

Supplementary appendix

Table S1: Study Covariates by Study Medications (n = number of study medication episodes)

	Nortriptyline (n=114 326)	Amitriptyline (n=14 672)	Venlafaxine (n=39 824)	Duloxetine (n=16 217)	Fluoxetine (n=176 743)	Paroxetine (n=65 081)	Sertraline (n=74 438)	Citalopram (n=95 226)	Escitalopram (n=13 338)	Gabapentin (n=77 653)	Total (N= 687 518)	p-value
Participant age at index date (years) - mean (SD)	71.8 (6.61)	71.2 (6.29)	69.2 (5.99)	70.0 (6.46)	71.0 (6.96)	71.5 (7.19)	71.3 (7.33)	72.5 (7.62)	70.2 (6.74)	72.8 (7.10)	71.5 (6.98)	<0.0001
Age range (years)	65.0-106.0	65.0-103.0	65.0-102.0	65.0-100.0	65.0-105.0	65.0-102.0	65.0-106.0	65.0-103.0	65.0-106.0	65.0-102.0	65.0-106.0	
Gender (female)	70 030 (61.3%)	10 532 (71.8%)	28 895 (72.6%)	11 081 (68.3%)	12 3274 (69.7%)	47 020 (72.2%)	50 216 (67.5%)	65 929 (69.2%)	8 883 (66.6%)	43 944 (56.6%)	45 9804 (66.9%)	<0.0001
Race / ethnicity												<0.0001
White	63 870 (55.9%)	9 576 (65.3%)	27 922 (70.1%)	10 517 (64.9%)	12 3888 (70.1%)	43 259 (66.5%)	49 531 (66.5%)	64 277 (67.5%)	9 136 (68.5%)	47 140 (60.7%)	449 116 (65.3%)	
Hispanic	28 269 (24.7%)	2 982 (20.3%)	7 398 (18.6%)	3 423 (21.1%)	35 495 (20.1%)	14 730 (22.6%)	16 336 (21.9%)	19 966 (21%)	2 596 (19.5%)	15 722 (20.2%)	14 6917 (21.4%)	
Black	13 718 (12%)	1 351 (9.2%)	2 853 (7.2%)	1 451 (8.9%)	8 898 (5.0%)	3 596 (5.5%)	4 453 (6.0%)	5 571 (5.9%)	798 (6.0%)	9 182 (11.8%)	51 871 (7.5%)	
Asian / Pacific Islander	7 211 (6.3%)	564 (3.8%)	1 225 (3.1%)	628 (3.9%)	5 695 (3.2%)	2 496 (3.8%)	3 165 (4.3%)	4 123 (4.3%)	640 (4.8%)	4707 (6.1%)	30 454 (4.4%)	
Other	1 258 (1.1%)	199 (1.4%)	426 (1.1%)	198 (1.2%)	2767 (1.6%)	1000 (1.5%)	953 (1.3%)	1289 (1.4%)	168 (1.3%)	902 (1.2%)	9160 (1.3%)	
Charlson co-morbidity score												<0.0001
Score 0	28 515 (24.9%)	4 940 (33.7%)	15 106 (37.9%)	4 784 (29.5%)	71 740 (40.6%)	27 736 (42.6%)	27 892 (37.5%)	36 057 (37.9%)	5 288 (39.6%)	16 772 (21.6%)	238830 (34.7%)	
Score 1-2	42 175 (36.9%)	5 042 (34.4%)	14 961 (37.6%)	6 178 (38.1%)	62 222 (35.2%)	22 666 (34.8%)	27 032 (36.3%)	34 122 (35.8%)	4 904 (36.8%)	27 801 (35.8%)	24 7103 (35.9%)	

Score ≥ 3	43 636 (38.2%)	4 690 (32%)	9 757 (24.5%)	5 255 (32.4%)	42 781 (24.2%)	14 679 (22.6%)	19 514 (26.2%)	25 047 (26.3%)	3 146 (23.6%)	33 080 (42.6%)	201 585 (29.3%)	
Sedating meds												<0.0001
None	90 422 (79.1%)	11 803 (80.4%)	31 966 (80.3%)	11 834 (73%)	15 2791 (86.4%)	56 902 (87.4%)	64 600 (86.8%)	81 517 (85.6%)	11 779 (88.3%)	57 424 (73.9%)	57 1038 (83.1%)	
1	20 011 (17.5%)	2 370 (16.2%)	6 303 (15.8%)	3 393 (20.9%)	20 393 (11.5%)	6 984 (10.7%)	8 384 (11.3%)	11 501 (12.1%)	1 371 (10.3%)	16 592 (21.4%)	97 302 (14.2%)	
2	3 385 (3.0%)	439 (3.0%)	1 323 (3.3%)	816 (5.0%)	3 185 (1.8%)	1 042 (1.6%)	1 226 (1.6%)	1 903 (2.0%)	159 (1.2%)	3 070 (4.0%)	16 548 (2.4%)	
≥ 3	508 (0.4%)	60 (0.4%)	232 (0.6%)	174 (1.1%)	374 (0.2%)	153 (0.2%)	228 (0.3%)	305 (0.3%)	29 (0.2%)	567 (0.7%)	2 630 (0.4%)	
ACB score												<0.0001
0	50 785 (44.4%)	5 843 (39.8%)	17 886 (44.9%)	6 845 (42.2%)	81 723 (46.2%)	30 292 (46.5%)	35 069 (47.1%)	43 831 (46%)	6 731 (50.5%)	33 454 (43.1%)	312 459 (45.4%)	
1-2	50 996 (44.6%)	6 687 (45.6%)	16 688 (41.9%)	6 925 (42.7%)	74 742 (42.3%)	27 096 (41.6%)	30 016 (40.3%)	39 293 (41.3%)	4 866 (36.5%)	33 486 (43.1%)	290 795 (42.3%)	
≥ 3	12 545 (11%)	2 142 (14.6%)	5 250 (13.2%)	2 447 (15.1%)	20 278 (11.5%)	7 693 (11.8%)	9 353 (12.6%)	12 102 (12.7%)	1 741 (13.1%)	10 713 (13.8%)	84 264 (12.3%)	
Diagnoses at baseline												
Angina	9 783 (8.6%)	1 197 (8.2%)	2 316 (5.8%)	1 113 (6.9%)	15 667 (8.9%)	5 053 (7.8%)	5 453 (7.3%)	7 445 (7.8%)	692 (5.2%)	7 573 (9.8%)	56 292 (8.2%)	<0.0001
Acute myocardial infarction	11 337 (9.9%)	1 167 (8%)	3 112 (7.8%)	1 596 (9.8%)	17 082 (9.7%)	5 689 (8.7%)	7 402 (9.9%)	9 085 (9.5%)	1 222 (9.2%)	11 201 (14.4%)	68 893 (10.0%)	<0.0001
Congestive heart failure	9 597 (8.4%)	1 335 (9.1%)	2 464 (6.2%)	1 152 (7.1%)	16 081 (9.1%)	5 874 (9%)	6 200 (8.3%)	9 043 (9.5%)	840 (6.3%)	9 099 (11.7%)	61 685 (9.0%)	<0.0001
Cardiomyopathy	5 652 (4.9%)	585 (4.0%)	1502 (3.8%)	837 (5.2%)	8 200 (4.6%)	2 876 (4.4%)	3 747 (5.0%)	4 242 (4.5%)	671 (5.0%)	5 780 (7.4%)	34 092 (5.0%)	<0.0001
Valvular disease	6 785 (5.9%)	938 (6.4%)	2 211 (5.6%)	1 055 (6.5%)	12 560 (7.1%)	4 455 (6.8%)	5 254 (7.1%)	7 447 (7.8%)	845 (6.3%)	6 557 (8.4%)	48 107 (7.0%)	<0.0001

Hypotension	3 232 (2.8%)	338 (2.3%)	1 292 (3.2%)	586 (3.6%)	5 845 (3.3%)	2 130 (3.3%)	2 565 (3.4%)	4 087 (4.3%)	361 (2.7%)	3 166 (4.1%)	23 602 (3.4%)	<0.0001
Dehydration/volume depletion	5 828 (5.1%)	732 (5.0%)	2 832 (7.1%)	1 087 (6.7%)	11 411 (6.5%)	4 084 (6.3%)	4 905 (6.6%)	6 771 (7.1%)	795 (6.0%)	5 694 (7.3%)	44 139 (6.4%)	<0.0001
Antihypertensive Overdose	400 (0.3%)	17 (0.1%)	168 (0.4%)	61 (0.4%)	638 (0.4%)	277 (0.4%)	321 (0.4%)	472 (0.5%)	66 (0.5%)	427 (0.5%)	2847 (0.4%)	<0.0001
Adrenal insufficiency	26 (0%)	0 (0%)	23 (0.1%)	25 (0.2%)	51 (0%)	6 (0%)	47 (0.1%)	21 (0%)	6 (0%)	53 (0.1%)	258 (0%)	<0.0001
Hypoglycemia	2103 (1.8%)	187 (1.3%)	589 (1.5%)	352 (2.2%)	2201 (1.2%)	861 (1.3%)	1060 (1.4%)	1357 (1.4%)	233 (1.7%)	1622 (2.1%)	10565 (1.5%)	<0.0001
Respiratory failure	1612 (1.4%)	181 (1.2%)	821 (2.1%)	351 (2.2%)	3397 (1.9%)	1392 (2.1%)	1539 (2.1%)	2078 (2.2%)	273 (2%)	1853 (2.4%)	13497 (2%)	<0.0001
Alcohol abuse	2949 (2.6%)	302 (2.1%)	2347 (5.9%)	812 (5%)	8404 (4.8%)	2761 (4.2%)	3886 (5.2%)	4583 (4.8%)	682 (5.1%)	2924 (3.8%)	29650 (4.3%)	<0.0001
Visual impairment	20 183 (17.7%)	2 336 (15.9%)	4 156 (10.4%)	1 787 (11%)	21 829 (12.4%)	7 723 (11.9%)	8 418 (11.3%)	11 653 (12.2%)	1 279 (9.6%)	12 583 (16.2%)	91 947 (13.4%)	<0.0001
Gait disorder	8 347 (7.3%)	543 (3.7%)	4 189 (10.5%)	1 970 (12.1%)	13 541 (7.7%)	5 055 (7.8%)	8 172 (11.0%)	10 321 (10.8%)	1 219 (9.1%)	8 735 (11.2%)	62 092 (9.0%)	<0.0001
Arthritis	26 958 (23.6%)	2 919 (19.9%)	10 740 (27.0%)	5 083 (31.3%)	38 557 (21.8%)	14 061 (21.6%)	16 570 (22.3%)	19 849 (20.8%)	2 910 (21.8%)	21 538 (27.7%)	159 185 (23.2%)	<0.0001
Dementia	30 145 (26.4%)	2 454 (16.7%)	13 837 (34.7%)	6 879 (42.4%)	47 532 (26.9%)	18 116 (27.8%)	26 608 (35.7%)	30 777 (32.3%)	5 238 (39.3%)	27 217 (35.0%)	208 803 (30.4%)	<0.0001
Peripheral neuropathy	64 454 (56.4%)	5 987 (40.8%)	10 062 (25.3%)	6 010 (37.1%)	29 653 (16.8%)	9 976 (15.3%)	11 978 (16.1%)	15 675 (16.5%)	1 836 (13.8%)	46 212 (59.5%)	201 843 (29.4%)	<0.0001
Low bone density	55 481 (48.5%)	6 583 (44.9%)	17 859 (44.8%)	7 440 (45.9%)	77 902 (44.1%)	29 713 (45.7%)	33 511 (45.0%)	44 541 (46.8%)	5 464 (41.0%)	38 036 (49.0%)	316 530 (46.0%)	<0.0001
Hyperthyroidism	1 408 (1.2%)	157 (1.1%)	378 (0.9%)	253 (1.6%)	2 299 (1.3%)	866 (1.3%)	928 (1.2%)	1 242 (1.3%)	216 (1.6%)	1 044 (1.3%)	8 791 (1.3%)	<0.0001
Malnutrition	3 796 (3.3%)	395 (2.7%)	1 480 (3.7%)	715 (4.4%)	6 971 (3.9%)	2 706 (4.2%)	3 490 (4.7%)	5 785 (6.1%)	511 (3.8%)	3 766 (4.8%)	29 615 (4.3%)	<0.0001
Parkinson's disease	259 (0.2%)	17 (0.1%)	242 (0.6%)	162 (1.0%)	478 (0.3%)	279 (0.4%)	604 (0.8%)	436 (0.5%)	166 (1.2%)	517 (0.7%)	3 160 (0.5%)	<0.0001
Cerebral palsy	27 (0%)	0 (0%)	7 (0%)	3 (0%)	43 (0%)	28 (0%)	38 (0.1%)	29 (0%)	5 (0%)	24 (0%)	204 (0%)	0.0031
Hypothyroidism	19 111 (16.7%)	2 679 (18.3%)	8 284 (20.8%)	3 409 (21%)	33 790 (19.1%)	12 472 (19.2%)	1 4571 (19.6%)	18 408 (19.3%)	2 646 (19.8%)	13 292 (17.1%)	128 662 (18.7%)	<0.0001

Cancer	38 267 (33.5%)	4 729 (32.2%)	15 933 (40.0%)	5 863 (36.2%)	64 800 (36.7%)	23 984 (36.9%)	2 6139 (35.1%)	34 158 (35.9%)	5 004 (37.5%)	28 853 (37.2%)	247 730 (36.0%)	<0.0001
Diabetes	53 566 (46.9%)	5 549 (37.8%)	11 915 (29.9%)	5 791 (35.7%)	49 626 (28.1%)	18 155 (27.9%)	20 243 (27.2%)	25 202 (26.5%)	3 287 (24.6%)	33 553 (43.2%)	226 887 (33.0%)	<0.0001
Epilepsy	913 (0.8%)	88 (0.6%)	462 (1.2%)	198 (1.2%)	1 970 (1.1%)	864 (1.3%)	1 094 (1.5%)	1 541 (1.6%)	201 (1.5%)	1 079 (1.4%)	8 410 (1.2%)	<0.0001
Stroke / Transient ischemic attack	8 045 (7%)	842 (5.7%)	2 973 (7.5%)	1 313 (8.1%)	14 055 (8%)	5 179 (8%)	6 196 (8.3%)	9 063 (9.5%)	1 039 (7.8%)	6 743 (8.7%)	55 448 (8.1%)	<0.0001
Unintentional weight loss	3 153 (2.8%)	492 (3.4%)	1 883 (4.7%)	718 (4.4%)	7 301 (4.1%)	3 047 (4.7%)	4 123 (5.5%)	5 281 (5.5%)	665 (5.0%)	3 096 (4.0%)	29 759 (4.3%)	<0.0001
Fall	5 623 (4.9%)	801 (5.5%)	2 787 (7%)	1 080 (6.7%)	10 444 (5.9%)	3 932 (6%)	4 817 (6.5%)	7 321 (7.7%)	898 (6.7%)	4 528 (5.8%)	42 231 (6.1%)	<0.0001

Medication episode: defined as index date until end of days-supply of dispensed prescriptions, allowing up to 100-day gaps.

Multiple medication episodes per participant allowed if no overlap between prescriptions.

Results in this table were derived based on the analysis of syncope.

Table S2: Study medication episodes* and average duration of treatment

Study medication	Number (%) study medication episodes	Mean patient-days (SD) of study medication episodes
Fluoxetine	176 743 (25.7%)	132.6 (144.90)
Nortriptyline	114 326 (16.6%)	93.3 (124.58)
Citalopram	95 226 (13.9%)	121.7 (140.29)
Gabapentin	77 653 (11.3%)	85.4 (110.64)
Sertraline	74 438 (10.8%)	121.9 (138.59)
Paroxetine	65 081 (9.5%)	140.3 (154.60)
Venlafaxine	39 824 (5.8%)	108.7 (131.46)
Duloxetine	16 217 (2.4%)	91.7 (107.57)
Amitriptyline	14 672 (2.1%)	130.1 (165.08)
Escitalopram	13 338 (1.9%)	108.2 (122.99)
TOTAL	687 518 (100%)	113.4 days (range 85.4-140.3 days)

SD: Standard Deviation

*Medication episode: Defined as index date until end of days-supply of dispensed prescriptions, allowing up to 100 days between dispenses.

Multiple medication episodes per participant allowed if no overlap between prescriptions.

Table S3: Outcome hazard ratios by age, sedating medication use, anticholinergic medication use and Charlson comorbidity score in 195,207 participants

Demographics	Syncope		Falls		Fractures	
	n= 687 518 study medication exposures		n= 611 258 study medication exposures		n= 652 861 study medication exposures	
Age bands	uHR (CI _{95%})	aHR (CI _{95%})	uHR (CI _{95%})	aHR (CI _{95%})	uHR (CI _{95%})	aHR (CI _{95%})
65-74 yrs	1.00	1.00	1.00	1.00	1.00	1.00
75-84	2.091 (2.017, 2.169)	1.645 (1.583, 1.709)	2.313 (2.248, 2.379)	1.975 (1.917, 2.035)	1.578 (1.527, 1.631)	1.324 (1.28, 1.371)
≥85	3.102 (2.952, 3.26)	2.103 (1.993, 2.219)	4.312 (4.158, 4.472)	3.219 (3.094, 3.349)	2.641 (2.527, 2.76)	1.828 (1.743, 1.918)
Sedating meds	uHR (CI _{95%})	aHR (CI _{95%})	uHR (CI _{95%})	aHR (CI _{95%})	uHR (CI _{95%})	aHR (CI _{95%})
0	1.00	1.00	1.00	1.00	1.00	1.00
1	1.278 (1.22, 1.338)	1.168 (1.114, 1.224)	2.688 (2.61, 2.768)	2.555 (2.479, 2.633)	3.431 (3.324, 3.542)	3.287 (3.18, 3.396)
2	1.396 (1.259, 1.547)	1.188 (1.071, 1.319)	2.736 (2.567, 2.917)	2.593 (2.43, 2.767)	3.679 (3.444, 3.93)	3.493 (3.265, 3.736)
≥3	1.58 (1.226, 2.035)	1.264 (0.980, 1.630)	3.647 (3.149, 4.224)	3.44 (2.967, 3.987)	4.702 (4.045, 5.466)	4.407 (3.786, 5.129)
Anticholinergic Cognitive Burden score	uHR (CI _{95%})	aHR (CI _{95%})	uHR (CI _{95%})	aHR (CI _{95%})	uHR (CI _{95%})	aHR (CI _{95%})
0	1.00	1.00	1.00	1.00	1.00	1.00
1-2	1.391 (1.341, 1.442)	1.140 (1.1, 1.186)	1.432 (1.392, 1.473)	1.137 (1.104, 1.171)	1.239 (1.201, 1.279)	1.001 (0.968, 1.034)
≥3	1.904 (1.816, 1.997)	1.309 (1.245, 1.377)	2.169 (2.092, 2.248)	1.371 (1.32, 1.425)	1.721 (1.651, 1.795)	1.084 (1.037, 1.134)
Charlson comorbidity score	uHR (CI _{95%})	aHR (CI _{95%})	uHR (CI _{95%})	aHR (CI _{95%})	uHR (CI _{95%})	aHR (CI _{95%})
0	1.00	1.00	1.00	1.00	1.00	1.00
1-2	1.367 (1.308, 1.429)	1.153 (1.1, 1.207)	1.326 (1.283, 1.370)	1.096 (1.059, 1.135)	1.249 (1.205, 1.296)	1.092 (1.052, 1.135)
≥3	2.266 (2.173, 2.364)	1.322 (1.251, 1.397)	1.941 (1.880, 2.004)	1.152 (1.104, 1.201)	1.593 (1.536, 1.652)	1.08 (1.030, 1.133)

Table S4: Sensitivity analysis: adjusted hazard ratios for sub-group of patients with single medication episode

		Syncope	Falls	Fracture
		HR (95% CI)	HR (95% CI)	HR (95% CI)
Study medication	Nortriptyline (ref.)	1.000	1.000	1.000
	Amitriptyline	1.115 (0.927, 1.342)	1.287 (1.118, 1.482)	0.868 (0.723, 1.042)
	Citalopram	1.296 (1.194, 1.406)	1.677 (1.571, 1.791)	1.379 (1.28, 1.486)
	Duloxetine	1.018 (0.842, 1.23)	1.259 (1.092, 1.452)	1.48 (1.288, 1.7)
	Escitalopram	0.936 (0.769, 1.14)	1.422 (1.233, 1.641)	1.96 (1.709, 2.247)
	Fluoxetine	1.195 (1.109, 1.288)	1.565 (1.473, 1.663)	1.37 (1.280, 1.466)
	Gabapentin	0.951 (0.868, 1.043)	0.98 (0.908, 1.058)	1.348 (1.246, 1.459)
	Paroxetine	1.212 (1.105, 1.328)	1.532 (1.425, 1.647)	1.304 (1.201, 1.416)
	Sertraline	1.284 (1.176, 1.400)	1.584 (1.476, 1.699)	1.437 (1.328, 1.554)
	Venlafaxine	1.139 (1.007, 1.289)	1.506 (1.371, 1.654)	1.513 (1.37, 1.672)
	None	1.125 (1.043, 1.213)	1.223 (1.149, 1.301)	1.23 (1.147, 1.319)
Charlson comorbidity score	None (ref.)			
	1-2	1.187 (1.125, 1.252)	1.091 (1.049, 1.136)	1.1 (1.053, 1.148)
	≥3	1.368 (1.285, 1.457)	1.148 (1.094, 1.205)	1.081 (1.024, 1.141)
Sex	Female (ref.)			
	Male	1.337 (1.283, 1.393)	0.778 (0.752, 0.805)	0.725 (0.696, 0.754)
Race/ethnicity	White (ref.)			
	Asian Pacific Island	0.863 (0.786, 0.948)	0.883 (0.819, 0.952)	0.782 (0.715, 0.854)

	Black	1.214 (1.134, 1.299)	0.792 (0.744, 0.843)	0.619 (0.572, 0.669)
	Hispanic	0.823 (0.781, 0.868)	1.073 (1.033, 1.114)	0.934 (0.894, 0.976)
	Other	1.007 (0.853, 1.188)	0.731 (0.631, 0.846)	0.893 (0.768, 1.039)
Index age (years)	65-74 (ref.)			
	75-84	1.658 (1.587, 1.732)	2.02 (1.953, 2.09)	1.329 (1.278, 1.382)
	≥85	2.198 (2.072, 2.333)	3.311 (3.169, 3.460)	1.849 (1.754, 1.95)
ACB score	0 (ref.)			
	1-2	1.148 (1.100, 1.198)	1.139 (1.102, 1.178)	1.006 (0.969, 1.044)
	≥3	1.295 (1.222, 1.372)	1.373 (1.314, 1.434)	1.097 (1.043, 1.154)
Sedating meds	0 (ref.)			
	1	1.168 (1.106, 1.234)	2.624 (2.535, 2.717)	3.471 (3.344, 3.604)
	2	1.162 (1.024, 1.319)	2.637 (2.44, 2.85)	3.735 (3.452, 4.041)
	≥3	1.285 (0.945, 1.749)	3.337 (2.779, 4.007)	4.827 (4.032, 5.780)

All analyses controlled for medical diagnoses.

Medication episode: defined as index date until end of days-supply of dispensed prescriptions, allowing up to 100 days between dispenses.