Supplementary Statistical Methods: Propensity Scores

We used propensity score (PS, the probability of receiving the actual treatment) methods[1] to account for baseline differences in characteristics between AA- and pimavanserin-treated patients. In this study, the PS for an individual was calculated using a logistic regression, modeling the probability of receiving pimavanserin versus AAs conditional on the baseline characteristics shown in Supplement Table 1.

In this study, we balanced the baseline characteristics using inverse probability of treatment weighting (IPTW).[2] With average-treatment-effect-on-the-treated (ATT) weighting, we weighted the AA treatment cohort to have baseline characteristics mirroring the pimavanserin cohort. Specifically, the pimavanserin-treated patients received a weight of 1 and AA users received a weight of PS/(1-PS). We evaluated the appropriateness of the PS model and weighting by inspection of the distributions of PSs and weights in the two groups.

TABLE S1. Baseline characteristics of patients in the sample (complete listing). Shading indicates a standardized mean difference > 0·10.

| Characteristic | Pimavanserin (N = 3,227) | Atypical Antipsychotics | | | |
| | | Before Weighting (N = 18,448) | | After Weighting (N = 3,251)[a] | |
	% of Eligible Patients	% of Eligible Patients	Std. Mean Diff. (vs Pimavanserin Cohort)	% of Eligible Patients	Std.Mean Diff. (vs Pimavanserin Cohort)
Eligible Population	**3,227**	**18,442**		**3,251**	
Age (Mean)	77·9	78·9	0·15	77·8	0·01
Male	55·4%	55·3%	0·00	55·7%	0·01
Reason for Entrance into Medicare					
Aged without ESRD	85·3%	86·4%	0·03	85·3%	0·00
Disabled without ESRD	14·7%	13·6%	0·03	14·7%	0·00
Race					
White	88·7%	89·1%	0·01	88·9%	0·01
Black	4·3%	3·8%	0·03	4·3%	0·00
Other	7.0%	7·1%	0·00	6·8%	0·01
Regions					
West	19·0%	18·5%	0·01	18·6%	0·01
Northeast	19·7%	20·9%	0·03	19·6%	0·00

Midwest	18·4%	22·0%	0·09	18·3%	0·00
Other	43·0%	38·5%	0·09	43·4%	0·01
Low Income Subsidy (LIS)[b]	24·6%	26·5%	0·04	24·5%	0·00
Area Deprivation Index (ADI)[c]					
Missing	2·6%	3·0%	0·02	2·6%	0·00
Low ADI	62·2%	61·0%	0·02	61·9%	0·01
High ADI	35·2%	36·0%	0·02	35·5%	0·01
Prescriber Specialty					
Neurology	71·5%	38·3%	0·71	71·9%	0·01
Psychiatry	3·0%	8·2%	0·23	2·9%	0·01
Primary Care	24·6%	51·0%	0·57	24·3%	0·01
Other	0·9%	2·5%	0·12	0·9%	0·00
Long Term Care Facilities on Index Date					
In Nursing Home	15·2%	13·4%	0·05	15·1%	0·00
Medical Comorbidities					
Neuropsychiatric Disorders					
Bipolar Disorder	1·7%	4·4%	0·16	1·7%	0·00
Depressive Disorder	42·1%	48·6%	0·13	41·6%	0·01
Anxiety	32·9%	40·4%	0·15	32·8%	0·00
Dementia	56·5%	60·2%	0·07	56·3%	0·00
Mild Cognitive Impairment	12·7%	12·2%	0·01	12·8%	0·00
Post Traumatic Stress Disorder (PTSD)	0·5%	0·8%	0·03	0·5%	0·00
Restless Leg Syndrome (RLS)	9·2%	8·8%	0·01	9·3%	0·00
Cardiovascular					
Atrial Fibrillation	16·0%	20·7%	0·12	15·9%	0·00
Hospitalized Myocardial Infarction	0·4%	1·1%	0·08	0·4%	0·00
Coronary Revascularization	9·2%	11·7%	0·08	9·2%	0·00
Congestive Heart Failure	14·3%	18·8%	0·12	14·4%	0·00
Other Ischemic Heart Disease	28·6%	34·2%	0·12	28·7%	0·00
Peripheral Vascular Disease	32·5%	34·9%	0·05	32·4%	0·00
Hospitalized Stroke	0·7%	1·5%	0·07	0·7%	0·00
Hypertension	76·1%	80·1%	0·1	76·0%	0·00
Transient Ischemic Attack	5·9%	7·8%	0·07	5·8%	0·00
Other Cerebrovascular Disease	19·5%	24·7%	0·12	19·3%	0·00
General Medical Conditions					
Alcohol Abuse	0·7%	1·9%	0·11	0·6%	0·01
Anemia	35·2%	37·9%	0·06	35·2%	0·00
Chronic Liver Disease	1·6%	2·1%	0·03	1·6%	0·00
Chronic Obstructive Pulmonary Disease (COPD)	12·0%	17·3%	0·15	12·0%	0·00

Diabetes	25·6%	31·8%	0·14	25·4%	0·01
Hypercholesterolemia	36·0%	38·1%	0·04	35·9%	0·00
Chronic Kidney Disease	17·0%	20·4%	0·09	16·8%	0·00
Kidney Failure-Acute	7·8%	10·5%	0·09	8·0%	0·01
Malignancy	16·0%	17·1%	0·03	16·0%	0·00
Obesity	11·4%	13·8%	0·07	11·5%	0·00
Rheumatic Disease	4·6%	5·0%	0·02	4·5%	0·00
Nicotine Dependency	21·9%	26·7%	0·11	22·0%	0·00
Hospitalized Pneumonia	3·4%	4·9%	0·08	3·4%	0·00
Frailty-Related Covariates					
Falls	35·5%	36·9%	0·03	35·4%	0·00
Fractures	10·6%	10·7%	0·00	10·4%	0·01
Home Health Care	40·3%	44·7%	0·09	40·2%	0·00
Syncope	15·8%	17·4%	0·04	15·9%	0·00
Walker Use	6·7%	7·4%	0·03	6·8%	0·01
Wheelchair Use	17·9%	17·5%	0·01	17·8%	0·00
Home Oxygen	3·9%	5·2%	0·07	3·8%	0·01
Indwelling urinary catheter	1·5%	2·1%	0·04	1·6%	0·00
Urinary Incontinence	17·7%	17·9%	0·01	17·7%	0·00
Urinary Tract Infection	41·2%	43·1%	0·04	41·1%	0·00
Health Care Utilization					
Number of Days In Nursing Home, Past 0-365 Days					
0 Day	74·7%	73·1%	0·04	74·8%	0·00
1 - 30 Days	5·4%	8·0%	0·11	5·3%	0·00
31 - 90 Days	5·6%	6·2%	0·02	5·6%	0·00
91 - 180 Days	2·1%	2·8%	0·04	2·2%	0·00
More than 180 Days	12·1%	10·0%	0·07	12·0%	0·00
Number of Days In Skilled Nursing Facility, Past 0-365 Days					
0 Day	84·9%	82·4%	0·07	84·9%	0·00
1 - 30 Days	6·1%	7·9%	0·07	6·2%	0·01
31 - 90 Days	7·0%	7·1%	0·01	6·9%	0·00
More than 90 Days	2·1%	2·6%	0·03	2·0%	0·00
Hospitalizations, Past 0-30 Days					
0 Visits	97·4%	92·4%	0·23	97·4%	0·00
1+ Visit	2·6%	7·6%	0·23	2·6%	0·00
Hospitalizations, Past 31-365 Days					
0 Visits	71·1%	65·8%	0·11	71·0%	0·00
1 Visit	18·3%	19·8%	0·04	18·4%	0·00
2 Visits	6·5%	8·6%	0·08	6·4%	0·00
3+ Visits	4·0%	5·8%	0·08	4·2%	0·01

ER Visits, Past 0-365 Days					
0 Visits	47·1%	42·7%	0·09	47·2%	0·00
1 Visit	27·2%	26·7%	0·01	27·2%	0·00
2 Visits	12·7%	13·8%	0·03	12·6%	0·00
3 Visits	6·0%	7·4%	0·05	6·1%	0·00
4+ Visits	6·9%	9·4%	0·09	6·9%	0·00
Doctor's Office Visits, Past 0-365 Days					
0-10 Visits	43·2%	44·4%	0·02	43·2%	0·00
11-20 Visits	40·7%	37·9%	0·06	40·7%	0·00
21-30 Visits	12·9%	12·7%	0·00	12·9%	0·00
>30 Visits	3·2%	5·0%	0·09	3·2%	0·00
Neurologist Visit, Past 0-90 Days					
0	49·7%	58·6%	0·18	49·2%	0·01
1	21·7%	17·9%	0·10	21·9%	0·00
2	12·2%	10·0%	0·07	12·1%	0·00
3+	16·4%	13·5%	0·08	16·8%	0·01
QT Drug Prescription Covering the Index Date	33·7%	38·1%	0·09	33·5%	0·01
L-dopa Usage					
Number of Days Covered by L-Dopa, Past 0-365 Days					
1-90	5·1%	11·4%	0·23	5·0%	0·00
91-180	5·7%	9·1%	0·13	5·7%	0·00
181-270	16·0%	16·7%	0·02	15·9%	0·00
271-365	73·3%	62·8%	0·23	73·5%	0·00
Total L-Dopa Dose (1000 mg)					
(0, 100]	21·1%	34·0%	0·29	20·7%	0·01
(100, 200]	33·6%	31·7%	0·04	33·7%	0·00
(200, 300]	22·3%	18·5%	0·10	22·6%	0·01
(300, 400]	11·9%	8·1%	0·13	11·9%	0·00
> 400	11·1%	7·6%	0·12	11·1%	0·00
Average L-Dopa Daily Dose[d] (mg)					
(0, 200]	2·4%	4·7%	0·12	2·4%	0·00
(200, 400]	23·6%	32·9%	0·21	23·0%	0·01
(400, 600]	22·4%	21·6%	0·02	22·6%	0·01
(600, 800]	18·9%	16·5%	0·06	19·0%	0·00
> 800	32·7%	24·2%	0·19	33·0%	0·01
Opioids Drug Utilization					
Number of Days Covered by Opioid Drugs, Past 0-365 Days					
0 Day	65·9%	62·1%	0·08	66·5%	0·01
1 - 30 Days	19·1%	19·7%	0·02	18·9%	0·00

31 - 180 Days	9·4%	10·3%	0·03	9·1%	0·01
More than 180 Days	5·6%	7·9%	0·09	5·5%	0·00
Medications					
Parkinson's Disease Medication					
Dopamine Agonist	35·0%	25·5%	0·21	35·4%	0·01
MAO B inhibitors	20·7%	11·8%	0·24	21·4%	0·02
Amantadine	12·9%	9·6%	0·10	13·2%	0·01
Anticholinergics	2·2%	2·1%	0·01	2·2%	0·00
General					
Estrogen replacement	0·7%	0·9%	0·02	0·7%	0·00
H2-antagonists	8·3%	10·3%	0·07	8·2%	0·00
NSAIDs	18·0%	17·9%	0·00	17·8%	0·01
Proton pump inhibitors	28·9%	34·2%	0·11	28·8%	0·00
Thyroid replacement	20·5%	21·9%	0·03	20·3%	0·00
Diabetes medications					
Insulin	4·4%	6·9%	0·11	4·3%	0·01
Metformin	8·9%	11·0%	0·07	8·9%	0·00
Sulfonylureas	4·2%	5·3%	0·05	4·2%	0·00
Other DM Drug	3·4%	5·1%	0·08	3·4%	0·00
Cardiovascular					
ACEI/ARBs	33·6%	38·1%	0·09	33·5%	0·00
Antiarrhythmics	2·1%	3·9%	0·10	2·1%	0·00
Anticoagulants (oral)	11·6%	13·7%	0·06	11·4%	0·00
Anticoagulants (injectable)	1·1%	1·3%	0·03	1·0%	0·00
Antiplatelets	8·6%	11·4%	0·09	8·5%	0·00
Beta blockers	31·5%	37·8%	0·13	31·3%	0·00
Calcium channel blockers	20·9%	24·0%	0·08	20·7%	0·00
Digoxin	2·0%	2·4%	0·03	1·9%	0·01
Diuretics (Loop)	18·3%	20·9%	0·07	18·2%	0·00
Diuretics (Potassium-sparing)	4·0%	5·0%	0·05	4·0%	0·00
Diuretics (Thiazides)	11·9%	13·8%	0·06	11·9%	0·00
Drugs for hypotension	13·4%	8·7%	0·15	13·6%	0·00
Nitrates	6·1%	8·1%	0·08	6·1%	0·00
Statins	45·3%	49·7%	0·09	45·1%	0·01
Fibrates	2·4%	2·5%	0·01	2·3%	0·00
Medications for Treatment of Neuropsychiatric Disorders					
Anti-dementia drugs	45·4%	42·2%	0·06	45·4%	0·00
Anti-anxiety drugs	22·6%	31·7%	0·21	22·5%	0·00
Clonazepam	14·0%	14·3%	0·01	13·9%	0·00
Hypnotics	4·8%	8·5%	0·15	4·7%	0·00
Mood stabilizers	1·6%	3·6%	0·12	1·5%	0·01

Anti-depressants	59·4%	67·0%	0·16	59·2%	0·00
Drugs for daytime sleepiness	1·2%	0·9%	0·03	1·3%	0·01
Charlson Comorbidity Index (CCI)					
0	12·9%	9·6%	0·11	13·2%	0·01
1	19·6%	16·9%	0·07	19·7%	0·00
2	19·8%	18·3%	0·04	19·7%	0·00
3	16·9%	15·5%	0·04	16·7%	0·01
4	10·8%	12·7%	0·06	10·7%	0·00
>=5	20·0%	27·2%	0·17	20·1%	0·00
Frailty Score (past 0 - 183 days) Mean	0·31	0·35	0·21	0·31	0·01
Antihistamine Usage	5·4%	7·3%	0·08	5·4%	0·00

[a]Denotes the weighted pseudo-population created by applying IPTW-ATT weights for the atypical antipsychotics cohort

[b]The LIS is a subsidy paid by the federal government to the prescription rug plan in which an eligible Medicare beneficiary enrolls. The income and resources of a beneficiary are considered in determining their eligibility for the subsidy.

[c]The ADI represents a geographic-area based measure of the socioeconomic deprivation experienced by a neighborhood. The scale is on a national rank from 0 to 100 and higher index values represent higher levels of deprivation. An ADI national rank of 50 was used as the cut point for low and high ADI categories.

[d]Average daily dose is calculated as total L-Dope dose/number of days covered with L-Dopa during lookback

TABLE S2. Number of prescriptions of 16 most common QT-prolonging drugs[a] during follow-up in the pimavanserin and atypical antipsychotics cohorts

QT Prolonging Drug	Prescriptions			
	Pimavanserin		Atypical Antipsychotics	
	#	%	#	%
Total Number of QT Drug Prescriptions during Follow-up	7,693		47,140	
Donepezil	3,334	43·3%	19,900	42·2%
Escitalopram	1,952	25·4%	9,322	19·8%
Citalopram	858	11·2%	6,212	13·2%
Ciprofloxacin	351	4·6%	2,537	5·4%
Ondansetron	253	3·3%	1,861	3·9%
Azithromycin	201	2·6%	1,221	2·6%
Levofloxacin	188	2·4%	1,518	3·2%
Quinidine	176	2·3%	686	1·5%
Amiodarone	106	1·4%	1,275	2·7%
Fluconazole	72	0·9%	673	1·4%
Sotalol	58	0·8%	456	1·0%
Hydroxychloroquine	51	0·7%	287	0·6%
Cilostazol	20	0·3%	297	0·6%
Flecainide	15	0·2%	197	0·4%
Haloperidol	15	0·2%	209	0·4%
Methadone	14	0·2%	199	0·4%

[a]Table only displays the 16 most commonly prescribed QT-prolonging drugs during follow-up in the study population. The other drugs not displayed in the table, but contributing to the 'Total Number of QT Drug Prescriptions during Follow-Up" are disopyramide, dronedarone, clarithromycin, erythromycin, dofetilide, moxifloxacin, thioridazine, pimozide, anagrelide, and chlorpromazine.

TABLE S3. Number of beneficiaries meeting study eligibility criteria at various steps in the cohort development process

Study Eligibility Criteria	Pimavanserin	Atypical Antipsychotics
Received pimavanserin or oral atypical antipsychotics prescription between April 29, 2016 and March 30, 2019	8,576	3,744,238
Had continuous Part A/B/D enrollment in 365 days before and the day after index date	5,308	2,188,672
Received Parkinson's Disease (PD) diagnosis and at least one Levodopa prescription in 365 days before index date	4,820	74,260
Age 65+ and did not receive pimavanserin or any typical or atypical antipsychotic in 365 days before index date	3,871	28,302
Not in hospital or hospice on index date and did not have a hospice stay in the 365 days before index	3,631	25,442
Not enrolled in Medicare with ESRD and did not have dialysis in 365 days before index date	3,576	22,817
No diagnoses of schizophrenia in 365 days before index	3,535	22,297
No skilled nursing facility (SNF) stay in the 30 days before index	3,232	18,470
Only in one cohort on index date and did not have prescriptions for different atypical antipsychotics on index date	3,227	18,445
Alive through the index date	**3,227**	**18,442**

FIGURE S1. Schoenfeld residuals[a] plot for overall Cox proportional hazards regression
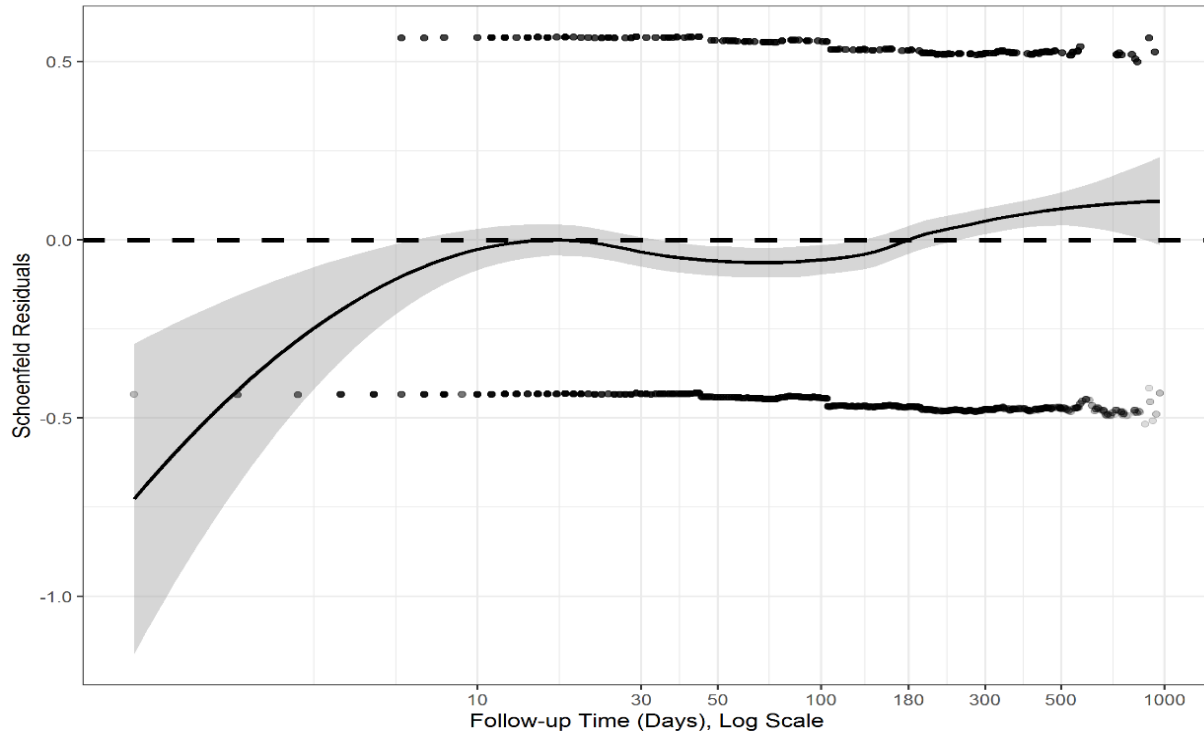
[a]*The Schoenfeld residuals examining the PH assumption of the treatment group are shown as the black dots -- the positive dots (>0) representing the residuals in pimavanserin group and the negative dots (<0) representing the residuals in the atypical antipsychotics group. The Schoenfeld residual[β] for a subject was calculated as the difference between the value of the treatment group (1 for a pimavanserin user and 0 for an atypical antipsychotics user) and the weighted average of the treatment group in a risk set, at each failure time. The solid black line is the fitted smoothing spline of the Schoenfeld residuals over time with its 95% confidence interval shown as the grey band. A plot where the fitted spline deviates remarkably from the dashed black line indicates that the proportional hazard assumption is violated.*

TABLE S4. Distribution of censoring reasons, by cohort

Censoring Reason	Pimavanserin		Atypical Antipsychotics	
	No. of Patients	% of Patients	No. of Patients	% of Patients
Total Eligible Population	3,227		18,442	
Death	207	6·4%	1,752	9·5%
Disenrollment	83	2·6%	395	2·1%
Receiving Typical Antipsychotics	13	0·4%	212	1·1%
Receiving Clozapine	16	0·5%	38	0·2%
Receiving Non-Oral Atypical Antipsychotics	2	0·1%	18	0·1%
End of Study Period	614	19·0%	3,399	18·4%
Switching Treatment*	447	13·9%	690	3·7%
Stopping Treatment**	1,845	57·2%	11,938	64·7%

*Defined as a patient with pimavanserin as their index prescription receiving an atypical antipsychotic or a patient with an atypical antipsychotic as their index prescription receiving pimavanserin

**Defined as a gap in days supply from the end of the previous prescription to the start of the subsequent prescription exceeding 14 days

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