Web extra

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Supplementary Figure 1: Study scheme and definitions of treatment periods for sensitivity analysis

	ICD-9-CM	ICD-10-CM
Comorbidities		
Major neurocognitive disorders	290.0, 290.1, 290.2, 290.3, 290.4, 294.1, 331.0, 331.1, 331.82	F01, F02, F03, G30, G31.83
Alzheimer's disease	331.0	G30
Parkinson's dementia*	331.82	G31.83
Vascular dementia	290.4	F01
Others or unspecified	290.0, 290.1, 290.2, 290.3, 294.1, 331.1	F02, F03
Schizophrenia	295	F20, F21, F25
Bipolar disorder	296.0, 296.1, 296.4–296.8	F30, F31
Depression	296.2, 296.3, 300.4, 311	F32, F33, F341
Parkinson's disease	332.0	G20
Epilepsy	345	G40
Hypertension	401-405	I10-I16
Diabetes mellitus	250	E11
Hyperlipidaemia	272	E78
Coronary artery disease	410-414	I20-I25
Atrial fibrillation	427.31	I48.91
Heart failure	428	I50
Ischemic stroke	433–437	I63-I68
Osteoarthritis	715	M15-M19
Osteoporosis	733.0	M80, M81
Cataract	366.0-366.4	H25, H26
Outcomes		
Falls	E880-E888	W00-W19
Falls from a different level	E880-E884	W00.1, W00.2, W05-W17
Falls on the same level	E885-E886	W00.0, W01-W04, W18
Traumatic fractures	800-829	S02, S12, S22, S32, S42, S52, S62,
		S72, S82, S92
Hip fractures	820	S72

Supplementary Table 1: ICD code of diseases included in our study

*Note: Parkinson's dementia was defined as dementia with Lewy bodies or any subtype of major neurocognitive disorders plus the diagnosis of Parkinson's disease.

Supplementary	Table 2:	ATC codes	of drugs	included	in our study.
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Category	Drugs	ATC codes
Cholinesterase inhibitors	Donepezil	N06DA02
Cholinesterase inhibitors	Rivastigmine	N06DA03
Cholinesterase inhibitors	Galantamine	N06DA04
Antipsychotic drugs	Chlorpromazine	N05AA01
Antipsychotic drugs	Levomepromazine	N05AA02
Antipsychotic drugs	Fluphenazine	N05AB02
Antipsychotic drugs	Perphenazine	N05AB03
Antipsychotic drugs	Trifluoperazine	N05AB06
Antipsychotic drugs	Thioridazine	N05AC02
Antipsychotic drugs	Pipotiazine	N05AC04
Antipsychotic drugs	Haloperidol	N05AD01
Antipsychotic drugs	Moperone	N05AD04
Antipsychotic drugs	Droperidol	N05AD08
Antipsychotic drugs	Flupentixol	N05AF01
Antipsychotic drugs	Clopenthixol	N05AF02
Antipsychotic drugs	Chlorprothixene	N05AF03
Antipsychotic drugs	Zuclopenthixol	N05AF05
Antipsychotic drugs	Pimozide	N05AG02
Antipsychotic drugs	Penfluridol	N05AG03
Antipsychotic drugs	Loxapine	N05AH01
Antipsychotic drugs	Sulpiride	N05AL01
Antipsychotic drugs	Ziprasidone	N05AE04
Antipsychotic drugs	Lurasidone	N05AE05
Antipsychotic drugs	Clozapine	N05AH02
Antipsychotic drugs	Olanzapine	N05AH03
Antipsychotic drugs	Quetiapine	N05AH04
Antipsychotic drugs	Clotiapine	N05AH06
Antipsychotic drugs	Amisulpride	N05AL05
Antipsychotic drugs	Risperidone	N05AX08
Antipsychotic drugs	Zotepine	N05AX11
Antipsychotic drugs	Aripiprazole	N05AX12
Antipsychotic drugs	Paliperidone	N05AX13
Antipsychotic drugs	Brexpiprazole	N05AX16
Co-administered drugs	Antidepressants	N06A
Co-administered drugs	Psychostimulants	N06B
Co-administered drugs	Anxiolytics	N05B
Co-administered drugs	Hypnotics and sedatives	N05C
Co-administered drugs	Antiparkinsonian agents	N04
Co-administered drugs	Anticonvulsants	N03A
Co-administered drugs	Muscle relaxants	M03
Co-administered drugs	Vasodilators	C01D, C04
Co-administered drugs	Antihypertensive drugs	C02
Co-administered drugs	Diuretics	C03
Co-administered drugs	Renin-angiotensin-aldosterone system inhibitors	C09
Co-administered drugs	Beta-blockers	C07
Co-administered drugs	Calcium channel blockers	C08
Co-administered drugs	Antidiabetic agents	A10
Co-administered drugs	Lipid modifying agents	C10
Co-administered drugs	Antiarrhythmic agents (class 1 and 3)	C01B
Co-administered drugs	Antithrombotic agents	B01A
Co-administered drugs	Steroid (systemic use)	H02
Co-administered drugs	Non-steroidal anti-inflammatory drugs	M01A
Co-administered drugs	Bisphosphonates	M05BA, M05BB
Co-administered drugs	Parasympathomimetic drugs	N07A
Co-administered drugs	Antihistamine	R06A

	Events, n	Follow-up time, person-years,	Follow-up time, years, median	Incidence rate (95% confidence interval),	Crude incidence rate ratio (95% confidence interval)	Adjusted incidence rate ratio (95% confidence interval)
		sum	(interquartile range)	/100 person-years	(93% confidence interval)	(95% confidence lifter var)
Male (n=5,088)						
Non-treatment	3,239	40,347.80	8.40 (4.08)	8.03 (7.76 to 8.31)	Reference	Reference
Pretreatment	285	421.32	0.07 (0.04)	67.64 (60.13 to 75.85)	8.43 (7.47 to 9.51)	7.63 (6.73 to 8.65)
Cholinesterase inhibitor alone	636	6,354.09	0.98 (1.82)	10.01 (9.25 to 10.81)	1.25 (1.15 to 1.36)	1.18 (1.06 to 1.30)
Antipsychotic drug alone	485	3,844.57	0.31 (1.01)	12.62 (11.53 to 13.78)	1.57 (1.43 to 1.73)	1.55 (1.38 to 1.75)
Combination	443	3,591.78	0.49 (1.15)	12.33 (11.22 to 13.52)	1.54 (1.39 to 1.70)	1.48 (1.31 to 1.67)
Female (n=10,190)						
Non-treatment	6,969	82,615.20	8.62 (3.97)	8.44 (8.24 to 8.64)	Reference	Reference
Pretreatment	372	833.58	0.07 (0.03)	44.63 (40.26 to 49.34)	5.29 (4.77 to 5.87)	5.35 (4.80 to 5.95)
Cholinesterase inhibitor alone	1,154	12,664.24	0.96 (1.96)	9.11 (8.60 to 9.65)	1.08 (1.01 to 1.15)	1.16 (1.07 to 1.25)
Antipsychotic drug alone	868	9,242.88	0.38 (1.33)	9.39 (8.78 to 10.03)	1.11 (1.04 to 1.19)	1.24 (1.13 to 1.35)
Combination	827	8,445.56	0.60 (1.38)	9.79 (9.14 to 10.48)	1.16 (1.08 to 1.25)	1.29 (1.18 to 1.41)

Supplementary Table 3-1: Sensitivity analysis (stratified by sex)

Supplementary Table 3-2: Sensitivity analysis (stratified by age group)

		Follow-up time,	Follow-up time,	Incidence rate	Crude incidence rate ratio	Adjusted incidence rate ratio
	Events, n	person-years,	years, median	(95% confidence interval),	(95% confidence interval)	(95% confidence interval)
		sum	(interquartile range)	/100 person-years	(9576 confidence mervar)	(95% confidence filtervar)
Age group 65-74 years (n=3,137)						
Non-treatment	2,694	26,387.62	8.97 (3.69)	10.21 (9.83 to 10.60)	Reference	Reference
Pretreatment	38	256.82	0.07 (0.03)	14.80 (10.62 to 20.10)	1.45 (1.05 to 2.00)	2.81 (2.03 to 3.90)
Cholinesterase inhibitor alone	183	3,882.57	0.98 (1.83)	4.71 (4.07 to 5.44)	0.46 (0.40 to 0.54)	1.16 (0.95 to 1.40)
Antipsychotic drug alone	131	2,621.04	0.32 (1.19)	5.00 (4.20 to 5.91)	0.49 (0.41 to 0.58)	1.56 (1.25 to 1.93)
Combination	91	2,323.16	0.55 (1.27)	3.92 (3.17 to 4.79)	0.38 (0.31 to 0.47)	1.67 (1.29 to 2.16)
Age group 75-84 years (n=8,703)						
Non-treatment	5,794	70,261.66	8.58 (3.97)	8.25 (8.04 to 8.46)	Reference	Reference
Pretreatment	377	713.91	0.07 (0.03)	52.81 (47.68 to 58.35)	6.40 (5.77 to 7.11)	6.11 (5.49 to 6.80)
Cholinesterase inhibitor alone	1,051	10,778.09	0.96 (1.90)	9.75 (9.18 to 10.35)	1.18 (1.11 to 1.26)	1.18 (1.09 to 1.28)
Antipsychotic drug alone	775	7,409.98	0.35 (1.21)	10.46 (9.47 to 11.22)	1.27 (1.18 to 1.37)	1.28 (1.17 to 1.41)
Combination	706	6,936.38	0.57 (1.27)	10.18 (9.45 to 10.95)	1.23 (1.14 to 1.33)	1.25 (1.14 to 1.37)
Age group 85+ years (n=3,438)						
Non-treatment	1,720	26,313.73	8.00 (4.31)	6.54 (6.23 to 6.85)	Reference	Reference
Pretreatment	242	284.17	0.07 (0.04)	85.16 (74.93 to 96.41)	13.03 (11.39 to14.90)	8.07 (7.03 to 9.26)
Cholinesterase inhibitor alone	556	4,357.67	0.95 (2.11)	12.76 (11.73 to 13.85)	1.95 (1.77 to 2.15)	1.29 (1.15 to 1.45)
Antipsychotic drug alone	447	3,056.43	0.37 (1.21)	14.62 (13.32 to 16.03)	2.24 (2.02 to 2.48)	1.20 (1.05 to 1.37)
Combination	473	2,777.82	0.55 (1.41)	17.03 (15.54 to 18.61)	2.61 (2.35 to 2.88)	1.51 (1.33 to 1.72)

Supplementary Table 3-3: Sensitivity analysis (stratified by anticholinergic burden indicator)

	Events, n	Follow-up time, person-years, sum	Follow-up time, years, median (interquartile range)	Incidence rate (95% confidence interval), /100 person-years	Crude incidence rate ratio (95% confidence interval)	Adjusted incidence rate ratio (95% confidence interval)
Anticholinergic drug scale 2+ (n= 6,579)				i i		
Non-treatment	4,008	51,202.55	8.23 (4.28)	7.83 (7.59 to 8.07)	Reference	Reference
Pretreatment	326	546.27	0.07 (0.04)	59.68 (53.46 to 66.43)	7.62 (6.81 to 8.53)	7.41 (6.60 to 8.33)
Cholinesterase inhibitor alone	828	8,133.35	0.97 (1.93)	10.18 (9.51 to 10.89)	1.30 (1.21 to 1.40)	1.35 (1.24 to 1.48)
Antipsychotic drug alone	745	6,076.65	0.38 (1.34)	12.26 (11.40 to 13.16)	1.57 (1.45 to 1.69)	1.76 (1.60 to 1.95)
Combination	672	5,664.66	0.64 (1.45)	11.86 (10.99 to 12.79)	1.52 (1.40 to 1.64)	1.67 (1.51 to 1.85)
Anticholinergic drug scale 0-1 (n=8,699)						
Non-treatment	6,200	71,760.45	8.75 (3.79)	8.64 (8.43 to 8.86)	Reference	Reference
Pretreatment	331	708.62	0.07 (0.03)	46.71 (41.88 to 51.95)	5.41 (4.84 to 6.04)	5.30 (4.74 to 5.94)
Cholinesterase inhibitor alone	962	10,884.98	0.96 (1.91)	8.84 (8.29 to 9.41)	1.02 (0.96 to 1.09)	1.05 (0.96 to 1.13)
Antipsychotic drug alone	608	7010.80	0.33 (1.14)	8.67 (8.00 to 9.38)	1.00 (0.92 to 1.09)	1.02 (0.93 to 1.13)
Combination	598	6372.69	0.50 (1.20)	9.38 (8.65 to 10.16)	1.09 (1.00 to 1.18)	1.11 (1.01 to 1.23)

Supplementary Table 3-4: Sensitiv	ity analysis	s (stratifie	d by	y cumulativ	ve dose	of antipsychotic drugs)	
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	Events,	Follow-up time,	Follow-up time,	Incidence rate	Crude incidence rate ratio	Adjusted incidence rate ratio
	,	person-years,	years, median	(95% confidence interval),	(95% confidence interval)	(95% confidence interval)
		sum	(interquartile range)	/100 person-years	() o / o contractice inter (ui)	(3570 contractice meet (ar)
Higher than the median value (n=3,232)						
Non-treatment	855	21,593.70	6.91 (4.36)	3.96 (3.70 to 4.23)	Reference	Reference
Pretreatment	78	279.17	0.07 (0.04)	27.94 (22.24 to 34.68)	7.06 (5.60 to 8.90)	5.73 (4.54 to 7.24)
Cholinesterase inhibitor alone	386	3,575.33	0.88 (1.89)	10.80 (9.76 to 11.91)	2.73 (2.42 to 3.07)	2.04 (1.77 to 2.35)
Antipsychotic drug alone	938	5,222.99	1.03 (2.28)	17.96 (16.84 to 19.14)	4.54 (4.13 to 4.98)	3.80 (3.38 to 4.27)
Combination	975	4,295.59	1.03 (1.79)	22.70 (21.31 to 24.16)	5.73 (5.23 to 6.28)	5.38 (4.79 to 6.05)
Equal to or lower than the median value						
(n=3,247)						
Non-treatment	1,818	27,044.47	8.90 (3.98)	6.72 (6.41 to 7.04)	Reference	Reference
Pretreatment	129	285.56	0.07 (0.04)	45.17 (37.87 to 53.49)	6.72 (5.62 to 8.03)	5.45 (4.54 to 6.53)
Cholinesterase inhibitor alone	590	4,464.33	0.97 (2.12)	13.22 (12.18 to 14.31)	1.97 (1.79 to 2.16)	1.66 (1.48 to 1.87)
Antipsychotic drug alone	415	2,041.81	0.21 (0.74)	20.33 (18.44 to 22.35)	3.02 (2.72 to 3.36)	2.91 (2.54 to 3.33)
Combination	295	1,797.32	0.38 (0.97)	16.41 (14.62 to 18.37)	2.44 (2.16 to 2.76)	2.12 (1.82 to 2.47)

Supplementary Table 3-5: Sensitivity analysis (restricted to outcomes at outpatient settings only, n=7,914)

	Events, n	Follow-up time, person-years, sum	Follow-up time, years, median (interquartile range)	Incidence rate (95% confidence interval), /100 person-years	Crude incidence rate ratio (95% confidence interval)	Adjusted incidence rate ratio (95% confidence interval)
Non-treatment	5,826	64,652.78	8.65 (3.86)	9.01 (8.78 to 9.25)	Reference	Reference
Pretreatment	141	646.13	0.07 (0.03)	21.82 (18.44 to 25.66)	2.42 (2.05 to 2.86)	2.54 (2.14 to 3.01)
Cholinesterase inhibitor alone	881	10,012.89	0.98 (1.98)	8.80 (8.23 to 9.39)	0.98 (0.91 to 1.05)	1.09 (1.00 to 1.19)
Antipsychotic drug alone	571	6,502.65	0.34 (1.16)	8.78 (8.08 to 9.52)	0.97 (0.89 to 1.06)	1.12 (1.01 to 1.25)
Combination	495	6,131.50	0.55 (1.27)	8.07 (7.39 to 8.81)	0.90 (0.82 to 0.98)	1.02 (0.91 to 1.13)

Supplementary Table 3-6: Sensit	vity analy	sis (re-selected r	patients without ex	xcluding schizophrenia a	nd bipolar disorder)

		Follow-up time,	Follow-up time,	Incidence rate	Crude incidence rate ratio	Adjusted incidence rate ratio
	Events, n	person-years,	years, median	(95% confidence interval),	(95% confidence interval)	(95% confidence interval)
		sum	(interquartile range)	/100 person-years	(5570 confidence interval)	(3570 confidence interval)
All patients (15,791)						
Non-treatment	10,541	126,870.74	8.54 (4.03)	8.31 (8.15 to 8.47)	Reference	Reference
Pretreatment	670	1,299.57	0.07 (0.03)	51.56 (47.76 to 55.57)	6.21 (5.74 to 6.71)	6.07 (5.60 to 6.57)
Cholinesterase inhibitor alone	1,829	19,437.05	0.96 (1.91)	9.41 (8.99 to 9.85)	1.13 (1.08 to 1.19)	1.17 (1.10 to 1.24)
Antipsychotic drug alone	1,435	13,941.15	0.36 (1.24)	10.29 (9.77 to 10.84)	1.24 (1.17 to 1.31)	1.32 (1.24 to 1.42)
Combination	1,316	12,567.72	0.56 (1.32)	10.47 (9.92 to 11.05)	1.26 (1.19 to 1.33)	1.33 (1.24 to 1.43)
With schizophrenia (n=98)						
Non-treatment	60	711.20	7.95 (5.66)	8.44 (6.50 to 10.78)	Reference	Reference
Pretreatment	2	8.70	0.07 (0.04)	22.99 (3.85 to 75.95)	2.76 (0.67 to 11.28)	2.94 (0.70 to 12.37)
Cholinesterase inhibitor alone	3	59.73	0.45 (1.06)	5.02 (1.28 to 13.67)	0.60 (0.19 to 1.90)	0.66 (0.16 to 2.72)
Antipsychotic drug alone	21	210.63	1.25 (2.79)	9.97 (6.34 to 14.98)	1.18 (0.72 to 1.94)	1.55 (0.80 to 2.99)
Combination	12	101.84	0.54 (0.96)	11.78 (6.38 to 20.03)	1.40 (0.75 to 2.60)	1.79 (0.75 to 4.28)
Without schizophrenia (n=15,693)						
Non-treatment	10,481	126,159.54	8.54 (4.02)	8.31 (8.15 to 8.47)	Reference	Reference
Pretreatment	668	1,290.97	0.07 (0.03)	51.74 (47.93 to 55.78)	6.23 (5.76 to 6.74)	6.08 (5.61 to 6.59)
Cholinesterase inhibitor alone	1,826	19,377.32	0.96 (1.91)	9.42 (9.00 to 9.86)	1.13 (1.08 to 1.19)	1.17 (1.10 to 1.24)
Antipsychotic drug alone	1,414	13,730.52	0.36 (1.23)	10.30 (9.77 to 10.85)	1.24 (1.17 to 1.31)	1.32 (1.23 to 1.42)
Combination	1,304	12,465.88	0.57 (1.32)	10.46 (9.90 to 11.04)	1.26 (1.19 to 1.33)	1.33 (1.24 to 1.43)
With bipolar disorder (n=426)						
Non-treatment	277	3,257.41	8.02 (4.10)	8.50 (7.55 to 9.55)	Reference	Reference
Pretreatment	11	37.04	0.07 (0.04)	29.70 (15.62 to 51.62)	3.49 (1.91 to 6.38)	3.24 (1.76 to 5.99)
Cholinesterase inhibitor alone	37	362.88	0.56 (1.60)	10.20 (7.29 to 13.91)	1.20 (0.85 to 1.69)	1.19 (0.79 to 1.81)
Antipsychotic drug alone	67	688.24	0.77 (2.41)	9.74 (7.60 to 12.29)	1.14 (0.88 to 1.49)	1.12 (0.80 to 1.58)
Combination	34	435.18	0.74 (1.68)	7.81 (5.50 to 10.79)	0.92 (0.64 to 1.31)	0.84 (0.55 to 1.30)
Without bipolar disorder (n=15,365)						
Non-treatment	10,264	123,613.33	8.55 (4.02)	8.30 (8.14 to 8.47)	Reference	Reference
Pretreatment	659	1,262.54	0.07 (0.03)	52.20 (48.32 to 56.30)	6.29 (5.81 to 6.80)	6.15 (5.67 to 6.67)
Cholinesterase inhibitor alone	1,792	19,074.17	0.96 (1.92)	9.40 (8.97 to 9.84)	1.13(1.08 to 1.19)	1.17(1.10 to 1.24)
Antipsychotic drug alone	1,368	13,252.92	0.35 (1.21)	10.32 (9.79 to 10.88)	1.24 (1.17 to 1.32)	1.33 (1.24 to 1.43)
Combination	1,282	12,132.54	0.56 (1.31)	10.57 (10.00 to 11.16)	1.27 (1.20 to 1.35)	1.35 (1.26 to 1.45)
With depression (n=4,743)		,	· · · · · · · · · · · · · · · · · · ·	``````````````````````````````````````	× , , , , , , , , , , , , , , , , , , ,	
Non-treatment	3,321	38,500.25	8.65 (3.92)	8.63 (8.34 to 8.92)	Reference	Reference
Pretreatment	144	399.33	0.07 (0.04)	36.06 (30.52 to 42.32)	4.18 (3.54 to 4.94)	4.13 (3.49 to 4.90)
Cholinesterase inhibitor alone	435	5,049.01	0.86 (1.76)	8.62 (7.83 to 9.45)	1.00 (0.90 to 1.10)	1.03 (0.91 to 1.16)
Antipsychotic drug alone	465	5,029.55	0.48 (1.51)	9.25 (8.43 to 10.11)	1.07(0.97 to 1.18)	1.12 (1.00 to 1.27)
Combination	378	4,287.04	0.67 (1.44)	8.82 (7.96 to 9.74)	1.02(0.92 to 1.14)	1.06 (0.93 to 1.20)
Without depression (n=11,048)					、	
Non-treatment	7,220	88,370.49	8.49 (4.09)	8.17 (7.98 to 8.36)	Reference	Reference
Pretreatment	526	900.25	0.07 (0.03)	58.43 (53.59 to 63.58)	7.15 (6.55 to 7.81)	6.95 (6.34 to 7.61)

Cholinesterase inhibitor alone	1,394	14,388.04	0.99 (1.98)	9.69 (9.19 to 10.21)	1.19 (1.12 to 1.26)	1.22 (1.14 to 1.31)
Antipsychotic drug alone	970	8,911.60	0.32 (1.13)	10.88 (10.22 to 11.59)	1.33 (1.25 to 1.42)	1.43 (1.32 to 1.56)
Combination	938	8,280.68	0.52 (1.24)	11.33 (10.62 to 12.07)	1.39 (1.30 to 1.48)	1.48 (1.37 to 1.61)

Supplementary Table 3-7: Sensitivity analysis (removed patients who died)

	Events, n	Follow-up time, person-years, sum	Follow-up time, years, median (interquartile range)	Incidence rate (95% confidence interval), /100 person-years	Crude incidence rate ratio (95% confidence interval)	Adjusted incidence rate ratio (95% confidence interval)
Removed patients who died during the		Sulli	(interquartite range)	/100 person-years		
study period (n=10,080)						
Non-treatment	7,017	89,208.04	9.43 (3.31)	7.87 (7.68 to 8.05)	Reference	Reference
Pretreatment	411	830.55	0.07 (0.03)	49.49 (44.87 to 54.45)	6.29 (5.70 to 6.95)	6.43 (5.80 to 7.12)
Cholinesterase inhibitor alone	1,127	13,412.55	1.02 (2.09)	8.40 (7.92 to 8.90)	1.07 (1.00 to 1.14)	1.10 (1.02 to 1.19)
Antipsychotic drug alone	802	8,744.27	0.34 (1.24)	9.17 (8.55 to 9.82)	1.17 (1.08 to 1.25)	1.25 (1.15 to 1.37)
Combination	723	8,203.00	0.57 (1.36)	8.81 (8.19 to 9.47)	1.12 (1.04 to 1.21)	1.18 (1.08 to 1.30)
Removed patients who died within three months after the events (n=15,014)						
Non-treatment	10,134	121,287.44	8.58 (4.00)	8.36 (8.19 to 8.52)	Reference	Reference
Pretreatment	634	1,233.55	0.07 (0.03)	51.40 (47.51 to 55.51)	6.15 (5.68 to 6.67)	6.12 (5.63 to 6.64)
Cholinesterase inhibitor alone	1,747	18,760.15	0.97 (1.92)	9.31 (8.88 to 9.76)	1.11 (1.06 to 1.17)	1.17 (1.10 to 1.24)
Antipsychotic drug alone	1,295	12,944.78	0.36 (1.22)	10.00 (9.47 to 10.56)	1.20 (1.13 to 1.27)	1.30 (1.21 to 1.40)
Combination	1,204	11,879.29	0.56 (1.32)	10.14 (9.58 to 10.72)	1.21 (1.14 to 1.29)	1.31 (1.22 to 1.41)

Supplementary Table 3-8: Sensitivity analysis (redefined outcome by specific codes)

	Events, n	Follow-up time, person-years,	ears vears median (05% confidence interval)		Crude incidence rate ratio (95% confidence interval)	Adjusted incidence rate ratio (95% confidence interval)
		sum	(interquartile range)	/100 person-years	(9378 confidence lifter var)	(93% confidence interval)
All event (n=5,458)						
Non-treatment	3,300	42,804.53	8.30 (4.06)	7.71 (7.45 to 7.98)	Reference	Reference
Pretreatment	379	453.89	0.07 (0.04)	83.50 (75.40 to 92.23)	10.83 (9.74 to 12.05)	10.16 (9.10 to 11.35)
Cholinesterase inhibitor alone	648	6,716.32	0.96 (1.90)	9.65 (8.93 to 10.41)	1.25 (1.15 to 1.36)	1.22 (1.11 to 1.35)
Antipsychotic drug alone	594	5,272.78	0.42 (1.41)	11.27 (10.39 to 12.20)	1.46 (1.34 to 1.59)	1.52 (1.36 to 1.69)
Combination	537	4,321.32	0.57 (1.34)	12.43 (11.41 to 13.51)	1.61 (1.47 to 1.77)	1.67 (1.49 to 1.87)
Falls (n=621)						
Non-treatment	272	5,468.39	9.24 (3.26)	4.97 (4.41 to 5.59)	Reference	Reference
Pretreatment	73	51.14	0.07 (0.03)	142.70 (112.70 to 178.50)	28.70 (22.16 to 37.16)	10.77 (8.19 to 14.16)
Cholinesterase inhibitor alone	95	780.78	1.01 (2.04)	12.17 (9.90 to 14.81)	2.45 (1.94 to 3.09)	0.87 (0.65 to 1.16)
Antipsychotic drug alone	89	474.53	0.28 (0.94)	18.76 (15.15 to 22.97)	3.77 (2.97 to 4.79)	1.26 (0.91 to 1.74)
Combination	92	404.43	0.50 (1.15)	22.75 (18.44 to 27.77)	4.57 (3.61 to 5.79)	1.49 (1.09 to 2.04)
Fractures (n=5,149)						
Non-treatment	3,139	40,185.37	8.25 (4.11)	7.81 (7.54 to 8.09)	Reference	Reference
Pretreatment	357	428.79	0.07 (0.04)	83.26 (74.95 to 92.24)	10.66 (9.55 to 11.89)	10.41 (9.29 to 11.66)
Cholinesterase inhibitor alone	603	6,325.23	0.96 (1.89)	9.53 (8.80 to 10.32)	1.22 (1.12 to 1.33)	1.26 (1.13 to 1.39)
Antipsychotic drug alone	554	5,014.47	0.42 (1.41)	11.05 (10.16 to 12.00)	1.41 (1.29 to 1.55)	1.57 (1.40 to 1.76)
Combination	496	4,115.68	0.57 (1.34)	12.05 (11.03 to 13.15)	1.54 (1.40 to 1.70)	1.70 (1.51 to 1.91)

Supplementary Table 3-9: Sensitivity analysis (counting all episodes of falls and fractures*, n=15,278)

	Events, n	Follow-up time, person-years, sum	Follow-up time, years, median (interquartile range)	Incidence rate (95% confidence interval), /100 person-vears	Crude incidence rate ratio (95% confidence interval)	Adjusted incidence rate ratio (95% confidence interval)
	16.440				D.C.	D.C.
Non-treatment	16,448	122,963.00	8.55 (4.01)	13.38 (13.17 to 13.58)	Reference	Reference
Pretreatment	1,159	1,254.90	0.07 (0.03)	92.36 (87.16 to 97.79)	6.92 (6.52 to 7.34)	5.53 (5.21 to 5.88)
Cholinesterase inhibitor alone	3,632	19,018.33	0.96 (1.92)	19.10 (18.48 to 19.73)	1.43 (1.38 to 1.48)	1.16 (1.11 to 1.21)
Antipsychotic drug alone	2,751	13,087.45	0.35 (1.21)	21.02 (20.25 to 21.82)	1.57 (1.51 to 1.63)	1.24 (1.18 to 1.31)
Combination	2,726	12,037.35	0.56 (1.31)	22.65 (21.81 to 23.51)	1.69 (1.62 to 1.76)	1.31 (1.25 to 1.38)

Supplementary Table 3-10: Sei	nsitivity analysis (radafin)	d the length of the	nratroatment nariad)
Supplementary rapid 5-10. Ser	isitivity analysis (icuciin	a me nengin or me	preneatment periou)

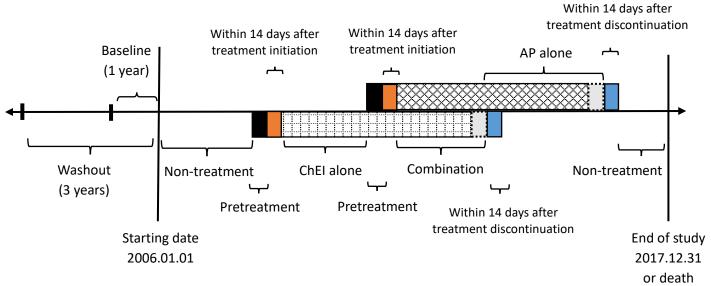
		Follow-up time,	Follow-up time,	Incidence rate	Crude incidence rate ratio	Adjusted incidence rate ratio
	Events, n	person-years,	years, median	(95% confidence interval),	(95% confidence interval)	(95% confidence interval)
		sum	(interquartile range)	/100 person-years	(3570 confidence interval)	
7 days prior to treatment (n=15,278)						
Non-treatment	10,343	123,433.84	8.58 (4.02)	8.38 (8.22 to 8.54)	Reference	Reference
Pretreatment	474	580.21	0.03 (0.02)	81.69 (74.58 to 89.30)	9.75 (8.89 to 10.69)	9.49 (8.64 to 10.43)
Cholinesterase inhibitor alone	1,827	19,125.99	0.97 (1.92)	9.55 (9.12 to 10.00)	1.14 (1.08 to 1.20)	1.17 (1.10 to 1.25)
Antipsychotic drug alone	1,364	13,180.82	0.36 (1.21)	10.35 (9.81 to 10.91)	1.23 (1.17 to 1.31)	1.30 (1.21 to 1.39)
Combination	1,270	12,037.35	0.56 (1.31)	10.55 (9.98 to 11.14)	1.26 (1.19 to 1.33)	1.32 (1.23 to 1.42)
21 days prior to treatment (n=15,278)						
Non-treatment	10,115	122,497.41	8.52 (4.01)	8.26 (8.10 to 8.42)	Reference	Reference
Pretreatment	792	1,924.81	0.11 (0.05)	41.15 (38.35 to 44.09)	4.98 (4.64 to 5.36)	4.91 (4.56 to 5.30)
Cholinesterase inhibitor alone	1,759	18,910.18	0.96 (1.91)	9.30 (8.88 to 9.74)	1.13 (1.07 to 1.19)	1.17 (1.10 to 1.24)
Antipsychotic drug alone	1,342	12,993.52	0.35 (1.21)	10.33 (9.79 to 10.89)	1.25 (1.18 to 1.32)	1.34 (1.25 to 1.44)
Combination	1,270	12,037.35	0.56 (1.31)	10.55 (9.98 to 11.14)	1.28 (1.21 to 1.35)	1.37 (1.27 to 1.47)
28 days prior to treatment (n=15,278)						
Non-treatment	10,001	122,034.57	8.49 (4.01)	8.20 (8.04 to 8.36)	Reference	Reference
Pretreatment	949	2,591.75	0.15 (0.07)	36.62 (34.34 to 39.00)	4.47 (4.18 to 4.78)	4.43 (4.14 to 4.75)
Cholinesterase inhibitor alone	1,736	18,802.14	0.96 (1.91)	9.23 (8.81 to 9.68)	1.13 (1.07 to 1.19)	1.18 (1.11 to 1.25)
Antipsychotic drug alone	1,322	12,901.92	0.35 (1.22)	10.25 (9.71 to 10.81)	1.25 (1.18 to 1.32)	1.35 (1.26 to 1.45)
Combination	1,270	12,037.35	0.56 (1.31)	10.55 (9.98 to 11.14)	1.29 (1.21 to 1.36)	1.39 (1.29 to 1.49)

Supplementary Table 3-11: Sensitivity analysis (focusing on individual antipsychotic drugs)

		Follow-up time,	Follow-up time,	Incidence rate	Crude incidence rate ratio	A divistad in aidemaa note notie
	Events, n	person-years,	years, median	(95% confidence interval),	(95% confidence interval)	Adjusted incidence rate ratio (95% confidence interval)
		sum	(interquartile range)	/100 person-years	(95% confidence interval)	(95% confidence interval)
Haloperidol (n=4,745)						
Non-treatment	3,307	40,792.32	9.19 (3.79)	8.11 (7.83 to 8.39)	Reference	Reference
Pretreatment	367	368.10	0.07 (0.00)	99.70 (89.89 to 110.30)	12.30 (11.04 to13.70)	12.11 (10.84 to 13.54)
Cholinesterase inhibitor alone	812	8,985.84	1.18 (2.31)	9.04 (8.43 to 9.67)	1.11 (1.03 to 1.20)	1.16 (1.06 to 1.27)
Antipsychotic drug alone	166	666.06	0.06 (0.08)	24.92 (21.34 to 28.94)	3.07 (2.63 to 3.59)	3.75 (3.15 to 4.47)
Combination	93	340.37	0.05 (0.07)	27.32 (22.18 to 33.32)	3.37 (2.74 to 4.14)	4.26 (3.37 to 5.37)
Risperidone (n=5,119)						
Non-treatment	3,716	42,362.60	8.78 (3.90)	8.72 (8.44 to 9.00)	Reference	Reference
Pretreatment	98	393.72	0.07 (0.00)	24.89 (20.32 to 30.20)	2.84 (2.32 to 3.47)	2.74 (2.23 to 3.35)
Cholinesterase inhibitor alone	886	8,724.17	1.17 (2.18)	10.16 (9.50 to 10.84)	1.16 (1.08 to 1.25)	1.23 (1.13 to 1.35)
Antipsychotic drug alone	209	2,132.31	0.18 (0.49)	9.80 (8.54 to 11.20)	1.12 (0.97 to 1.28)	1.15 (0.99 to 1.35)
Combination	210	1,907.57	0.25 (0.58)	11.01 (9.59 to 12.58)	1.26 (1.09 to 1.44)	1.32 (1.13 to 1.54)
Olanzapine (n=1,314)						
Non-treatment	946	11,324.34	9.21 (3.50)	8.35 (7.83 to 8.90)	Reference	Reference
Pretreatment	30	97.09	0.07 (0.00)	30.90 (21.23 to 43.55)	3.70 (2.57 to 5.32)	3.72 (2.57 to 5.37)
Cholinesterase inhibitor alone	217	2,167.76	1.10 (2.08)	10.01 (8.74 to 11.41)	1.20 (1.03 to 1.39)	1.31 (1.09 to 1.56)
Antipsychotic drug alone	59	569.52	0.18 (0.53)	10.36 (7.96 to 13.27)	1.24 (0.95 to 1.61)	1.35 (1.00 to 1.82)
Combination	62	469.79	0.26 (0.67)	13.20 (10.21 to 16.81)	1.58 (1.22 to 2.04)	1.77 (1.31 to 2.39)
Quetiapine (n=12,851)						
Non-treatment	8,769	104,168.20	8.61 (3.96)	8.42 (8.24 to 8.60)	Reference	Reference
Pretreatment	481	1,013.41	0.07 (0.00)	47.46 (43.36 to 51.85)	5.64 (5.14 to 6.18)	5.40 (4.91 to 5.93)
Cholinesterase inhibitor alone	1,635	16,682.60	0.98 (1.94)	9.80 (9.33 to 10.28)	1.16 (1.10 to 1.23)	1.18 (1.11 to 1.26)
Antipsychotic drug alone	1,002	10,353.62	0.34 (1.19)	9.68 (9.09 to 10.29)	1.15 (1.08 to 1.23)	1.16 (1.07 to 1.26)
Combination	964	9,884.87	0.54 (1.27)	9.75 (9.15 to 10.38)	1.16 (1.08 to 1.24)	1.16 (1.07 to 1.26)

Supplementary Table 3-12: Sensitivity analysis (Further defined two study periods of 14 days: one after treatment initiation, and the other following treatment discontinuation, n=15,278)

	Events, n	Follow-up time, person-years, sum	Follow-up time, years, median (interquartile range)	Incidence rate (95% confidence interval), /100 person-years	Crude incidence rate ratio (95% confidence interval)	Adjusted incidence rate ratio (95% confidence interval)
Non-treatment	10,066	121,519.29	8.45 (4.05)	8.28 (8.12 to 8.45)	Reference	Reference
Pretreatment (day -14 days of treatment)	657	1,254.90	0.07 (0.03)	52.35 (48.46 to 56.47)	6.32 (5.84 to 6.84)	6.12 (5.64 to 6.64)
Treatment (day 1 to day 14 of treatment)	325	1,136.03	0.08 (0)	28.61 (25.62 to 31.85)	3.45 (3.09 to 3.86)	3.31 (2.96 to 3.70)
Cholinesterase inhibitor (day 14+ of treatment)	1,746	18,613.18	0.95 (1.92)	9.38 (8.95 to 9.83)	1.13 (1.08 to 1.19)	1.16 (1.09 to 1.24)
Antipsychotic drug (day 14+ of treatment)	1,164	12,666.02	0.35 (1.27)	9.19 (8.67 to 9.73)	1.11 (1.04 to 1.18)	1.13 (1.05 to 1.22)
Combination (day 14+ of treatment)	1,178	11,652.41	0.58 (1.34)	10.11 (9.55 to 10.70)	1.22 (1.15 to 1.30)	1.26 (1.17 to 1.36)
Day 1 to day 14 after drug discontinuation	142	1,362.32	0.07 (0.10)	10.42 (8.81 to 12.25)	1.26 (1.07 to 1.49)	1.24 (1.05 to 1.47)



Abbreviation: ChEI, cholinesterase inhibitor; AP, antipsychotic drug

Supplementary Figure 1. Study scheme and definitions of treatment periods for sensitivity analysis

We defined a 3-year washout period before the starting date to exclude patients with a prior history of falls and fractures. We defined a 1-year baseline period to assess patients' baseline covariates. 1) 14-day pretreatment period prior to the treatment to drugs, 2) treatment to ChEIs alone, 3) treatment to antipsychotic drugs alone, 4) treatment to a combination of ChEIs and antipsychotic drugs, and 5) non-treatment when neither ChEIs nor antipsychotic drugs were given. If a refill was noted within 14 days after the end date of the last prescription (i.e., 14-day grace period), it was considered as a continuation of a previous prescription. We further classified the periods 6) within 1-14 days after treatment, and 7) within 1-14 days after discontinuation of treatment. The remaining time periods without prescription of ChEIs or antipsychotic drugs were defined as non-treatment.