Appendix 4 (as supplied by the authors)

Table 1. Baseline Characteristics of a Cohort of Older Adults Prescribed Trazodone or Atypical Antipsychotics using High Dimensional Propensity Score Model for Inverse Probability of Treatment Weighting

Characteristic		Trazodone N=6,588	Atypical Antipsychotics N=2,875	Crude Standardized Difference	Trazodone N=6,587	Atypical Antipsychotics N=2,875	Weighted Standardized Difference
Demographics							
Age at cohort entry, mean (SD)		85.5 (7.2)	85.0 (7.1)	0.07	85.3 (7.2)	85.3 (7.2)	<0.01
Age, n (%)	66-74	556 (8.4%)	236 (8.2%)	0.01	8.6%	8.6%	<0.01
	75-84	2,128 (32.3%)	1,004 (34.9%)	0.06	33.4%	33.2%	<0.01
	85+	3,904 (59.3%)	1,635 (56.9%)	0.05	58.1%	58.2%	<0.01
Female, n (%)		4,594 (69.7%)	1,908 (66.4%)	0.07	68.6%	67.8%	0.02
Weight at cohort entry, mean (SD)		65.9 (29.1)	65.2 (30.0)	0.02	65.6 (28.8)	65.1 (26.0)	0.02
Income quintile	missing	66 (1.0%)	36 (1.3%)	0.02	0.9%	1.5%	0.05
	1	1,549 (23.5%)	663 (23.1%)	0.01	23.3%	22.9%	<0.01
	2	1,274 (19.3%)	532 (18.5%)	0.02	19.3%	18.7%	0.02
	3	1,335 (20.3%)	600 (20.9%)	0.01	20.5%	21.3%	0.02
	4	1,254 (19.0%)	508 (17.7%)	0.04	18.8%	18.0%	0.02
	5	1,110 (16.8%)	536 (18.6%)	0.05	17.3%	17.8%	0.01
Dependency in >= 1 ADLs		6,556 (99.5%)	2,859 (99.4%)	0.01	99.6%	99.5%	<0.01
Dependency in ADLs, mean (SD)		5.2 (1.3)	5.4 (1.2)	0.12	5.3 (1.3)	5.3 (1.2)	0.04
Healthcare Utilization							
Prescriptions, mean (SD)		19.4 (10.0)	17.6 (9.7)	0.18	18.9 (9.9)	19.2 (10.3)	0.03
ER visits, mean (SD)		1.5 (2.8)	1.4 (2.0)	0.05	1.5 (2.7)	1.6 (2.1)	0.03
Psychiatrist visits, mean (SD)		0.3 (2.4)	0.4 (2.4)	0.03	0.4 (2.6)	0.4 (2.1)	<0.01

Geriatrician visits, mean (SD)	0.6 (3.5)	0.6 (2.9)	0	0.6 (3.4)	0.9 (5.4)	0.08
Inpatient hospitalizations, mean (SD)	0.7 (1.0)	0.6 (1.0)	0.09	0.6 (1.0)	0.6 (1.0)	0.02
Johns Hopkins ACG score, n (%) 0-5	1,601 (24.3%)	812 (28.2%)	0.09	25.0%	26.0%	0.02
6-10	2,173 (33.0%)	965 (33.6%)	0.01	40.9%	42.8%	0.06
11+	2,814 (42.7%)	1,098 (38.2%)	0.09	34.0%	31.3%	0.04
Medications						
Antiarrhythmics, n (%)	2,981 (45.2%)	1,060 (36.9%)	0.17	43.2%	41.3%	0.04
Anticoagulants, n (%)	1,498 (22.7%)	515 (17.9%)	0.12	21.2%	22.2%	0.02
Hypoglycemics, n (%)	1,416 (21.5%)	570 (19.8%)	0.04	20.8%	20.6%	<0.01
Antihypertensives, n (%)	4,606 (69.9%)	1,895 (65.9%)	0.09	68.5%	68.5%	<0.01
Antilipemics, n (%)	3,015 (45.8%)	1,252 (43.5%)	0.04	45.1%	45.0%	<0.01
Diuretics, n (%)	2,301 (34.9%)	798 (27.8%)	0.16	32.8%	32.6%	<0.01
Glucocorticoids, n (%)	607 (9.2%)	205 (7.1%)	0.08	8.5%	8.6%	<0.01
Hormone therapies, n (%)	150 (2.3%)	32 (1.1%)	0.09	2.2%	1.8%	0.03
Osteoporosis treatments, n (%)	1,551 (23.5%)	663 (23.1%)	0.01	23.5%	22.9%	0.01
Antiparkinsonian agents, n (%)	501 (7.6%)	220 (7.7%)	0	7.5%	8.4%	0.03
Antiplatelets, n (%)	1,089 (16.5%)	406 (14.1%)	0.07	15.8%	16.2%	<0.01
Pain treatments, n (%)	2,892 (43.9%)	1,106 (38.5%)	0.11	41.9%	42.6%	0.02
Psychoactive agents, n (%)	4,842 (73.5%)	2,273 (79.1%)	0.13	75.1%	76.4%	0.03
Medical History						
Alcoholism, n (%)	329 (5.0%)	128 (4.5%)	0.03	5.2%	5.4%	<0.01
Cardiac dysrhythmias, n (%)	1,838 (27.9%)	683 (23.8%)	0.09	26.7%	26.3%	<0.01

Cerebrovascular disease, n (%)	1,526 (23.2%)	607 (21.1%)	0.05	22.5%	22.6%	<0.01
Delusions or hallucinations, n (%)	251 (3.8%)	266 (9.3%)	0.22	5.8%	5.7%	<0.01
Depression, n (%)	2,072 (31.5%)	871 (30.3%)	0.03	31.9%	30.4%	0.03
Diabetes mellitus, n (%)	2,285 (34.7%)	947 (32.9%)	0.04	33.9%	34.4%	<0.01
Falls, n (%)	1,619 (24.6%)	679 (23.6%)	0.02	24.4%	25.7%	0.03
Major osteoporotic fracture, n (%)	975 (14.8%)	373 (13.0%)	0.05	14.3%	15.6%	0.04
Unsteady gait, n (%)	6,069 (92.1%)	2,527 (87.9%)	0.14	91.5%	89.5%	0.07
Hearing impairment, n (%)	2,967 (45.0%)	1,307 (45.5%)	0.01	45.3%	45.2%	<0.01
Ischemic heart disease, n (%)	1,774 (26.9%)	678 (23.6%)	0.08	25.8%	25.1%	0.02
Hypertension, n (%)	5,564 (84.5%)	2,296 (79.9%)	0.12	83.4%	81.2%	0.06
Chronic kidney disease, n (%)	54 (0.8%)	10 (0.3%)	0.06	0.8%	0.3%	0.06
Chronic liver disease, n (%)	64 (1.0%)	24 (0.8%)	0.01	1.0%	0.8%	0.01
Malignancy, n (%)	612 (9.3%)	247 (8.6%)	0.02	9.0%	8.4%	0.02
Osteoporosis, n (%)	3,044 (46.2%)	1,252 (43.5%)	0.05	45.9%	43.8%	0.04
Parkinsonism, n (%)	481 (7.3%)	212 (7.4%)	0	7.4%	7.9%	0.02
Peripheral vascular disease, n (%)	496 (7.5%)	148 (5.1%)	0.1	7.3%	6.0%	0.05
Rheumatoid arthritis, n (%)	219 (3.3%)	83 (2.9%)	0.03	3.1%	3.5%	0.02
Seizure disorder, n (%)	237 (3.6%)	107 (3.7%)	0.01	3.7%	3.3%	0.02
Visual impairment, n (%)	5,383 (81.7%)	2,259 (78.6%)	0.08	81.0%	80.1%	0.02
Wheelchair ambulation, n (%)	3,676 (55.8%)	1,364 (47.4%)	0.17	53.3%	54.9%	0.03

Performance Scales

Cognitive Performance Scale*

0	1,007 (15.3%)	144 (5.0%)	0.35	12.07%	12.5%	0.01
1	855 (13.0%)	199 (6.9%)	0.2	11.02%	10.5%	0.02
2	1,261 (19.1%)	522 (18.2%)	0.03	18.73%	18.9%	<0.01
3	2,241 (34.0%)	1,323 (46.0%)	0.25	37.88%	38.2%	<0.01
4	437 (6.6%)	284 (9.9%)	0.12	7.82%	7.9%	<0.01
5	519 (7.9%)	328 (11.4%)	0.12	8.92%	8.8%	<0.01
6	268 (4.1%)	75 (2.6%)	0.08	3.57%	3.3%	0.01

Aggressive Behaviour Scale*

missing	<=5 (0.0%)	0 (0.0%)	0.02	0%	0.0%	N/A
0	3,683 (55.9%)	1,014 (35.3%)	0.42	50.23%	46.1%	0.08
1	863 (13.1%)	402 (14.0%)	0.03	13.28%	14.6%	0.04
2	610 (9.3%)	364 (12.7%)	0.11	9.70%	11.8%	0.07
3	582 (8.8%)	351 (12.2%)	0.11	9.35%	10.1%	0.02
4	262 (4.0%)	208 (7.2%)	0.14	4.64%	5.5%	0.04
5	150 (2.3%)	155 (5.4%)	0.16	2.95%	3.7%	0.04
6	193 (2.9%)	127 (4.4%)	0.08	3.89%	3.1%	0.04
7	79 (1.2%)	80 (2.8%)	0.11	1.94%	1.8%	0.01
8	55 (0.8%)	64 (2.2%)	0.11	1.18%	1.3%	0.01
9	48 (0.7%)	48 (1.7%)	0.09	1.14%	0.9%	0.02
10	22 (0.3%)	29 (1.0%)	0.08	0.63%	0.6%	0.01
11	13 (0.2%)	11 (0.4%)	0.03	0.33%	0.2%	0.03
12	27 (0.4%)	22 (0.8%)	0.05	0.75%	0.4%	0.05

Depression Rating Scale*

missing	<=5 (0.0%)	0 (0.0%)	0.02	0%	0.0%	N/A
0	2,229 (33.8%)	621 (21.6%)	0.28	30.30%	27.4%	0.06
1	1,013 (15.4%)	413 (14.4%)	0.03	14.74%	15.0%	<0.01
2	1,068 (16.2%)	487 (16.9%)	0.02	16.16%	18.1%	0.05
3	683 (10.4%)	335 (11.7%)	0.04	10.59%	11.3%	0.02
4	561 (8.5%)	317 (11.0%)	0.08	9.45%	10.7%	0.04
5	382 (5.8%)	203 (7.1%)	0.05	6.54%	5.7%	0.04

6	247 (3.7%)	165 (5.7%)	0.09	4.33%	3.9%	0.02
7	154 (2.3%)	120 (4.2%)	0.1	2.85%	3.2%	0.02
8	111 (1.7%)	75 (2.6%)	0.06	2.06%	1.7%	0.03
9	52 (0.8%)	53 (1.8%)	0.09	0.99%	1.2%	0.02
10	41 (0.6%)	40 (1.4%)	0.08	0.86%	0.8%	<0.01
11	26 (0.4%)	24 (0.8%)	0.06	0.58%	0.7%	0.01
12	14 (0.2%)	10 (0.3%)	0.03	0.37%	0.1%	0.05
13	6 (0.1%)	<=5 (0.1%)	0.01	0.18%	0.1%	0.02
14	0 (0.0%)	8 (0.3%)	0.07	0%	0.1%	0.05

Abbreviations: number (n), standard deviation (SD), emergency room (ER), Adjusted Clinical Group (ACG), activities of daily living (ADL)

*Higher scores indicate poorer performance on the scale (e.g. a Cognitive Performance Scale score of 6 means a patient has very severe cognitive impairment, patients with a higher Aggressive Behavior Scale score are more aggressive, patients with a higher Depression Rating Scale score have more depressive symptoms).

Table 2a. Primary Analyses of Primary and Secondary Outcomes based on Inverse Probability of Treatment Weights Derived from a High Dimensional Propensity Score Model

Outcome	Crude			Weighted		
	Events/100 Person-Years: Trazodone	Events/100 Person-Years: Atypical Antipsychotic	HR (95% CI)	Events/100 Person-Years: Trazodone	Events/100 Person-Years: Atypical Antipsychotic	HR (95% CI)
Fall or major osteoporotic fracture	21	28	0.71 (0.60-0.85)	23	25	0.9 (0.76-1.09)
Fall	20	27	0.72 (0.60-0.86)	22	24	0.93 (0.77-1.12)
Major osteoporotic fracture	7	8	0.81 (0.59-1.12)	8	7	1.12 (0.79-1.58)

Outcome	Crude Events/100 Person-Years: Trazodone	Crude Events/100 Person-Years: Atypical Antipsychotic	HR (95% CI)	Weighted Events/100 Person-Years: Trazodone	Weighted Events/100 Person-Years: Atypical Antipsychotic	HR (95% CI)
Hip fracture	4	6	0.72 (0.48-1.08)	5	5	0.97 (0.64-1.48)
All-cause mortality	59	74	0.78 (0.70-0.86)	60	74	0.78 (0.71-0.87)

Table 2b. Secondary Analyses of Primary and Secondary Outcomes based on Inverse Probability of Treatment Weights Derived from a High Dimensional Propensity Score Model

	Crude			Weighted		
Outcome	Events/100 Person-Years: Trazodone	Events/100 Person-Years: Atypical Antipsychotic	HR (95% CI)	Events/100 Person-Years: Trazodone	Events/100 Person-Years: Atypical Antipsychotic	HR (95% CI)
Fall or major osteoporotic fracture	19	27	0.67 (0.56-0.81)	21	24	0.85 (0.71-1.03)
Fall	19	26	0.68 (0.57-0.82)	20	23	0.87 (0.72-1.05)
Major osteoporotic fracture	6	8	0.74 (0.53-1.03)	7	7	1.02 (0.71-1.44)
Hip fracture	4	6	0.66 (0.43-0.99)	4	5	0.89 (0.58-1.37)
All-cause mortality	83	103	0.78 (0.71-0.85)	88	100	0.86 (0.78-0.94)

Abbreviations: hazard ratio (HR), confidence interval (CI)