	189	37.1	154	37.5	142	39.9
Fair	510	7.3	54	10.6	45	10.9	27	7.6
Poor	92	1.3	16	3.1	18	4.4	15	4.2
Registered Blind	9	0.1	1	0.2	2	0.5	1	0.3
Hearing								
Excellent	2,045	29.1	130	25.5	92	22.4	84	23.6
Very good	2,139	30.4	139	27.3	113	27.5	104	29.2
Good	1,899	27.0	153	30.0	119	29.0	112	31.5
Fair	800	11.4	71	13.9	66	16.1	41	11.5
Poor	144	2.1	17	3.3	21	5.1	15	4.2

Self-reported doctor-diagnosed conditions								
High blood pressure	2,496	35.5	238	46.7	189	46.0	168	47.2
Angina	356	5.1	45	8.8	46	11.2	32	9.0
Heart attack	293	4.2	26	5.1	24	5.8	27	7.6
Heart failure	71	1.0	11	2.2	6	1.5	4	1.1
Diabetes	504	7.2	67	13.1	37	9.0	34	9.6
Transient ischaemic attack	137	2.0	12	2.4	14	3.4	10	2.8
High cholesterol	2,688	38.3	232	45.5	178	43.3	167	46.9
Heart murmur	338	4.8	34	6.7	27	6.6	27	7.6
Cataracts								
Yes	677	9.6	76	14.9	77	18.7	61	17.1
Missing	11	0.2	1	0.2	2	0.5	2	0.6
Glaucoma								
Yes	148	2.1	22	4.3	11	2.7	12	3.4
Missing	11	0.2	1	0.2	2	0.5	2	0.6
Age-related macular degeneration								
Yes	113	1.6	16	3.1	8	1.9	10	2.8
Missing	11	0.2	1	0.2	2	0.5	2	0.6
Lung disease	274	3.9	24	4.7	30	7.3	31	8.7
Asthma	624	8.9	70	13.7	64	15.6	40	11.2
Osteoporosis	669	9.5	93	18.2	72	17.5	67	18.8
Cancer	407	5.8	45	8.8	32	7.8	30	8.4
Arthritis	1,857	26.4	233	45.7	166	40.4	160	44.9
Abnormal heart rhythm	500	7.1	48	9.4	56	13.6	46	12.9
Stroke	96	1.4	16	3.1	16	3.9	12	3.4
Gastric ulcer	479	6.8	41	8.0	34	8.3	37	10.4
Liver disease	36	0.5	3	0.6	7	1.7	3	0.8
Varicose ulcer	221	3.2	32	6.3	22	5.4	18	5.1
Parkinson's disease	33	0.5	11	2.2	9	2.2	3	0.8
Anxiety	334	4.8	75	14.7	80	19.5	45	12.6
Depression	376	5.4	86	16.9	74	18.0	49	13.8
Manic depression	27	0.4	14	2.7	11	2.7	5	1.4
Other psychiatric condition	136	1.9	40	7.8	34	8.3	22	6.2
Stroke (between wave 1 and 2)	27	0.4	9	1.8	4	1.0	5	1.4
Heart attack (between wave 1 and 2)	51	0.7	4	0.8	9	2.2	4	1.1

* Data on cataracts missing for 11 (0.2%)

eTable 4. Self-reported anticholinergic medication use by class and cognitive decline over 2-year follow-up in TILDA

Anticholinergic medication usage	N	2-year cognitive decline, mean (SD)	b (95% CI), age, sex, wave adjusted†	b (95% CI), fully adjusted†#	p-value for equality of class effects
MMSE					
None	10,863	0.06 (1.75)	0	0	
New antidepressant	79	-0.16 (2.20)	-0.20 (-0.67, 0.27)	-0.20 (-0.66, 0.26)	0.59
New urological	86	0.05 (1.95)	0.01 (-0.40, 0.42)	0.08 (-0.32, 0.48)	
New antipsychotic	45	0.33 (2.73)	0.25 (-0.55, 1.05)	0.36 (-0.42, 1.14)	
New other ACB3	42	0.29 (1.63)	0.16 (-0.33, 0.64)	0.12 (-0.38, 0.61)	
Discontinued antidepressant	64	0.33 (2.23)	0.32 (-0.21, 0.85)	0.34 (-0.19, 0.87)	0.54
Discontinued urological	66	0.11 (2.13)	0.09 (-0.42, 0.59)	0.15 (-0.35, 0.65)	
Discontinued antipsychotic	21	0.05 (1.24)	0.06 (-0.44, 0.56)	0.16 (-0.33, 0.65)	
Discontinued other ACB3	36	-0.11 (1.28)	-0.17 (-0.56, 0.22)	-0.16 (-0.56, 0.24)	
Recurrent antidepressant	146	0.08 (1.72)	0.08 (-0.16, 0.32)	0.09 (-0.15, 0.33)	0.28
Recurrent urological	91	0.02 (1.96)	0.05 (-0.27, 0.37)	0.14 (-0.20, 0.47)	
Recurrent antipsychotic	44	-0.43 (2.22)	-0.43 (-1.06, 0.20)	-0.38 (-1.00, 0.25)	
Recurrent other ACB3	34	-0.18 (1.53)	-0.27 (-0.73, 0.20)	-0.27 (-0.74, 0.20)	
Animal Naming					
None	12,260	-1.18 (6.01)	0	0	
New antidepressant	94	-1.72 (5.51)	-0.54 (-1.64, 0.57)	-0.58 (-1.68, 0.53)	0.93
New urological	104	-1.88 (6.65)	-0.57 (-1.84, 0.69)	-0.55 (-1.81, 0.71)	
New antipsychotic	51	-2.22 (5.18)	-1.01 (-2.48, 0.47)	-0.95 (-2.39, 0.49)	
New other ACB3	50	-1.40 (6.01)	-0.17 (-1.83, 1.49)	-0.27 (-1.92, 1.39)	
Discontinued antidepressant	70	-0.70 (5.60)	0.43 (-0.90, 1.77)	0.37 (-0.99, 1.73)	0.52
Discontinued urological	73	-0.81 (4.65)	0.48 (-0.58, 1.55)	0.45 (-0.65, 1.56)	
Discontinued antipsychotic	24	0.92 (7.44)	1.96 (-0.94, 4.86)	2.00 (-0.93, 4.94)	
Discontinued other ACB3	38	-1.45 (5.25)	-0.47 (-2.11, 1.16)	-0.56 (-2.18, 1.07)	
Recurrent antidepressant	165	-1.32 (5.17)	-0.15 (-0.86, 0.56)	-0.20 (-0.90, 0.50)	0.61
Recurrent urological	103	-0.75 (5.91)	0.44 (-0.51, 1.39)	0.44 (-0.52, 1.40)	
Recurrent antipsychotic	45	-1.44 (4.24)	-0.33 (-1.44, 0.78)	-0.45 (-1.59, 0.69)	
Recurrent other ACB3	38	-1.45 (4.64)	-0.27 (-1.57, 1.03)	-0.10 (-1.40, 1.20)	
Recall					
None	12,202	0.00 (4.37)	0	0	
New antidepressant	92	-0.80 (4.64)	-0.74 (-1.66, 0.18)	-0.77 (-1.70, 0.17)	0.62
New urological	102	-1.14 (4.64)	-0.95 (-1.85, -0.06)	-0.98 (-1.87, -0.09)	
New antipsychotic	50	-1.68 (4.41)	-1.60 (-2.80, -0.40)	-1.54 (-2.72, -0.35)	
New other ACB3	48	-0.35 (5.18)	-0.31 (-1.74, 1.12)	-0.29 (-1.68, 1.10)	
Discontinued antidepressant	69	-0.94 (5.52)	-0.74 (-2.05, 0.56)	-0.90 (-2.24, 0.43)	0.18
Discontinued urological	71	-0.39 (4.19)	-0.16 (-1.11, 0.79)	-0.17 (-1.12, 0.79)	
Discontinued antipsychotic	24	1.58 (4.76)	1.53 (-0.32, 3.38)	1.76 (-0.12, 3.64)	
Discontinued other ACB3	37	-0.38 (4.35)	-0.35 (-1.75, 1.04)	-0.32 (-1.76, 1.12)	
Recurrent antidepressant	163	-0.46 (4.56)	-0.33 (-0.94, 0.29)	-0.38 (-0.99, 0.24)	0.92
Recurrent urological	102	-0.72 (5.17)	-0.40 (-1.18, 0.38)	-0.46 (-1.27, 0.34)	
Recurrent antipsychotic	46	-0.83 (4.22)	-0.65 (-1.75, 0.46)	-0.47 (-1.59, 0.64)	
Recurrent other ACB3	38	-0.18 (5.20)	-0.23 (-1.83, 1.36)	0.08 (-1.37, 1.54)	

† b coefficients shown are change relative to 'None' category.

Adjusted for demographics, baseline wave, self-reported incontinence, pain, and sleep difficulties, reported doctor-diagnosed eye, cardiovascular and other health conditions, self-rated vision and hearing, screened depressive symptoms, and smoking status.

eTable 5. Cognitive change over 2-year follow-up after self-reported anticholinergic medication use reported over 2-years in TILDA, stratified by age group.

Change in medication use	50-59 years				60-69 years				70+ years				p for age interaction *
	N	Cognitive change over 2 years, mean (SD)	b (95% CI), age, sex, wave adjusted†	b (95% CI), fully adjusted†#	N	Cognitive change over 2 years, mean (SD)	b (95% CI), age, sex, wave adjusted†	b (95% CI), fully adjusted†#	N	Cognitive change over 2 years, mean (SD)	b (95% CI), age, sex, wave adjusted†#	b (95% CI), fully adjusted†#	
Anticholinergic													
MMSE													
None	4,565	0.10 (1.57)	0	0	3,691	0.08 (1.69)	0	0	2,607	-0.04 (2.09)	0	0	
New	55	0.05 (1.56)	-0.08 (-0.48, 0.32)	-0.11 (-0.53, 0.31)	79	-0.01 (1.89)	-0.11 (-0.53, 0.31)	-0.07 (-0.47, 0.32)	87	0.16 (2.58)	0.21 (-0.34, 0.75)	0.30 (-0.21, 0.82)	0.49
Discontinued	58	0.43 (2.12)	0.35 (-0.19, 0.88)	0.35 (-0.18, 0.88)	53	-0.02 (2.00)	-0.10 (-0.63, 0.44)	0.01 (-0.52, 0.53)	54	-0.07 (1.86)	-0.02 (-0.51, 0.47)	0.10 (-0.38, 0.59)	0.50
Recurrent	97	0.07 (1.27)	-0.02 (-0.27, 0.22)	-0.06 (-0.33, 0.22)	106	0.31 (1.59)	0.22 (-0.07, 0.51)	0.29 (-0.02, 0.60)	109	-0.46 (2.36)	-0.38 (-0.75, 0.00)	-0.20 (-0.59, 0.20)	0.27
Animal naming													
None	5,151	-1.06 (6.20)	0	0	4,066	-1.21 (6.01)	0	0	3,043	-1.33 (5.66)	0	0	
New	72	-2.75 (7.42)	-1.73 (-3.44, -0.02)	-1.80 (-3.56, -0.03)	87	-1.39 (5.39)	-0.21 (-1.36, 0.94)	0.00 (-1.15, 1.15)	106	-1.75 (5.24)	-0.40 (-1.42, 0.62)	-0.36 (-1.39, 0.67)	0.26
Discontinued	63	-0.76 (6.20)	0.23 (-1.31, 1.78)	0.08 (-1.50, 1.66)	59	-0.10 (5.28)	1.05 (-0.32, 2.41)	0.80 (-0.59, 2.20)	59	-0.93 (5.33)	0.39 (-0.98, 1.75)	0.46 (-0.96, 1.88)	0.85
Recurrent	111	-0.73 (5.32)	0.14 (-0.81, 1.08)	0.12 (-0.88, 1.12)	115	-1.31 (4.93)	-0.14 (-0.97, 0.68)	-0.12 (-0.96, 0.73)	123	-1.59 (5.49)	-0.30 (-1.16, 0.56)	-0.29 (-1.22, 0.65)	0.60
Recall													
None	5,148	0.32 (4.14)	0	0	4,063	0.00 (4.37)	0	0	2,991	-0.53 (4.70)	0	0	
New	71	-0.31 (4.08)	-0.69 (-1.65, 0.26)	-0.94 (-1.91, 0.04)	85	-1.11 (4.58)	-1.15 (-2.14, -0.17)	-1.06 (-2.04, -0.09)	103	-1.75 (4.75)	-1.28 (-2.21, -0.35)	-1.17 (-2.11, -0.22)	0.47
Discontinued	63	-0.87 (5.17)	-1.23 (-2.52, 0.07)	-1.25 (-2.59, 0.09)	58	0.09 (4.13)	0.13 (-0.95, 1.21)	0.12 (-0.99, 1.24)	56	-0.61 (4.97)	-0.16 (-1.44, 1.13)	-0.29 (-1.56, 0.98)	0.40
Recurrent	111	0.33 (4.44)	-0.10 (-0.93, 0.73)	-0.16 (-1.00, 0.68)	115	-0.58 (4.65)	-0.61 (-1.25, 0.03)	-0.59 (-1.26, 0.08)	121	-1.16 (5.23)	-0.62 (-1.42, 0.18)	-0.35 (-1.19, 0.50)	0.40
Z-drug													
MMSE													
None	4,674	0.10 (1.57)	0	0	3,756	0.08 (1.68)	0	0	2,655	-0.03 (2.09)	0	0	
New	41	0.49 (1.85)	0.41 (-0.15, 0.96)	0.35 (-0.18, 0.88)	66	0.26 (1.85)	0.18 (-0.27, 0.63)	0.11 (-0.35, 0.57)	71	-0.07 (2.80)	-0.07 (-0.71, 0.58)	0.04 (-0.60, 0.68)	0.61
Discontinued	22	-0.45 (1.68)	-0.58 (-1.28, 0.12)	-0.50 (-1.26, 0.26)	46	-0.15 (2.24)	-0.25 (-0.90, 0.40)	-0.26 (-0.91, 0.39)	52	-0.69 (2.47)	-0.67 (-1.32, -0.02)	-0.34 (-0.92, 0.24)	0.57
Recurrent	38	0.08 (1.51)	0.00 (-0.54, 0.53)	0.13 (-0.39, 0.65)	61	0.08 (2.08)	-0.01 (-0.49, 0.48)	-0.02 (-0.48, 0.44)	79	-0.35 (1.92)	-0.32 (-0.76, 0.12)	-0.29 (-0.72, 0.15)	0.22
Animal naming													
None	5,282	-1.09 (6.21)	0	0	4,139	-1.20 (5.99)	0	0	3,096	-1.31 (5.66)	0	0	
New	49	-1.08 (5.63)	0.23 (-1.31, 1.77)	0.22 (-1.39, 1.83)	72	-1.85 (5.92)	-0.73 (-2.10, 0.64)	-0.87 (-2.05, 0.31)	88	-1.84 (5.29)	-0.50 (-1.63, 0.62)	-0.50 (-1.63, 0.64)	0.33
Discontinued	24	-0.04 (5.61)	1.08 (-1.15, 3.31)	1.15 (-1.02, 3.31)	50	-1.24 (4.75)	-0.21 (-1.54, 1.12)	-0.50 (-1.89, 0.90)	57	-1.79 (5.17)	-0.50 (-1.88, 0.87)	-0.41 (-1.78, 0.95)	0.32
Recurrent	42	0.79 (5.82)	1.93 (0.43, 3.43)	1.54 (0.00, 3.07)	66	-0.52 (5.18)	0.65 (-0.43, 1.72)	0.17 (-0.91, 1.26)	90	-1.87 (5.42)	-0.54 (-1.52, 0.44)	-0.56 (-1.60, 0.48)	0.005
Recall													
None	5,277	0.29 (4.16)	0	0	4,135	-0.01 (4.37)	0	0	3,044	-0.62 (4.75)	0	0	
New	49	0.41 (4.49)	0.10 (-1.18, 1.38)	0.21 (-1.07, 1.50)	71	0.01 (4.71)	0.01 (-1.07, 1.09)	0.11 (-0.97, 1.19)	83	0.28 (4.41)	1.07 (0.09, 2.05)	1.11 (0.06, 2.15)	0.31
Discontinued	25	0.32 (3.51)	0.00 (-1.39, 1.39)	0.08 (-1.32, 1.47)	49	-0.24 (4.04)	-0.27 (-1.40, 0.86)	-0.22 (-1.35, 0.92)	54	-0.65 (4.43)	0.03 (-1.17, 1.24)	0.19 (-1.02, 1.41)	0.81

Recurrent	42	1.07 (4.30)	0.77 (-0.44, 1.98)	0.97 (-0.26, 2.19)	66	-1.39 (4.77)	-1.30 (-2.40, -0.19)	-1.34 (-2.43, -0.25)	90	-0.64 (4.77)	0.03 (-0.87, 0.93)	-0.13 (-1.05, 0.79)	0.31
<i>Benzodiazepines</i>													
MMSE													
None	4,647	0.10 (1.56)	0	0	3,741	0.07 (1.68)	0	0	2,633	-0.06 (2.10)	0	0	
New	43	0.30 (1.83)	0.16 (-0.37, 0.70)	0.16 (-0.33, 0.65)	63	0.22 (2.35)	0.15 (-0.43, 0.73)	0.00 (-0.54, 0.55)	70	0.03 (2.06)	0.15 (-0.36, 0.65)	0.15 (-0.34, 0.64)	0.98
Discontinued	40	0.00 (2.20)	-0.16 (-0.83, 0.51)	-0.10 (-0.74, 0.53)	53	0.38 (1.82)	0.32 (-0.16, 0.80)	0.33 (-0.16, 0.81)	62	0.37 (2.59)	0.48 (-0.17, 1.13)	0.45 (-0.19, 1.09)	0.32
Recurrent	45	0.00 (1.43)	-0.08 (-0.49, 0.33)	-0.07 (-0.50, 0.36)	72	0.13 (1.94)	0.03 (-0.37, 0.43)	0.04 (-0.37, 0.45)	92	-0.24 (2.20)	-0.11 (-0.53, 0.31)	0.09 (-0.34, 0.51)	0.79
Animal naming													
None	5,241	-1.08 (6.21)	0	0	4,115	-1.22 (5.98)	0	0	3,077	-1.36 (5.70)	0	0	
New	54	0.00 (5.74)	1.09 (-0.46, 2.63)	1.00 (-0.54, 2.55)	68	-0.75 (6.34)	0.49 (-1.04, 2.02)	0.38 (-1.16, 1.91)	80	-0.21 (4.47)	1.22 (0.22, 2.22)	1.26 (0.24, 2.28)	0.40
Discontinued	43	-2.37 (5.51)	-1.36 (-3.01, 0.28)	-1.55 (-3.23, 0.13)	60	-0.37 (5.64)	0.83 (-0.63, 2.29)	0.66 (-0.89, 2.21)	73	-2.03 (4.71)	-0.60 (-1.70, 0.49)	-0.78 (-1.90, 0.34)	0.91
Recurrent	59	-0.69 (5.69)	0.25 (-1.07, 1.56)	0.13 (-1.30, 1.56)	84	-1.61 (4.96)	-0.41 (-1.42, 0.60)	-0.55 (-1.65, 0.56)	101	-1.45 (5.07)	-0.03 (-0.88, 0.81)	0.14 (-0.75, 1.02)	0.85
Recall													
None	5,236	0.30 (4.15)	0	0	4,111	-0.05 (4.36)	0	0	3,021	-0.59 (4.71)	0	0	
New	54	-0.59 (4.30)	-0.76 (-1.93, 0.41)	-0.89 (-2.09, 0.31)	67	0.70 (5.31)	0.88 (-0.37, 2.13)	0.73 (-0.53, 1.99)	77	-1.01 (5.19)	-0.32 (-1.50, 0.85)	-0.20 (-1.37, 0.97)	0.31
Discontinued	43	1.09 (3.87)	0.89 (-0.28, 2.06)	0.95 (-0.25, 2.14)	61	0.08 (4.68)	0.18 (-0.99, 1.36)	-0.06 (-1.23, 1.10)	73	-0.66 (4.15)	-0.10 (-1.06, 0.85)	-0.16 (-1.11, 0.78)	0.09
Recurrent	60	0.47 (5.08)	0.15 (-1.00, 1.30)	0.21 (-1.01, 1.43)	82	0.22 (4.25)	0.43 (-0.44, 1.29)	0.28 (-0.61, 1.18)	100	-0.30 (5.44)	0.49 (-0.46, 1.44)	0.66 (-0.30, 1.62)	0.55

† b coefficients shown are change relative to 'None' category.

Adjusted for demographics, baseline wave, self-reported incontinence, pain, and sleep difficulties, reported doctor-diagnosed eye, cardiovascular and other health conditions, self-rated vision and hearing, screened depressive symptoms, and smoking status

* p value based on interaction term between continuous age and medication exposure dummy variable in the main non-stratified analyses presented in Table 2

eTable 6. Characteristics of TILDA participants with linked pharmacy claims data by anticholinergic medication, benzodiazepine, and Z-drug dispensing.

Characteristic at wave 1	Medication use at wave 1, 2 or 3							
	All (n=2,905)		ACB3 use (n=482)		Benzo use (n=562)		Z-drug use (n=403)	
	n	%	n	%	n	%	n	%
Women	1,636	56.3	309	64.1	382	68.0	269	66.7
Age (years), mean SD	67.5	9.99	68.0	9.92	67.6	9.96	68.6	9.96
Education								
Primary/none	1,253	43.1	203	42.1	257	45.7	193	47.9
Secondary	1,131	38.9	197	40.9	222	39.5	148	36.7
Third/higher	521	17.9	82	17.0	83	14.8	62	15.4
Marital status								
Married	1,787	61.5	277	57.5	304	54.1	205	50.9
Never married	295	10.2	51	10.6	60	10.7	36	8.9
Separated/divorced	241	8.3	51	10.6	64	11.4	53	13.2
Widowed	582	20.0	103	21.4	134	23.8	109	27.0
Employment								
Employed	419	14.4	44	9.1	68	12.1	40	9.9
Retired	1,445	49.7	235	48.8	257	45.7	217	53.8
Other	1,041	35.8	203	42.1	237	42.2	146	36.2
Incontinence	445	15.3	131	27.8	105	18.7	83	20.6
Quintiles of CES-D score								
1	542	18.7	60	12.4	56	10.0	52	12.9
2	453	15.6	63	13.1	69	12.3	47	11.7
3	652	22.4	101	21.0	117	20.8	92	22.8
4	573	19.7	102	21.2	114	20.3	92	22.8
5	634	21.8	147	30.5	193	34.3	109	27.0
Missing	51	1.8	9	1.9	13	2.3	11	2.7
CES-D (median, IQR)	4	1-10	6	2-12	7	3-14	6	2-11
Pain								
None	1,681	57.9	225	46.7	260	46.3	189	46.9
Mild	293	10.1	46	9.5	44	7.8	44	10.9
Moderate	582	20.0	116	24.1	135	24.0	93	23.1
Severe	346	11.9	95	19.7	122	21.7	77	19.1
Missing	3	0.1	0	0.0	1	0.2	0	0.0
Trouble falling asleep								
Most of the time	380	13.1	87	18.0	120	21.4	104	25.8
Sometimes	759	26.1	130	27.0	184	32.7	129	32.0
Rarely or never	1,766	60.8	265	55.0	258	45.9	170	42.2
Disabilities								
Not disabled	2,418	83.2	351	72.8	428	76.2	316	78.4
IADL disability only	137	4.7	33	6.8	40	7.1	25	6.2
Any ADL disability	350	12.0	98	20.3	94	16.7	62	15.4
Smoker								
Never	1,190	41.0	192	39.8	213	37.9	172	42.7
Past	1,144	39.4	193	40.0	203	36.1	150	37.2
Current	571	19.7	97	20.1	146	26.0	81	20.1
Vision								
Excellent	442	15.2	54	11.2	68	12.1	52	12.9
Very good	1,086	37.4	173	35.9	199	35.4	132	32.8
Good	1,035	35.6	188	39.0	206	36.7	155	38.5
Fair	263	9.1	46	9.5	59	10.5	44	10.9
Poor	72	2.5	21	4.4	27	4.8	20	5.0
Registered Blind	7	0.2	0	0.0	3	0.5	0	0.0

Hearing								
Excellent	650	22.4	107	22.2	132	23.5	91	22.6
Very good	870	29.9	133	27.6	160	28.5	115	28.5
Good	856	29.5	150	31.1	164	29.2	129	32.0
Fair	435	15.0	71	14.7	76	13.5	49	12.2
Poor	94	3.2	21	4.4	30	5.3	19	4.7
Self-reported doctor-diagnosed conditions								
High blood pressure	1,340	46.1	233	48.3	261	46.4	196	48.6
Angina	251	8.6	44	9.1	52	9.3	38	9.4
Heart attack	195	6.7	27	5.6	40	7.1	34	8.4
Heart failure	45	1.5	8	1.7	8	1.4	10	2.5
Diabetes	302	10.4	65	13.5	54	9.6	38	9.4
Transient ischaemic attack	92	3.2	18	3.7	18	3.2	17	4.2
High cholesterol	1,192	41.0	215	44.6	239	42.5	186	46.2
Heart murmur	174	6.0	28	5.8	47	8.4	32	7.9
Cataracts*	448	15.4	83	17.2	100	17.8	74	18.4
Glaucoma	97	3.3	17	3.5	16	2.8	9	2.2
Age-related macular degeneration	71	2.4	16	3.3	20	3.6	16	4.0
Lung disease	159	5.5	31	6.4	37	6.6	38	9.4
Asthma	298	10.3	64	13.3	84	14.9	46	11.4
Osteoporosis	365	12.6	91	18.9	99	17.6	77	19.1
Cancer	226	7.8	40	8.3	47	8.4	34	8.4
Arthritis	1,043	35.9	227	47.1	243	43.2	185	45.9
Abnormal heart rhythm	270	9.3	43	8.9	74	13.2	44	10.9
Stroke	78	2.7	16	3.3	19	3.4	16	4.0
Gastric ulcer	230	7.9	41	8.5	55	9.8	38	9.4
Liver disease	22	0.8	3	0.6	8	1.4	3	0.7
Varicose ulcer	123	4.2	29	6.0	27	4.8	19	4.7
Parkinson's disease	18	0.6	9	1.9	8	1.4	2	0.5
Anxiety	166	5.7	51	10.6	70	12.5	36	8.9
Depression	190	6.5	59	12.2	71	12.6	36	8.9
Manic depression	14	0.5	10	2.1	7	1.2	1	0.2
Other psychiatric condition	80	2.8	27	5.6	30	5.3	21	5.2
Stroke (between wave 1 and 2)	19	0.7	7	1.5	9	1.6	4	1.0
Heart attack (between wave 1 and 2)	31	1.1	7	1.5	13	2.3	7	1.7

eTable 7. Cognitive change at 2-year follow-up compared to baseline and pharmacy claims based anticholinergic, benzodiazepine, and Z-drug medication use in TILDA, including cumulative dose for recurrent use

Benzodiazepine, and Z-drug medication use in HEDS, including cumulative dose for recurrent use					
Medication usage	N	2-year cognitive change, mean (SD)	b (95% CI), age, sex, wave adjusted†	b (95% CI), fully adjusted†#	Fully adjusted model test for trend p-value
<i>Anticholinergic</i>					
MMSE					
Cumulative use in recurrent users					
< 262 DDDs	70	0.49 (2.59)	0.43 (-0.06, 0.93)	0.46 (-0.02, 0.95)	0.824
262-528 DDDs	69	-0.14 (1.81)	-0.19 (-0.59, 0.21)	-0.18 (-0.61, 0.25)	
529-855 DDDs	69	-0.04 (1.95)	-0.07 (-0.52, 0.39)	0.04 (-0.43, 0.52)	
>855 DDDs	78	0.28 (2.24)	0.22 (-0.26, 0.70)	0.27 (-0.20, 0.75)	
Animal Naming					
Cumulative use in recurrent users					
< 262 DDDs	83	-2.27 (4.96)	-1.21 (-2.27, -0.16)	-1.40 (-2.39, -0.42)	0.869
262-528 DDDs	85	-0.66 (5.42)	0.46 (-0.74, 1.66)	0.34 (-0.89, 1.57)	
529-855 DDDs	83	-1.34 (4.84)	-0.36 (-1.42, 0.71)	-0.35 (-1.43, 0.72)	
>855 DDDs	84	-1.49 (5.38)	-0.64 (-1.76, 0.48)	-0.63 (-1.71, 0.45)	
Recall					
Cumulative use in recurrent users					
< 262 DDDs	81	-0.86 (5.33)	-0.72 (-1.77, 0.33)	-0.75 (-1.77, 0.27)	0.077
262-528 DDDs	84	-0.75 (5.31)	-0.68 (-1.69, 0.34)	-0.66 (-1.67, 0.36)	
529-855 DDDs	83	-1.06 (4.90)	-0.96 (-2.00, 0.08)	-0.99 (-2.07, 0.09)	
>855 DDDs	82	-1.09 (4.55)	-1.03 (-1.99, -0.07)	-0.94 (-1.93, 0.06)	
<i>Benzodiazepine</i>					
MMSE					
Cumulative use in recurrent users					
< 198 DDDs	90	-0.12 (1.95)	-0.16 (-0.53, 0.21)	-0.09 (-0.46, 0.29)	0.001*
198-419 DDDs	99	0.11 (1.79)	0.05 (-0.30, 0.40)	0.06 (-0.29, 0.41)	
420-735 DDDs	83	0.31 (2.43)	0.24 (-0.28, 0.75)	0.29 (-0.21, 0.79)	
>736 DDDs	87	0.64 (2.33)	0.57 (0.12, 1.03)	0.71 (0.25, 1.16)*	
Animal Naming					
Cumulative use in recurrent users					
< 198 DDDs	112	-1.66 (5.51)	-0.44 (-1.37, 0.49)	-0.41 (-1.38, 0.56)	0.007
198-419 DDDs	114	-1.89 (5.35)	-0.59 (-1.55, 0.37)	-0.74 (-1.70, 0.23)	
420-735 DDDs	105	-0.75 (4.75)	0.65 (-0.20, 1.49)	0.65 (-0.26, 1.56)	
>736 DDDs	103	-0.25 (4.68)	1.05 (0.19, 1.90)	0.96 (0.13, 1.79)	
Recall					
Cumulative use in recurrent users					
< 198 DDDs	109	-0.33 (4.43)	-0.09 (-0.86, 0.68)	-0.15 (-0.90, 0.60)	0.373
198-419 DDDs	114	-0.23 (4.65)	0.15 (-0.65, 0.95)	0.13 (-0.70, 0.95)	
420-735 DDDs	104	-0.79 (4.93)	-0.38 (-1.23, 0.47)	-0.35 (-1.22, 0.53)	
>736 DDDs	103	0.04 (5.14)	0.50 (-0.41, 1.41)	0.55 (-0.36, 1.45)	
<i>Z-drug</i>					
MMSE					
Cumulative use in recurrent users					
< 421 DDDs	74	-0.47 (2.41)	-0.50 (-0.99, -0.01)	-0.50 (-1.00, 0.01)	0.899
421-698 DDDs	67	0.24 (1.63)	0.21 (-0.18, 0.60)	0.23 (-0.17, 0.63)	
699-829 DDDs	68	0.15 (1.93)	0.04 (-0.33, 0.41)	0.06 (-0.33, 0.45)	
>830 DDDs	72	-0.49 (2.34)	-0.44 (-0.98, 0.11)	-0.32 (-0.84, 0.21)	
Animal Naming					
Cumulative use in recurrent users					
< 421 DDDs	83	-1.60 (6.28)	-0.35 (-1.52, 0.82)	-0.54 (-1.74, 0.66)	0.193
421-698 DDDs	83	-1.11 (5.62)	0.15 (-1.05, 1.34)	0.21 (-0.98, 1.40)	
699-829 DDDs	81	-1.48 (4.98)	-0.22 (-1.26, 0.82)	-0.23 (-1.27, 0.80)	
>830 DDDs	78	-0.32 (4.87)	0.75 (-0.13, 1.64)	0.64 (-0.26, 1.54)	
Recall					

Cumulative use in recurrent users					
< 421 DDDs	82	0.13 (4.39)	0.56 (-0.36, 1.49)	0.42 (-0.55, 1.38)	0.970
421-698 DDDs	80	0.18 (5.01)	0.56 (-0.51, 1.63)	0.60 (-0.51, 1.70)	
699-829 DDDs	81	-0.32 (4.19)	-0.01 (-0.94, 0.91)	-0.05 (-0.99, 0.88)	
>830 DDDs	76	-0.43 (4.65)	0.14 (-0.86, 1.15)	0.26 (-0.77, 1.28)	

† b coefficients shown are change relative to 'None' category.

Adjusted for other patterns of medication use (i.e. new, discontinued, and temporary), demographics, baseline wave, self-reported incontinence, pain, and sleep difficulties, reported doctor-diagnosed eye, cardiovascular and other health conditions, self-rated vision and hearing, screened depressive symptoms, and smoking status.

* Fully-adjusted beta remaining statistically significant after controlling the false discovery rate to <5% (based on 45 tests)

** Test for linear trend by cumulative DDDs among recurrent users p<0.05