

Mortality in Patients With Parkinson's Disease-related Psychosis Treated With Pimavanserin Compared With Other Atypical Antipsychotics: A Cohort Study

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eTable 1. ICD-9-CM and ICD-10-CM Codes to Identify Psychosis Diagnoses in Medicare Claims

Code type	Psychosis code	Description
ICD-9-CM	293.81	Psychotic disorder with delusions in conditions classified elsewhere
	293.82	Psychotic disorder with hallucinations in conditions classified elsewhere
	297.0	Paranoid state, simple
	297.1	Delusional disorder
	297.2	Paraphrenia
	297.3	Shared psychotic disorder
	297.8	Other specified paranoid states
	297.9	Unspecified paranoid state
	298.1	Excitative type psychosis
	298.2	Reactive confusion
	298.3	Acute paranoid reaction
	298.4	Psychogenic paranoid psychosis
	298.8	Other and unspecified reactive psychosis
	298.9	Unspecified psychosis
	368.16	Psychophysical visual disturbances
	780.1	Hallucinations
	290.12	Presenile dementia with delusional features
	290.20	Senile dementia with delusional features
	290.9	Unspecified senile psychotic condition
ICD-10-CM	F06.0	Psychotic disorder with hallucinations due to known physiological condition
	F06.2	Psychotic disorder with delusions due to known physiological condition
	F22	Delusional disorders
	F23	Brief psychotic disorder
	F24	Shared psychotic disorder
	F28	Other psychotic disorder not due to a substance or known physiological condition
	F29	Unspecified psychosis not due to a substance or known physiological condition
	F44.89	Other dissociative and conversion disorders
	H53.16	Psychophysical visual disturbances

Code type	Psychosis code	Description
	R44.0	Auditory hallucinations
	R44.1	Visual hallucinations
	R44.2	Other hallucinations
	R44.3	Hallucinations, unspecified
	R48.3	Visual agnosia

eTable 2. Covariates Included in Analysis

Category	Assessment period	Covariate	Form in propensity score model
Demographic characteristics	On index date	Age	Continuous: age, age ² , age ³
		Sex	Binary (female, male)
		Race/ethnicity	Categorical ▪ Black ▪ White ▪ Other/unknown
		Low-income status	Binary (yes, no)
		US geographic region	Categorical ▪ Northeast ▪ Midwest ▪ South ▪ West
		LTC/SNF residence	Binary (yes, no)
		Calendar year	Categorical (2016–2019)
Clinical characteristics	On index date	Index medication prescriber specialty	Categorical ▪ Neurology ▪ Psychiatry ▪ Other/unknown
Comorbidities and frailty indicators	365 days before index date ^a	Dementia	Binary (yes, no)
		Mild cognitive impairment	Binary (yes, no)
		Use of SNF	Binary (yes, no)
		Use of home health aide/nurse	Binary (yes, no)
		Chronic pulmonary disease	Binary (yes, no)
		Rheumatic disease	Binary (yes, no)
		Peptic ulcer disease	Binary (yes, no)
		Liver disease	Binary (yes, no)
		Renal disease	Binary (yes, no)
		Peripheral vascular disease	Binary (yes, no)
		Hemiplegia or paraplegia	Binary (yes, no)
		Home hospital bed	Binary (yes, no)
		Wheelchair use	Binary (yes, no)
		Home oxygen	Binary (yes, no)
		Use of ambulance/life support	Binary (yes, no)
		Paralysis	Binary (yes, no)
		Cancer screening	Binary (yes, no)

Category	Assessment period	Covariate	Form in propensity score model
		Lipid abnormality	Binary (yes, no)
		Vertigo	Binary (yes, no)
		Difficulty walking	Binary (yes, no)
		Podiatric care	Binary (yes, no)
		Rehabilitation services	Binary (yes, no)
		Arthritis	Binary (yes, no)
		Sepsis	Binary (yes, no)
		Weakness	Binary (yes, no)
		Hypertension or hypertensive heart disease	Binary (yes, no)
		Osteoporosis	Binary (yes, no)
		Mood disorders other than bipolar disorder	Binary (yes, no)
		Anxiety disorders	Binary (yes, no)
		Other psychiatric disorders (eating disorders, unspecified mental or psychiatric disorders)	Binary (yes, no)
		Huntington's disease	Binary (yes, no)
		Tourette's syndrome/other tics	Binary (yes, no)
		Falls and/or fractures	Binary (yes, no)
		Aspiration pneumonia	Binary (yes, no)
		Anemia	Binary (yes, no)
		Obesity ^b	Binary (yes, no)
		Alcohol abuse ^b	Binary (yes, no)
		Other substance abuse ^b	Binary (yes, no)
		Upper respiratory tract infection	Binary (yes, no)
		Lower respiratory tract infection	Binary (yes, no)
		Urinary tract infection	Binary (yes, no)
		Severe sepsis	Binary (yes, no)
		Serious hospitalized infection	Binary (yes, no)
		Myocardial infarction	Binary (yes, no)

Category	Assessment period	Covariate	Form in propensity score model
Comorbidities and frailty indicators	All available history ^a	Congestive heart failure	Binary (yes, no)
		Cerebrovascular disease	Binary (yes, no)
		Diabetes mellitus	Binary (yes, no)
		Malignancy	Binary (yes, no)
		HIV/AIDS	Binary (yes, no)
		Chronic cardiovascular disease	Binary (yes, no)
		Tobacco use ^b	Binary (yes, no)
Comedications	365 days before index date ^a	Acetylcholinesterase inhibitors	Binary (yes, no)
		Memantine	Binary (yes, no)
		Antidepressants	Binary (yes, no)
		Anxiolytics	Binary (yes, no)
		Drugs used in opioid dependence	Binary (yes, no)
		Drugs used in alcohol dependence	Binary (yes, no)
		Sedatives	Binary (yes, no)
		Antiparkinson drugs	Binary (yes, no)
		Antiepileptics	Binary (yes, no)
		Anticoagulants	Binary (yes, no)
		Antihypertensives	Binary (yes, no)
		Cholesterol-lowering medications	Binary (yes, no)
		Anti-inflammatory drugs	Binary (yes, no)
		Bronchodilators	Binary (yes, no)
		Opioids	Binary (yes, no)
		Osteoporosis treatment	Binary (yes, no)
		Oral anti-infectives	Binary (yes, no)
		Parenteral anti-infectives	Binary (yes, no)
Comedications	All available history ^a	Drugs used in tobacco dependence	Binary (yes, no)
Health care utilization	365 days before index date ^a	Hospital admission	Categorical ^c ▪ 0 ▪ 1 ▪ 2+
		ED visits	Categorical ^c ▪ 0 ▪ 1-2 ▪ 3+
		Unique days on which a clinic visit occurred	Categorical ^d ▪ 0-6

Category	Assessment period	Covariate	Form in propensity score model
			▪ 7-12 ▪ 13+
		Influenza vaccination	Binary (yes, no)
		Shingles vaccination	Binary (yes, no)
		Pneumococcal vaccination	Binary (yes, no)

ED = emergency department; LTC = long-term care; SNF = skilled nursing facility; US = United States.

^a Before, but not including, the index date.

^b Identified through diagnosis coding.

^c Groupings defined *a priori* in statistical analysis plan.

^d Groupings determined by distribution observed in data.

eTable 3. Characteristics of Initial Atypical Antipsychotic Treatment in Patients With Parkinson's Disease Psychosis, Before Matching

Type of antipsychotic initially prescribed, N (%)	Overall	2016^a	2017	2018	2019
Total	21,975	4,644	6,238	5,789	5,304
Pimavanserin	2,892 (13.2)	381 (8.2)	887 (14.2)	739 (12.8)	885 (16.7)
Comparator atypical antipsychotics	19,083 (86.8)	4,263 (91.8)	5,351 (85.8)	5,050 (87.2)	4,419 (83.3)
Clozapine	37 (0.2)	NR	NR	NR	NR
Quetiapine	14,458 (65.8)	3,062 (65.9)	3,980 (63.8)	3,925 (67.8)	3,491 (65.8)
Olanzapine	1,309 (6.0)	337 (7.3)	402 (6.4)	323 (5.6)	247 (4.7)
Risperidone	2,531 (11.5)	671 (14.4)	750 (12.0)	614 (10.6)	496 (9.4)
Aripiprazole	719 (3.3)	177 (3.8)	199 (3.2)	172 (3.0)	171 (3.2)
Brexpiprazole	29 (0.1)	NR	NR	NR	NR

NR = not reportable.

^a April 1, 2016, through December 31, 2016.

eTable 4. Demographic Characteristics of Patients With Parkinson's Disease Psychosis Who Initiated Treatment With Atypical Antipsychotics, Before Matching

Characteristic	Pimavanserin N (%)	Comparator antipsychotics N (%)	ASD
Age at treatment initiation			0.29
Mean (SD)	79.3 (6.19)	81.1 (6.69)	
Age categories, N (%)			
65 to < 75 years	757 (26.2)	3,764 (19.7)	
75 to < 85 years	1,591 (55.0)	9,733 (51.0)	
≥ 85 years	544 (18.8)	5,586 (29.3)	
Sex			0.05
Females	1,300 (45.0)	9,070 (47.5)	
Males	1,592 (55.0)	10,013 (52.5)	
Race/ethnicity			0.00
White	2,506 (86.7)	16,539 (86.7)	
Black	117 (4.0)	804 (4.2)	
Other or unknown	269 (9.3)	1,740 (9.1)	
Socioeconomic information ^a			0.13
Low-income status	741 (25.6)	6,050 (31.7)	
Not low-income status	2,151 (74.4)	13,033 (68.3)	
US geographic region			0.13
Northeast	574 (19.8)	3,768 (19.7)	
Midwest	577 (20.0)	4,771 (25.0)	
South	1,260 (43.6)	7,392 (38.7)	
West	481 (16.6)	3,152 (16.5)	
LTC/SNF resident at treatment initiation ^b	665 (23.0)	5,893 (30.9)	0.18
Calendar year of the index date			0.25
2016 ^c	381 (13.2)	4,263 (22.3)	
2017	887 (30.7)	5,351 (28.0)	
2018	739 (25.6)	5,050 (26.5)	
2019	885 (30.6)	4,419 (23.2)	

ASD = absolute standardized difference; LTC = long-term care; SD = standard deviation; SNF = skilled nursing facility.

^a Defined from patients having subsidized or unsubsidized Medicare Part D coverage.

^b Defined as a patient being a resident of a Medicare-certified nursing facility or SNF.

^c April 1, 2016, through December 31, 2016.

eTable 5. Clinical Characteristics of Patients With Parkinson’s Disease Psychosis Who Initiated Treatment With Atypical Antipsychotics, Before Matching

Characteristic	Pimavanserin N (%)	Comparator antipsychotics N (%)	ASD
Dementia diagnosis	2,063 (71.3)	15,292 (80.1)	0.21
Mild cognitive impairment diagnosis	433 (15.0)	2,548 (13.4)	0.05
Use of SNF services within the 365 days before the index date	694 (24.0)	6,871 (36.0)	0.26
Use of home health aide/nurse within the 365 days before the index date	1,188 (41.1)	8,927 (46.8)	0.12
Prescriber specialty			0.86
Neurology	1,789 (61.9)	4,404 (23.1)	
Psychiatry	100 (3.5)	1,387 (7.3)	
Other or unknown	1,003 (34.7)	13,292 (69.7)	

ASD = absolute standardized difference; SNF = skilled nursing facility.

eTable 6. Comorbidities of Patients With Parkinson's Disease Psychosis Who Initiated Treatment With an Atypical Antipsychotic, Before Matching

Characteristic	Pimavanserin N (%)	Comparator antipsychotics N (%)	ASD
Charlson Comorbidity Index components			
Myocardial infarction ^a	507 (17.5)	4,712 (24.7)	0.18
Congestive heart failure ^a	1,007 (34.8)	8,908 (46.7)	0.24
Peripheral vascular disease	1,013 (35.0)	7,785 (40.8)	0.12
Cerebrovascular disease ^a	1,882 (65.1)	13,884 (72.8)	0.17
Chronic pulmonary disease	578 (20.0)	5,515 (28.9)	0.21
Rheumatic disease	116 (4.0)	1,015 (5.3)	0.06
Peptic ulcer disease	46 (1.6)	527 (2.8)	0.08
Liver disease	122 (4.2)	1,041 (5.5)	0.06
Diabetes mellitus ^a	1,007 (34.8)	8,173 (42.8)	0.16
Renal disease	572 (19.8)	5,472 (28.7)	0.21
Hemiplegia or paraplegia	94 (3.3)	1,018 (5.3)	0.10
Malignancy ^a	808 (27.9)	5,910 (31.0)	0.07
HIV/AIDS ^a	NR	NR	0.02
Frailty indicators			
Home hospital bed	129 (4.5)	1,071 (5.6)	0.05
Wheelchair use	232 (8.0)	1,883 (9.9)	0.06
Home oxygen	80 (2.8)	958 (5.0)	0.12
Use of ambulance or life support	1,321 (45.7)	11,642 (61.0)	0.31
Paralysis	153 (5.3)	1,698 (8.9)	0.14
Cancer screening	597 (20.6)	3,211 (16.8)	0.10
Lipid abnormality	1,901 (65.7)	13,402 (70.2)	0.10
Vertigo	659 (22.8)	4,686 (24.6)	0.04
Difficulty walking	2,029 (70.2)	13,928 (73.0)	0.06
Podiatric care	736 (25.4)	5,277 (27.7)	0.05
Rehabilitation services	2,178 (75.3)	14,167 (74.2)	0.02
Arthritis	1,785 (61.7)	13,201 (69.2)	0.16
Sepsis	709 (24.5)	6,284 (32.9)	0.19
Weakness	1,495 (51.7)	11,531 (60.4)	0.18
Additional comorbidities			
Chronic cardiovascular disease ^a	2,307 (79.8)	16,625 (87.1)	0.20
Hypertension or hypertensive heart disease	2,284 (79.0)	16,510 (86.5)	0.20

Characteristic	Pimavanserin N (%)	Comparator antipsychotics N (%)	ASD
Osteoporosis	482 (16.7)	3,446 (18.1)	0.04
Mood disorders ^b	1,391 (48.1)	10,807 (56.6)	0.17
Anxiety disorders	1,254 (43.4)	9,828 (51.5)	0.16
Other psychiatric disorders (e.g., eating disorders, unspecified mental/psychiatric disorders) ^c	54 (1.9)	335 (1.8)	0.01
Huntington's disease	0 (0.0)	20 (0.1)	0.05
Tourette's syndrome and other tics	NR	NR	0.01
Falls and/or fractures	1,220 (42.2)	8,929 (46.8)	0.09
Aspiration pneumonia	98 (3.4)	976 (5.1)	0.09
Anemia	1,069 (37.0)	8,731 (45.8)	0.18
Obesity, identified by diagnosis	323 (11.2)	2,668 (14.0)	0.08
Substance use, identified by diagnosis			
Tobacco use ^a	298 (10.3)	2,670 (14.0)	0.11
Alcohol abuse	35 (1.2)	530 (2.8)	0.11
Other substance abuse	79 (2.7)	761 (4.0)	0.07
Infections			
Upper respiratory tract infections	278 (9.6)	2,086 (10.9)	0.04
Lower respiratory tract infections	354 (12.2)	4,071 (21.3)	0.25
Urinary tract infections	1,283 (44.4)	9,843 (51.6)	0.14
Severe sepsis	80 (2.8)	1,219 (6.4)	0.17
Serious hospitalized infections	325 (11.2)	3,845 (20.1)	0.25

ASD = absolute standardized difference; NR = not reportable.

^a Defined using all available lookback data. All other variables defined using a 365-day lookback window.

^b Other than bipolar disorder.

^c Not including schizophrenia or other schizophrenic disorders or major depressive disorder with psychosis.

eTable 7. Comedications in Patients With Parkinson's Disease Psychosis Who Initiated Treatment With An Atypical Antipsychotic, Before Matching

Comedications	Pimavanserin N (%)	Comparator antipsychotics N (%)	ASD
Neurological or psychiatric medications			
Acetylcholinesterase inhibitors	1,175 (40.6)	7,177 (37.6)	0.06
Memantine	492 (17.0)	3,352 (17.6)	0.01
Antidepressants	1,693 (58.5)	12,450 (65.2)	0.14
Anxiolytics	135 (4.7)	1,272 (6.7)	0.09
Drugs used in opioid dependence	NR	NR	0.02
Drugs used in tobacco dependence ^a	NR	NR	0.08
Drugs used in alcohol dependence	0 (0.0)	19 (0.1)	0.04
Sedatives	126 (4.4)	1,347 (7.1)	0.12
Antiparkinson drugs ^b	2,760 (95.4)	14,460 (75.8)	0.58
Antiepileptics ^c	938 (32.4)	6,961 (36.5)	0.09
Cardiovascular medications			
Anticoagulants	620 (21.4)	5,433 (28.5)	0.16
Antihypertensives	1,769 (61.2)	13,175 (69.0)	0.17
Cholesterol-lowering medications	1,356 (46.9)	9,878 (51.8)	0.10
Pain, inflammatory, or musculoskeletal medications			
Anti-inflammatory drugs	955 (33.0)	6,154 (32.2)	0.02
Bronchodilators	235 (8.1)	1,870 (9.8)	0.06
Opioids	831 (28.7)	6,191 (32.4)	0.08
Osteoporosis treatment	236 (8.2)	1,454 (7.6)	0.02
Anti-infectives			
Oral anti-infectives	1,763 (61.0)	12,169 (63.8)	0.06
Parenteral anti-infectives	528 (18.3)	3,936 (20.6)	0.06

ASD = absolute standardized difference; NR = not reportable.

^a Defined using all available lookback data. All other variables defined using a 365-day lookback window.

^b Including anticholinergic agents, dopaminergic agents, and other antiparkinson drugs.

^c Including barbiturates and derivatives, hydantoin derivatives, oxazolidine derivatives, succinimide derivatives, benzodiazepine derivatives, carboxamide derivatives, fatty acid derivatives, and other antiepileptics.

eTable 8. Health Care Utilization in the Year Before the Treatment Initiation Date in Patients With Parkinson's Disease Psychosis Who Initiated Treatment With An Atypical Antipsychotic, Before Matching

Health care resource	Pimavanserin N (%)	Comparator antipsychotics N (%)	ASD
Number of hospital admissions			
Mean (SD)	0.6 (0.91)	1.0 (1.29)	
Categorized, N (%)			0.41
0	1,820 (62.9)	8,375 (43.9)	
1	688 (23.8)	5,824 (30.5)	
2+	384 (13.3)	4,884 (25.6)	
Number of ED visits ^a			
Mean (SD)	1.6 (1.93)	2.3 (2.39)	
Categorized, N (%)			0.33
0	1,027 (35.5)	4,435 (23.2)	
1-2	1,204 (41.6)	8,147 (42.7)	
3+	661 (22.9)	6,501 (34.1)	
Number of unique days on which a clinic visit occurred ^b			
Mean (SD)	12.1 (7.97)	10.8 (8.54)	
Categorized, N (%)			0.22
0-6	716 (24.8)	6,643 (34.8)	
7-12	972 (33.6)	5,749 (30.1)	
13+	1,204 (41.6)	6,691 (35.1)	
Influenza vaccination received, N (%)	1,757 (60.8)	11,355 (59.5)	0.03
Shingles vaccination received, N (%)	75 (2.6)	433 (2.3)	0.02
Pneumococcal vaccination received, N (%)	463 (16.0)	2,829 (14.8)	0.03

ASD = absolute standardized difference; ED = emergency department; MedPAR = Medicare Provider Analysis and Review; SD = standard deviation.

^a Identified as the number of unique days with an emergency depart visit from the MedPAR files where emergency room charge amount is > \$0 or in the outpatient file where the revenue center code is indicated an ED visit.

^b Evaluated as days without a hospital or ED claim in outpatient and physician billing claims.

eTable 9. Length of Follow-up and Reasons for Censoring by Treatment Group Among Patients With Parkinson's Disease Psychosis Who Initiated An Atypical Antipsychotic, Before Matching

Demographic	By treatment group		
	Overall N = 21,975	Pimavanserin N = 2,892	Comparator antipsychotics N = 19,083
Duration of follow-up, total, person-years	11,147.4	1,674.9	9,472.5
Mean (SD), person-years	0.5 (0.58)	0.6 (0.62)	0.5 (0.57)
Reasons for end of follow-up, N (%)			
Death	3,197 (14.5)	317 (11.0)	2,880 (15.1)
Censoring			
End of study period	3,499 (15.9)	660 (22.8)	2,839 (14.9)
Disenrollment from eligible Medicare plan	549 (2.5)	79 (2.7)	470 (2.5)
End of continuous use of the study antipsychotic drug	12,040 (54.8)	1,224 (42.3)	10,816 (56.7)
Switching to or adding a different antipsychotic ^a	2,690 (12.2)	612 (21.2)	2,078 (10.9)

SD = standard deviation.

^a Defined as patients in the pimavanserin group receiving a prescription for a different atypical antipsychotic, or patients in the comparator atypical antipsychotics group receiving a prescription for pimavanserin or a different comparator antipsychotic.

eTable 10. Demographic Characteristics of Patients With Parkinson's Disease Psychosis Residing in Long-term Care or Skilled Nursing Facilities at Treatment Initiation Who Initiated an Atypical Antipsychotic, by Treatment Group, Before Matching

Demographic	Pimavanserin N (%)	Comparator antipsychotics N (%)	ASD
Age at treatment initiation			0.18
Mean (SD)	81.3 (6.32)	82.4 (6.64)	
Age categories, N (%)			
65 to < 75 years	112 (16.8)	851 (14.4)	
75 to < 85 years	360 (54.1)	2,917 (49.5)	
≥ 85 years	193 (29.0)	2,125 (36.1)	
Sex			0.01
Females	347 (52.2)	3,060 (51.9)	
Males	318 (47.8)	2,833 (48.1)	
Race/ethnicity			0.06
White	586 (88.1)	5,194 (88.1)	
Black	27 (4.1)	268 (4.5)	
Other or unknown	52 (7.8)	431 (7.3)	
Socioeconomic information ^a			0.12
Low-income status	433 (65.1)	3,490 (59.2)	
Not low-income status	232 (34.9)	2,403 (40.8)	
US geographic region			0.15
Northeast	170 (25.6)	1,236 (21.0)	
Midwest	167 (25.1)	1,851 (31.4)	
South	250 (37.6)	2,208 (37.5)	
West	78 (11.7)	598 (10.1)	
Calendar year of the index date			0.41
2016 ^b	68 (10.2)	1,479 (25.1)	
2017	204 (30.7)	1,669 (28.3)	
2018	192 (28.9)	1,461 (24.8)	
2019	201 (30.2)	1,284 (21.8)	

ASD = absolute standardized difference; SD = standard deviation.

^a Defined as patients having subsidized or unsubsidized Medicare Part D coverage.

^b April 1, 2016, through December 31, 2016.

eTable 11. Clinical Characteristics of Patients With Parkinson’s Disease Psychosis Residing in Long-term Care or Skilled Nursing Facilities On the Index Date Who Initiated An Atypical Antipsychotic, by Treatment Group, Before Matching

Characteristic	Pimavanserin N (%)	Comparator antipsychotics N (%)	ASD
Dementia diagnosis	578 (86.9)	5,338 (90.6)	0.12
Mild cognitive impairment diagnosis	95 (14.3)	701 (11.9)	0.07
Use of SNF services within the 365 days before the index date	355 (53.4)	3,858 (65.5)	0.25
Use of home health aide/nurse within the 365 days before the index date	198 (29.8)	1,963 (33.3)	0.08
Prescriber specialty			0.51
Neurology	122 (18.3)	156 (2.6)	
Psychiatry	42 (6.3)	288 (4.9)	
Other or unknown	501 (75.3)	5,449 (92.5)	

ASD = absolute standardized difference; SNF = skilled nursing facility.

eTable 12. Comorbidities of Patients With Parkinson's Disease Psychosis Residing in Long-term Care Facilities or Skilled Nursing Facilities at Treatment Initiation Who Initiated an Atypical Antipsychotic, by Treatment Group, Before Matching

Comorbidity	Pimavanserin N (%)	Comparator antipsychotics N (%)	ASD
Charlson Comorbidity Index components			
Myocardial infarction ^a	158 (23.8)	1,654 (28.1)	0.10
Congestive heart failure ^a	335 (50.4)	3,338 (56.6)	0.13
Peripheral vascular disease	378 (56.8)	3,211 (54.5)	0.05
Cerebrovascular disease ^a	488 (73.4)	4,523 (76.8)	0.08
Chronic pulmonary disease	186 (28.0)	2,049 (34.8)	0.15
Rheumatic disease	29 (4.4)	297 (5.0)	0.03
Peptic ulcer disease	14 (2.1)	204 (3.5)	0.08
Liver disease	28 (4.2)	323 (5.5)	0.06
Diabetes mellitus ^a	302 (45.4)	2,829 (48.0)	0.05
Renal disease	174 (26.2)	2,079 (35.3)	0.20
Hemiplegia or paraplegia	44 (6.6)	447 (7.6)	0.04
Malignancy ^a	174 (26.2)	1,766 (30.0)	0.08
HIV/AIDS ^a	NR	NR	0.03
Frailty indicators			
Home hospital bed	23 (3.5)	197 (3.3)	0.01
Wheelchair use	47 (7.1)	455 (7.7)	0.02
Home oxygen	18 (2.7)	251 (4.3)	0.08
Use of ambulance or life support	457 (68.7)	4,477 (76.0)	0.16
Paralysis	69 (10.4)	718 (12.2)	0.06
Cancer screening	60 (9.0)	596 (10.1)	0.04
Lipid abnormality	412 (62.0)	4,066 (69.0)	0.15
Vertigo	142 (21.4)	1,309 (22.2)	0.02
Difficulty walking	596 (89.6)	4,997 (84.8)	0.14
Podiatric care	267 (40.2)	2,094 (35.5)	0.10
Rehabilitation services	586 (88.1)	4,773 (81.0)	0.20
Arthritis	486 (73.1)	4,500 (76.4)	0.08
Sepsis	240 (36.1)	2,491 (42.3)	0.13
Weakness	576 (86.6)	4,929 (83.6)	0.08
Additional comorbidities			
Chronic cardiovascular disease ^a	586 (88.1)	5,397 (91.6)	0.11

Comorbidity	Pimavanserin N (%)	Comparator antipsychotics N (%)	ASD
Hypertension or hypertensive heart disease	583 (87.7)	5,439 (92.3)	0.15
Osteoporosis	120 (18.0)	1,179 (20.0)	0.05
Mood disorders ^b	457 (68.7)	4,108 (69.7)	0.02
Anxiety disorders	406 (61.1)	3,730 (63.3)	0.05
Other psychiatric disorders (eating disorders or unspecified mental/psychiatric disorders) ^c	21 (3.2)	153 (2.6)	0.03
Huntington's disease	NR	NR	0.06
Tourette's syndrome and other tics	NR	NR	0.05
Falls and/or fractures	335 (50.4)	3,175 (53.9)	0.07
Aspiration pneumonia	52 (7.8)	417 (7.1)	0.03
Anemia	377 (56.7)	3,318 (56.3)	0.01
Obesity, identified by diagnosis	84 (12.6)	886 (15.0)	0.07
Substance use, identified by diagnosis			
Tobacco use ^a	88 (13.2)	953 (16.2)	0.08
Alcohol abuse	15 (2.3)	182 (3.1)	0.05
Other substance abuse	18 (2.7)	229 (3.9)	0.07
Infections			
Upper respiratory tract infections	83 (12.5)	688 (11.7)	0.02
Lower respiratory tract infections	143 (21.5)	1,714 (29.1)	0.18
Urinary tract infections	416 (62.6)	3,778 (64.1)	0.03
Severe sepsis	37 (5.6)	561 (9.5)	0.15
Serious hospitalized infections	132 (19.8)	1,617 (27.4)	0.18

ASD = absolute standardized difference; NR = not reportable.

^a Defined using all available lookback data. All other variables defined using a 365-day lookback window.

^b Other than bipolar disorder.

^c Not including schizophrenia or other schizophrenic disorders or major depressive disorder with psychosis.

eTable 13. Comedications in Patients With Parkinson's Disease Psychosis Residing in Long-term Care or Skilled Nursing Facilities at Treatment Initiation Who Initiated an Atypical Antipsychotic, by Treatment Group, Before Matching

Comedications	Pimavanserin N (%)	Comparator antipsychotics N (%)	ASD
Neurological or psychiatric medications			
Acetylcholinesterase inhibitors	251 (37.7)	2,069 (35.1)	0.05
Memantine	116 (17.4)	1,074 (18.2)	0.02
Antidepressants	468 (70.4)	4,106 (69.7)	0.02
Anxiolytics	51 (7.7)	487 (8.3)	0.02
Drugs used in opioid dependence	NR	NR	0.01
Drugs used in tobacco dependence ^a	0 (0.0)	20 (0.3)	0.08
Drugs used in alcohol dependence	NR	NR	0.04
Sedatives	27 (4.1)	360 (6.1)	0.09
Antiparkinson drugs ^b	631 (94.9)	4,142 (70.3)	0.69
Antiepileptics ^c	234 (35.2)	2,288 (38.8)	0.08
Cardiovascular medications			
Anticoagulants	155 (23.3)	1,854 (31.5)	0.18
Antihypertensives	446 (67.1)	4,261 (72.3)	0.11
Cholesterol-lowering medications	291 (43.8)	2,942 (49.9)	0.12
Pain, inflammatory, or musculoskeletal medications			
Anti-inflammatory drugs	215 (32.3)	1,815 (30.8)	0.03
Bronchodilators	67 (10.1)	692 (11.7)	0.05
Opioids	273 (41.1)	2,358 (40.0)	0.02
Osteoporosis treatment	48 (7.2)	384 (6.5)	0.03
Anti-infectives			
Oral anti-infectives	459 (69.0)	3,964 (67.3)	0.04
Parenteral anti-infectives	167 (25.1)	1,455 (24.7)	0.01

ASD = absolute standardized difference; NR = not reportable.

^a Defined using all available lookback data. All other variables defined using a 365-day lookback window.

^b Including anticholinergic agents, dopaminergic agents, and other antiparkinson drugs.

^c Including barbiturates and derivatives, hydantoin derivatives, oxazolidine derivatives, succinimide derivatives, benzodiazepine derivatives, carboxamide derivatives, fatty acid derivatives, and other antiepileptics.

eTable 14. Health Care Utilization in the Year Before the Treatment Initiation Date in Patients With Parkinson’s Disease Psychosis Residing in Long-term Care or Skilled Nursing Facilities Who Initiated an Atypical Antipsychotic, by Treatment Group, Before Matching

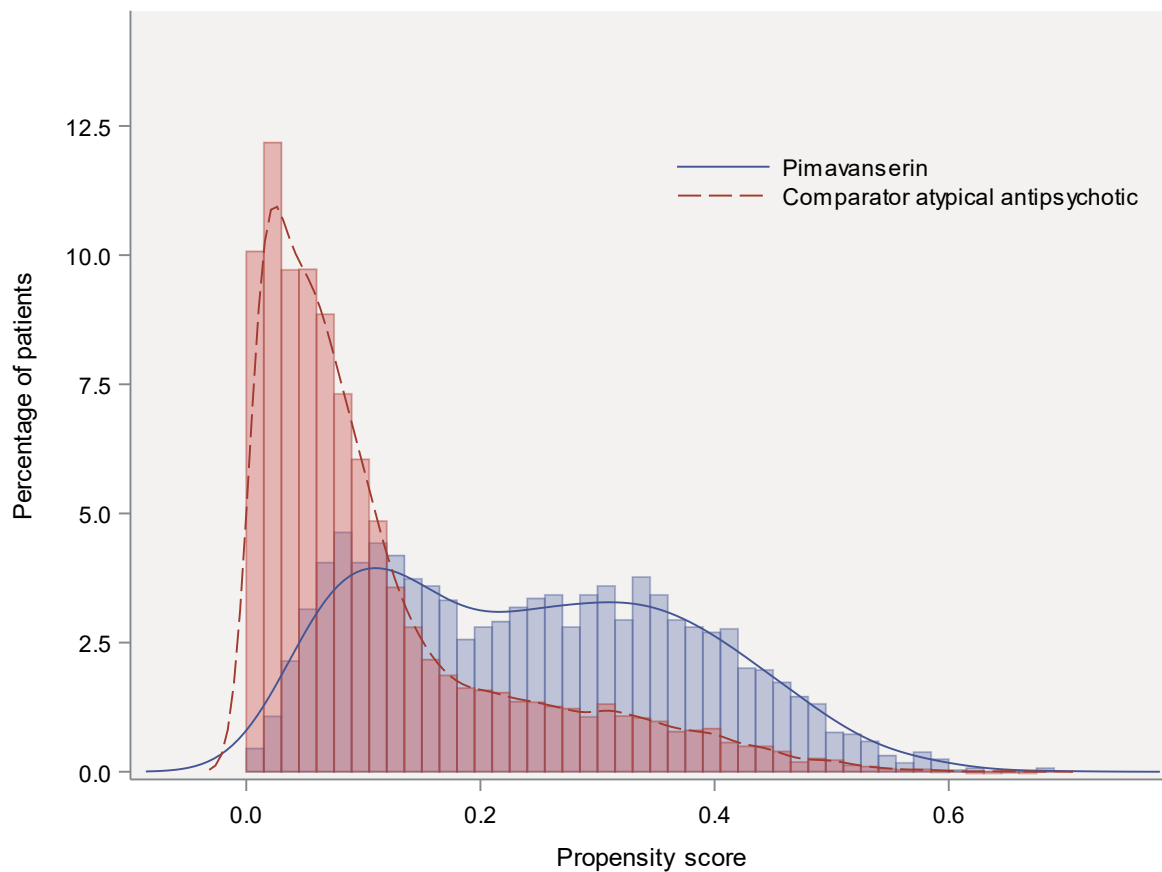
Health care resource	Pimavanserin N (%)	Comparator antipsychotics N (%)	ASD
Number of hospital admissions			
Mean (SD)	0.9 (1.11)	1.4 (1.40)	
Categorized, N (%)			0.39
0	313 (47.1)	1,776 (30.1)	
1	204 (30.7)	2,015 (34.2)	
2+	148 (22.3)	2,102 (35.7)	
Number of ED visits ^a			
Mean (SD)	2.0 (2.34)	2.6 (2.56)	
Categorized, N (%)			0.20
0	176 (26.5)	1,122 (19.0)	
1-2	284 (42.7)	2,446 (41.5)	
3+	205 (30.8)	2,325 (39.5)	
Number of unique days on which a clinic visit occurred ^b			
Mean (SD)	6.5 (6.63)	6.8 (6.89)	
Categorized, N (%)			0.08
0-6	408 (61.4)	3,445 (58.5)	
7-12	161 (24.2)	1,431 (24.3)	
13+	96 (14.4)	1,017 (17.3)	
Influenza vaccination received, N (%)	342 (51.4)	3,077 (52.2)	0.02
Shingles vaccination received, N (%)	NR	NR	0.01
Pneumococcal vaccination received, N (%)	76 (11.4)	778 (13.2)	0.05

ASD = absolute standardized difference; ED = emergency department; MedPAR = Medicare Provider Analysis and Review; NR = not reportable; SD = standard deviation.

^a Identified as the number of unique days with an emergency depart visit from the MedPAR files where the emergency room charge amount is > \$0 or in the outpatient file where the revenue center code indicated an ED visit.

^b Evaluated as days without a hospital or ED claim in outpatient and physician billing claims.

eFig 1. Overlap of Propensity Score Distributions Between the Pimavanserin and Comparator Atypical Antipsychotic Treatment Groups Among Patients With Parkinson's Disease Psychosis



Note: The distributions of propensity scores—the predicted probability of pimavanserin initiation versus comparator atypical antipsychotic initiation—are displayed by treatment group. The greater extent of overlap between the 2 distributions indicates the extent of comparability between the 2 groups.

eFig 2. Balance of Covariates Between the Pimavanserin and Comparator Atypical Antipsychotic Treatment Groups Before and After Propensity Score Matching

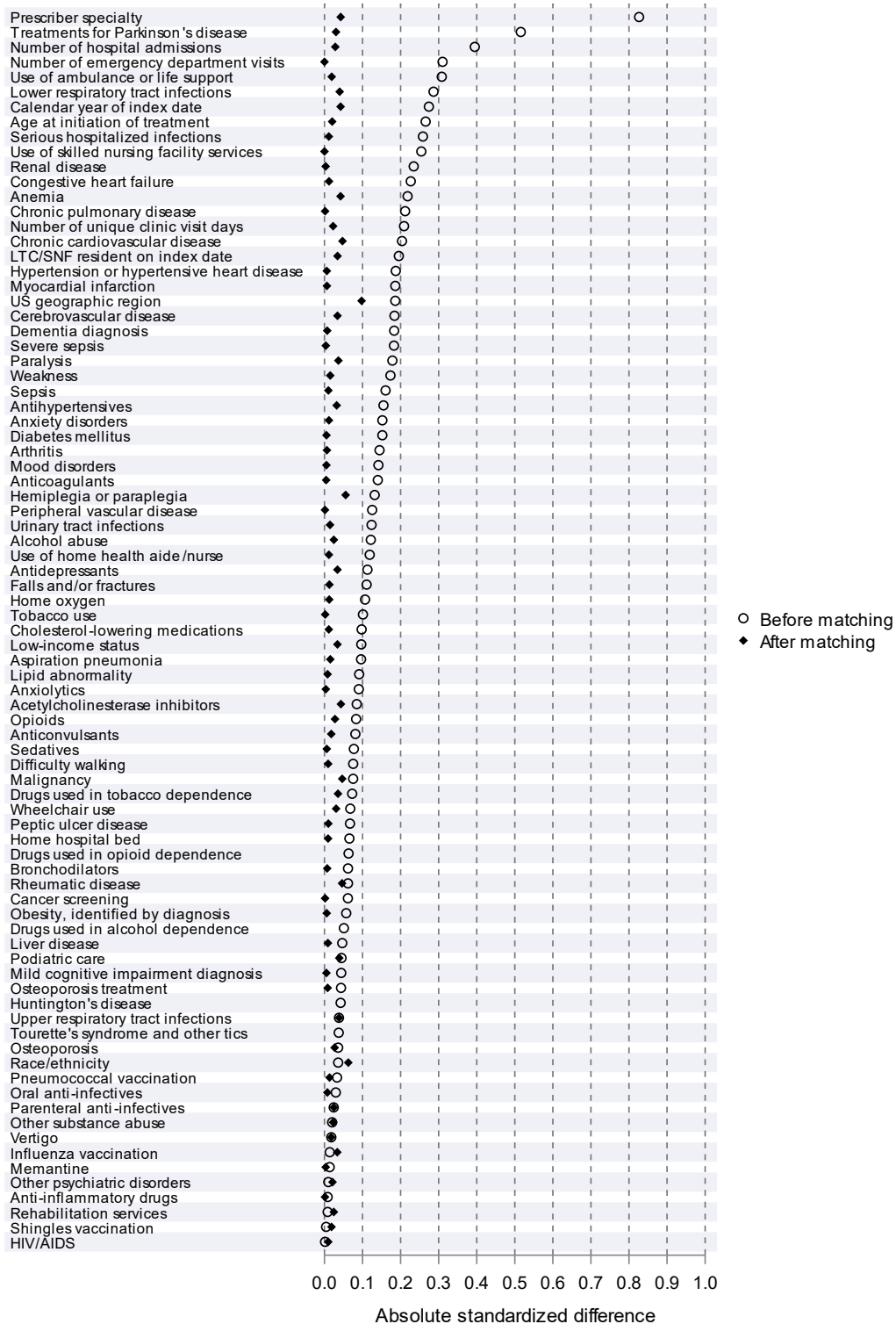


LTC = long-term care facility; SNF = skilled nursing facility.

Note: Absolute standardized difference after matching was not estimable for Huntington's disease and drugs used in alcohol dependence, given that there were no pimavanserin or comparator atypical antipsychotic users for those variables in the matched cohort.

eFig 3. Balance of Covariates Between the Pimavanserin and Comparator Atypical Antipsychotic Treatment Groups Before and After Propensity Score Matching Within Subgroups

A. Males



LTC = long-term care facility; SNF = skilled nursing facility.

Note: Absolute standardized difference after matching was not estimable for Huntington's disease, Tourette's syndrome and other tics, drugs used in opioid dependence, and drugs used in alcohol dependence, given that there were no pimavanserin or comparator atypical antipsychotic users for those variables in the matched cohort.

B. Females



LTC = long-term care facility; SNF = skilled nursing facility.

Note: Absolute standardized difference after matching was not estimable for HIV/AIDS, Huntington's disease, and drugs used in alcohol dependence, given that there were no pimavanserin or comparator atypical antipsychotic users for those variables in the matched cohort.

C. Aged 65 to < 75 Years



LTC = long-term care facility; SNF = skilled nursing facility.

Note: Absolute standardized difference after matching was not estimable for Huntington's disease, Tourette's syndrome and other tics, and drugs used in alcohol dependence, given that there were no pimavanserin or comparator atypical antipsychotic users for those variables in the matched cohort.

D. Aged 75 to < 85 Years



LTC = long-term care facility; SNF = skilled nursing facility.

Note: Absolute standardized difference after matching was not estimable for Huntington's disease, Tourette's syndrome and other tics, drugs used in tobacco dependence, and drugs used in alcohol dependence, given that there were no pimavanserin or comparator atypical antipsychotic users for those variables in the matched cohort.

E. Aged ≥ 85 years



LTC = long-term care facility; SNF = skilled nursing facility.

Note: Absolute standardized difference after matching was not estimable for HIV/AIDS, Huntington's disease, drugs used in tobacco dependence, and drugs used in alcohol dependence, given that there were no pimavanserin or comparator atypical antipsychotic users for those variables in the matched cohort.

F. Diagnosis of Dementia



LTC = long-term care facility; SNF = skilled nursing facility.

Note: Absolute standardized difference after matching was not estimable for Huntington's disease, Tourette's syndrome and other tics, drugs used in alcohol dependence, given that there were no pimavanserin or comparator atypical antipsychotic users for those variables in the matched cohort.

G. Without a Diagnosis of Dementia

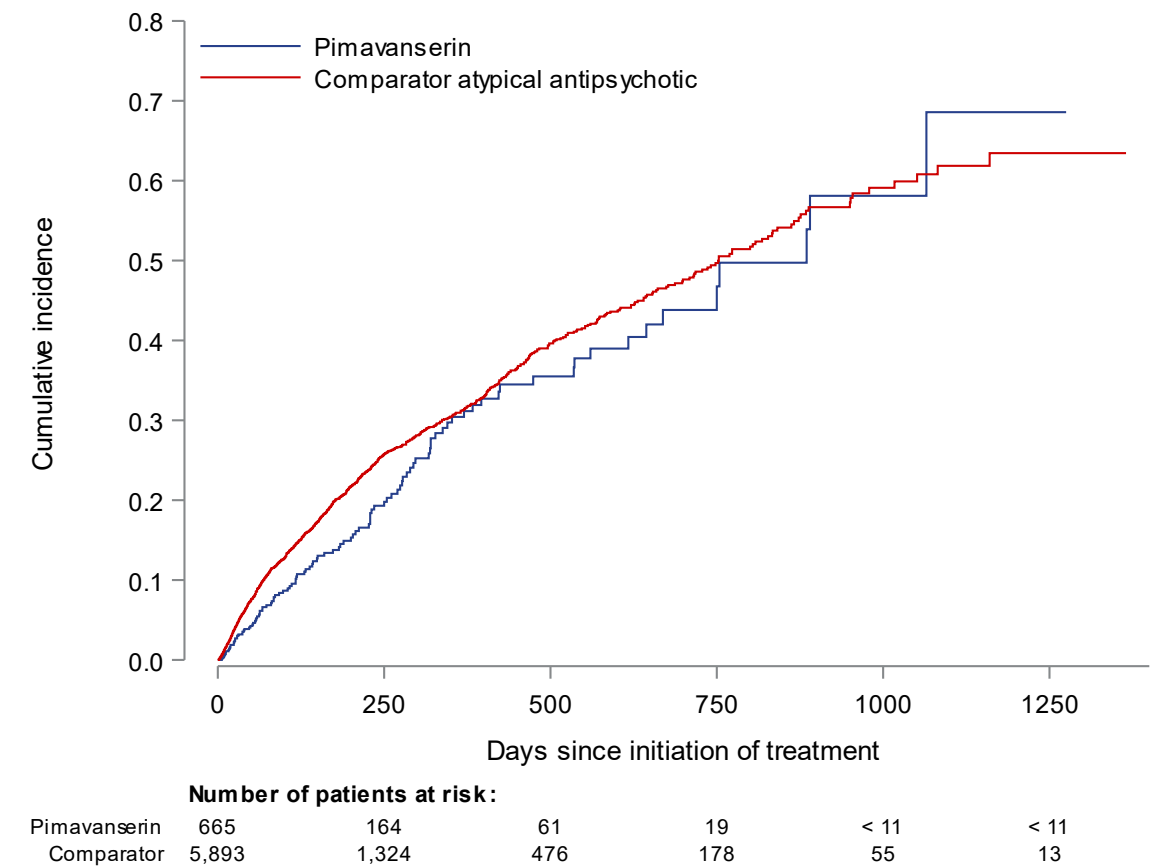


LTC = long-term care facility; SNF = skilled nursing facility.

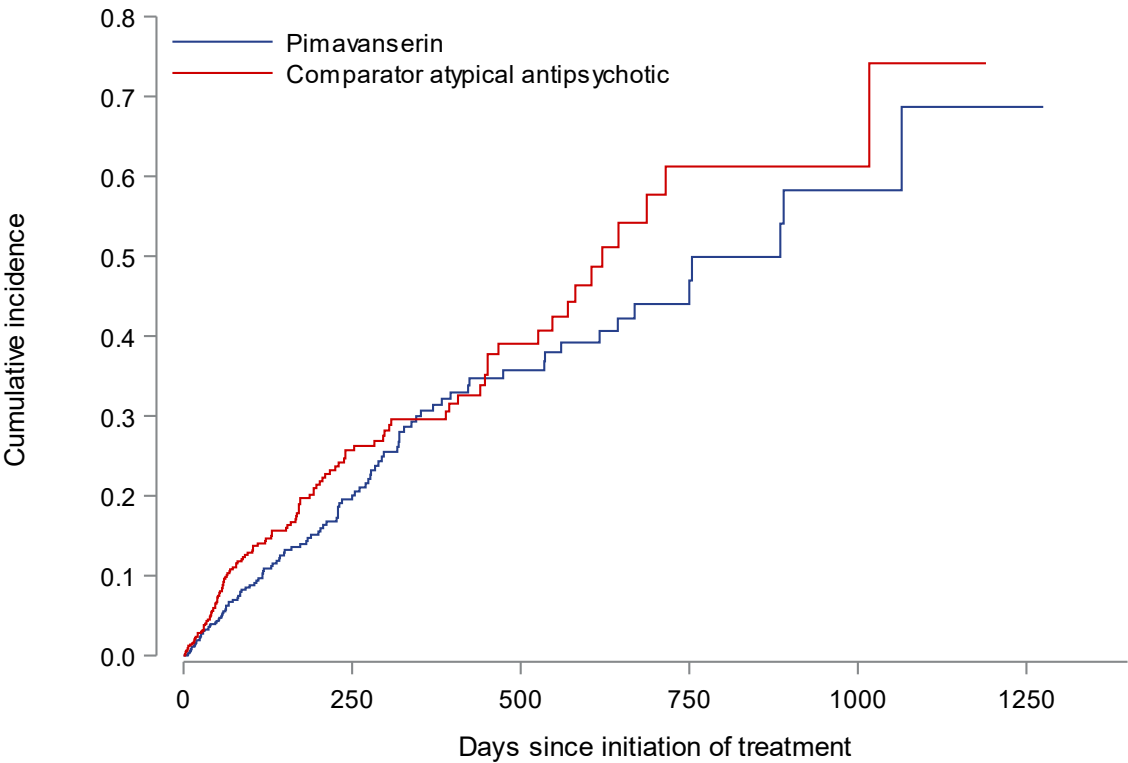
Note: Absolute standardized difference after matching was not estimable for Huntington's disease, Tourette's syndrome and other tics, drugs used in opioid dependence, and drugs used in alcohol dependence, given that there were no pimavanserin or comparator atypical antipsychotic users for those variables in the matched cohort.

eFig 4. Cumulative Incidence of Mortality by Time Since Atypical Antipsychotic Initiation Among Patients With Parkinson’s Disease Psychosis Residing in Long-term Care or Skilled Nursing Facilities at Treatment Initiation, Before and After Matching

Before Matching



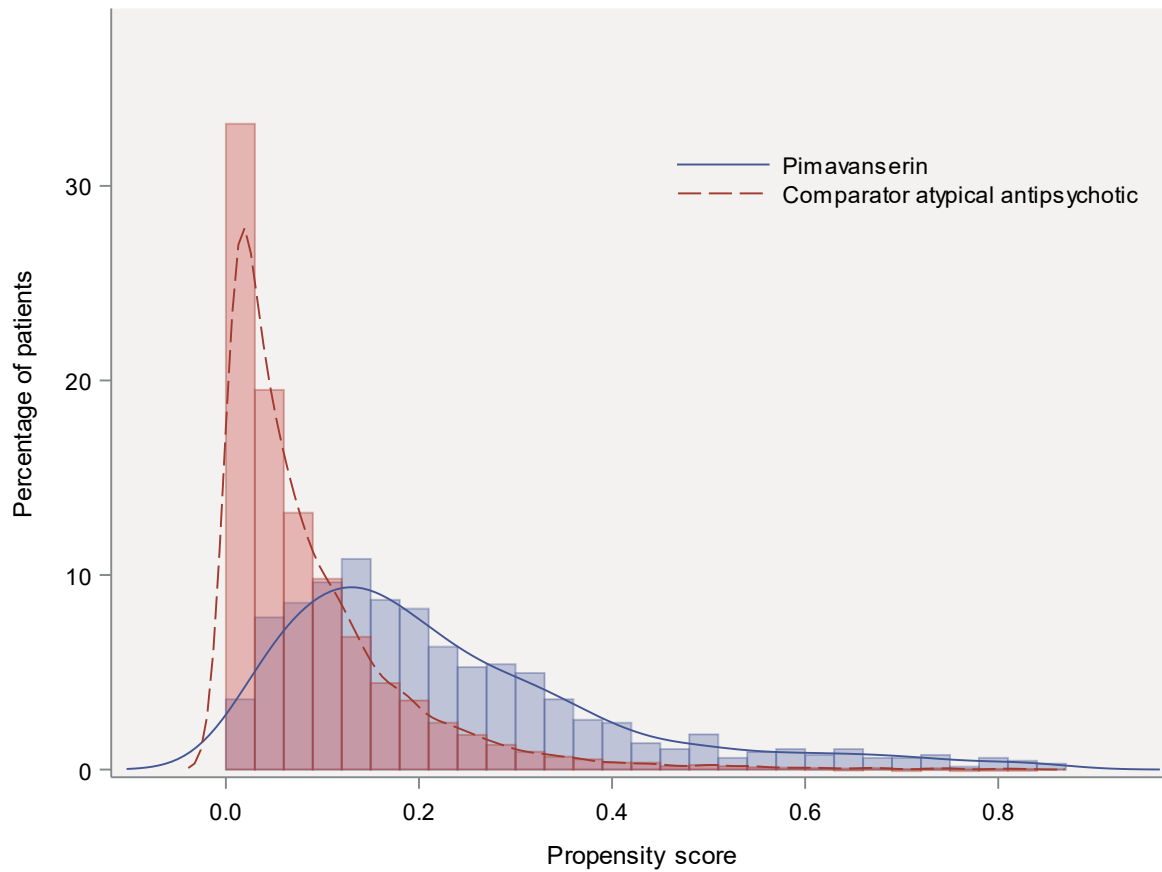
After Matching



Number of patients at risk :

Pimavanserin	652	163	61	19	< 11	< 11
Comparator	652	140	37	< 11	< 11	0

eFig 5. Overlap of Propensity Score Distributions Between the Pimavanserin and Comparator Atypical Antipsychotic Treatment Groups Among Patients With Parkinson's Disease Psychosis Residing in Long-term Care or Skilled Nursing Facilities at Treatment Initiation



Note: The distribution of propensity scores—the predicted probability of pimavanserin initiation versus comparator atypical antipsychotic initiation—is displayed by treatment group. The greater extent of overlap between the 2 distributions indicates the extent of comparability between the 2 groups.

eFig 6. Balance of Covariates Between the Pimavanserin and Comparator Atypical Antipsychotic Treatment Groups Among Patients With Parkinson's Disease Psychosis Residing in Long-term Care or Skilled Nursing Facilities at Treatment Initiation Before and After Propensity Score Matching



Note: Absolute standardized difference after matching was not estimable for Huntington's disease, Tourette's syndrome and other tics, drugs used in tobacco dependence, and drugs used in alcohol dependence, given that there were no pimavanserin or comparator atypical antipsychotic users for those variables in the matched cohort.

Supplementary Methods

In addition to the prespecified sensitivity analyses, the E-value was calculated in a post hoc analysis to assess the strength of association an unmeasured confounder would need to have with the exposure (pimavanserin or comparator atypical antipsychotic) and the outcome (mortality) to “explain away” the observed exposure-outcome association if the true association was null, conditional on the measured covariates [1]. The E-value was estimated as follows, where E is the E-value, and HR is the observed hazard ratio from the primary analysis:

$$E = \frac{1}{HR} + \sqrt{\frac{1}{HR} \times \left(\frac{1}{HR} - 1\right)}$$

The original E-value formula was developed for risk ratios, but guidance for using other effect measures in the formula have been developed [1]. Because mortality occurred in less than 15% of the sample by the end of follow-up, the HR was used in the formula without modification.

The E-value for the primary analysis was estimated to be 1.9 (E-value for upper bound of the 95% confidence interval = 1.4), which indicates that a potential unmeasured confounder associated with risk ratio of 1.9 or higher with both pimavanserin use (versus comparator antipsychotic use) and mortality could “explain away” the observed HR being treated with pimavanserin and mortality.

Reference

1. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med*. 2017 Aug 15;167(4):268-74. doi:<http://dx.doi.org/10.7326/M16-2607>.