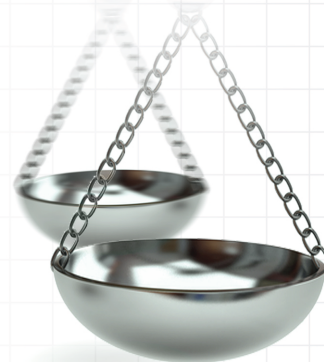




Real-world evidence of pimavanserin utilization among patients with Parkinson's disease psychosis: a review of real-world data that augments data from randomized controlled trials

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Aim: Pimavanserin (PIM) is the only US FDA-approved atypical antipsychotics (AAPs) for the treatment for hallucinations and delusions associated with Parkinson's disease psychosis (PDP). In addition to demonstrating symptom improvements in clinical trials, PIM appears to consistently show favorable outcomes among published real-world evidence (RWE) studies compared with off-label AAPs (e.g., quetiapine [QUE]). A comprehensive review of these RWE studies was conducted to summarize the overall benefits of PIM among PDP patients residing in community or nursing home/long-term care (NH/LTC) settings. **Materials & methods:** A literature review of published comparative RWE studies of PIM among PDP patients from 1 January 2017 to 1 April 2025 was conducted. Eligible studies examined the following outcomes in community and NH/LTC settings: clinical (e.g., falls, fractures), adherence (e.g., discontinuations), all-cause and psychiatric (psych)-related healthcare resource use (e.g., hospitalizations, emergency room (ER) visits, office visits, etc.), and mortality. **Results:** Sixteen RWE studies of PIM versus other-AAPs or QUE and PIM nonusers were included for review. In these studies, PIM had 20–37% lower all-cause and psych-related hospitalizations, 7–15% lower ER visits, significant delays to LTC admissions, lower rates of falls or fractures in NH/LTC settings and lower observed rates of mortality versus other-AAPs. Similar results were found for PIM versus QUE. **Conclusion:** PDP patients initiating PIM versus other-AAPs or QUE were associated with lower all-cause and psychiatric healthcare resource use burden, longer community-stays and delayed NH/LTC admissions. Additionally, PIM was associated with higher treatment compliance, fewer falls or fractures and lower overall mortality risk versus other-AAPs or QUE. PIM's favorable real-world profile versus other-AAPs or QUE across community and NH/LTC settings complement the favorable clinical trial findings.

Plain Language Summary: Real-world benefits of pimavanserin for hallucinations & delusions in Parkinson's disease psychosis

What is this article about? Parkinson's disease psychosis (PDP) can cause hallucinations or delusions, greatly affecting quality of life. Pimavanserin (PIM) is the only medicine in the US to be approved specifically for PDP. This review examined studies from everyday healthcare settings to see the benefits of PIM compared with other antipsychotic medicines, such as quetiapine (often used off-label).

What are the results? We reviewed 16 real-world studies from the US. Compared with other antipsychotics, PIM was linked to fewer hospital stays, fewer admissions to long-term care facilities, fewer falls and fractures, and in most studies, lower risk of death. People taking PIM were also more likely to continue in community setting longer. These advantages appeared in both community and nursing home settings. One study found notable cost savings when PIM was used instead of other antipsychotics, due to fewer hospital and care facility stays.

Why is this important? PDP can be challenging to treat, and some antipsychotics may worsen movement symptoms in Parkinson's disease. PIM works differently, without blocking dopamine, and may help control symptoms without harming mobility. This review of real-world research shows that PIM use is associated

with better long-term outcomes, reduced hospitalizations, and may have the potential to result in healthcare cost savings. These findings support its role as a treatment for PDP and provide valuable information for physicians, patients and healthcare decision makers when planning care.

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Keywords: healthcare resource utilization • mortality • Parkinson's disease psychosis • pimavanserin • real-world evidence

Pimavanserin (PIM), a selective 5-HT_{2A}/5-HT_{2C} receptor inverse agonist/antagonist agent was the first atypical antipsychotics (AAPs) medication to be approved by the US FDA in April 2016 for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP) among patients with or without dementia [1]. PIM demonstrated significant efficacy in reducing the frequency and severity of psychotic symptoms compared with placebo in randomized controlled clinical trials (RCTs) [1,2], with long-term safety and efficacy demonstrated in open-label extensions trials [3,4]. To date, PIM remains the only approved AAPs treatment for PDP; however, other-AAPs (e.g., quetiapine [QUE], risperidone, olanzapine, etc.) have been commonly used off-label [5,6]. PIM is administered orally once a day to treat hallucinations and delusions associated with PDP, can be taken with or without food, does not require titration or gradual dose reduction, and did not impact motor symptoms associated with Parkinson's disease (PD) [7].

PIM's mechanism of action, mediated through a combination of potent serotonin 5-HT_{2A} receptor inverse agonist and antagonist activity and to a lesser extent serotonin 5-HT_{2C}, has been shown to be advantageous in PDP treatment without impacting dopamine agonist effect of PD medication. On the other hand, off-label AAPs may antagonize the dopamine agonist effects of levodopa which may precipitate worsening of PD. Recognizing this, the American Geriatrics Society's (AGS) 2022 Beers Criteria recommends avoiding all antipsychotics other than PIM, QUE and clozapine in older adults [8]. Additionally, the International Parkinson and Movement Disorder Society Evidence-Based Medicine Committee recommended PIM as a clinically useful treatment for PDP [9].

Historically, RCTs have been the gold standard for establishing Class I evidence about a treatment's efficacy and safety for regulatory approval. Alternatively, clinicians, providers and payor healthcare decision makers require real-world evidence (RWE) related to treatment outcomes (e.g., treatment patterns related to continuation, discontinuation, adherence, or persistency; rates of healthcare resource utilization [HCRU], and healthcare costs) that occur in usual clinical practice which cannot be studied in RCTs due to short time period and the controlled setting of many trials. Therefore, real-world data (RWD) generated from uncontrolled usual care settings from a broader, diverse, non-RCT population has become increasingly vital. The insights from RWD can augment evidence from clinical trial data to provide guidance about day-to-day clinical practice and aid US formulary decision making and global health technology assessments [10]. It is important to note that, during the same time of PIM's FDA approval in 2016, the approval of 21st Century Cures Act (i.e., Cures Act) allowed the FDA to create a framework for evaluating the potential use of RWE to help support the approval of a new indication for a drug already approved under section 505(c) of the FD&C Act [11].

Since the approval of Cures Act, the FDA has issued several guidance documents intended to provide direction for the purpose of standardizing RWD and RWE generation. These guidance documents have accelerated the generation of RWE using RWD in the last 8 years to establish the real-world value proposition of FDA-approved drugs. The generation of RWE has been listed among the "Top 10 Trends in Health Economics and Outcomes Research" in 2024–2025 [12]. Since the FDA approval of PIM in April 2016, several real-world research studies have been completed using claims data from Medicare 100% sample data and other commercial payors to study the benefit of PIM versus other-AAPs or QUE only. This literature review aims to identify and highlight the real-world benefits of PIM as a treatment for PDP from published real-world studies which may complement the benefits of PIM that have been demonstrated in clinical trials.

Materials & methods

A targeted literature review of peer-reviewed publications focusing on RWE studies of PIM versus other-AAPs, including QUE, were conducted in patients with PDP. The literature search was conducted using search engines such as PubMed, EMBASE and Google scholar and terms: 'pimavanserin', 'real-world data', 'Parkinson's disease', and 'Parkinson's disease psychosis'. Outcomes of interest included treatment patterns, adherence, healthcare resource

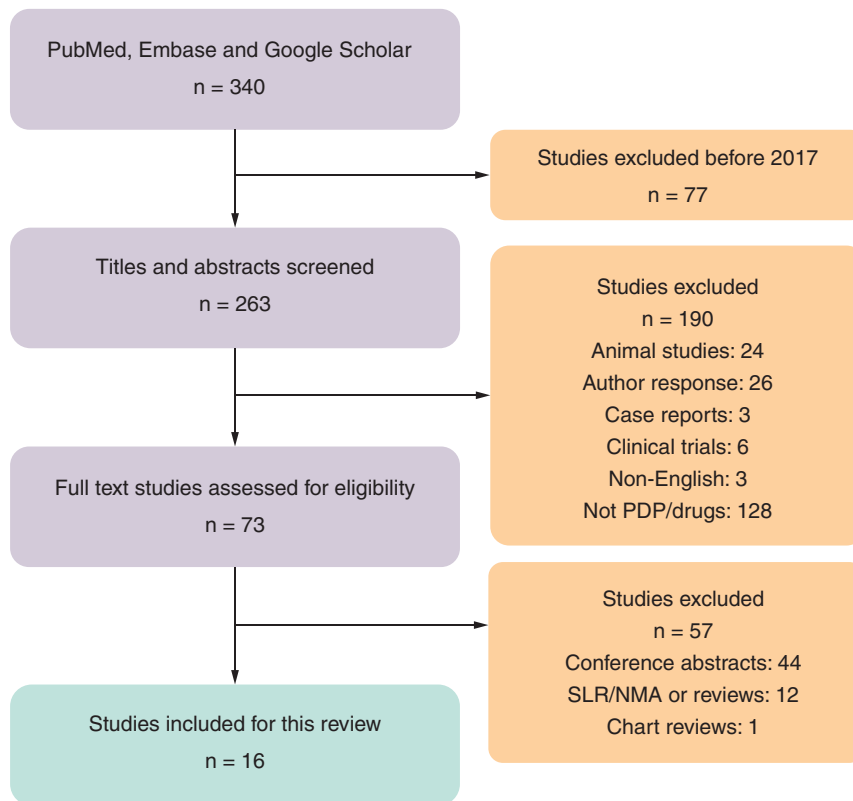


Figure 1. PRISMA diagram.

PDP: Parkinson's disease psychosis; SLR/NMA: Systematic literature reviews/network meta-analysis.

use or HCRU, costs, mortality, psychiatric-related or disease-related visits: inpatient hospitalizations (IP), IP visits by hospitalization type (i.e., short-term [ST] stay, skilled nursing facilities [SNF] stay, long-term care [LTC] stay, LTC admissions [LTCA]), emergency room (ER) visits, outpatient visits, and office visits. Studies were included if they met the following criteria: conducted in the USA, published between 1 January 2017 and 1 April 2025, focused on the use of PIM for PDP, and non-RCT RWD sources such as electronic health records, administrative insurance claims, or patient registries. Studies that met the criteria for inclusion were further categorized into community or nursing home/long-term care (NH/LTC) settings since PDP populations in the two different settings were expected to have different treatment strategies.

Results

Study designs & data sources

The study selection process is outlined in the PRISMA diagram (Figure 1). A total of 16 RWE published studies were eligible: fifteen retrospective observational studies and one cost offset model (Table 1); additionally, Figure 2 provides a summary of the studies categorized by the type of real-world outcomes since the post-launch of PIM. The data generated for PIM from the time of FDA approval to present is summarized in Figure 3 as a stepwise process to exhibit the type of data that supplements data produced during post-launch.

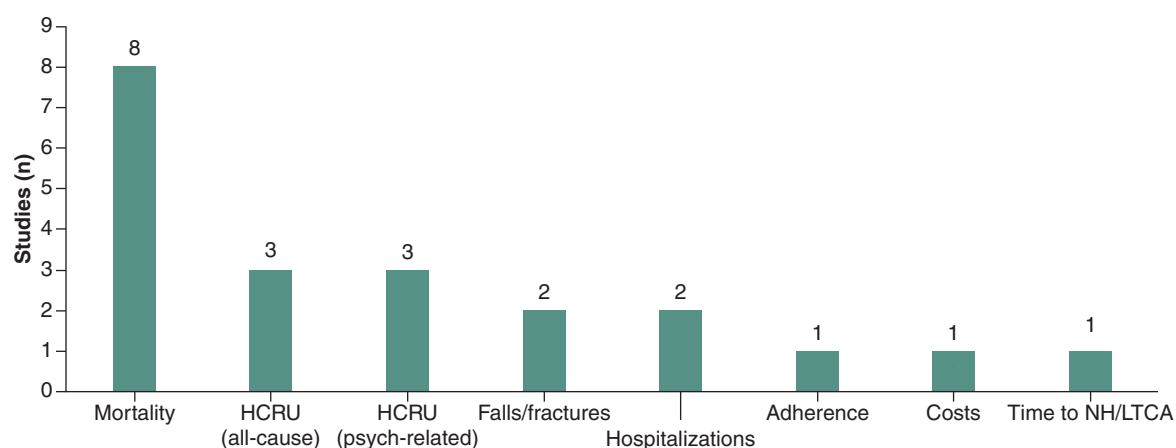
Eleven of the sixteen studies utilized Parts A, B, and D claims data from the Centers for Medicare and Medicaid Services (CMS) 100% Medicare sample of fee-for-service (FFS) beneficiaries, one study used 15% Medicare sample FFS data, two studies used a large US national commercial insurance plan (Optum), and the remaining two studies used electronic medical record (EMR) data from University of California San Diego medical center. In terms of comparators, six studies compared PIM versus other-AAPs, four studies compared PIM versus QUE, four compared both PIM versus QUE and other-AAPs, one study compared PIM-users versus non-PIM-users, one study compared PIM versus untreated patients and the last one compared PIM versus QUE and patients receiving PIM versus PIM in combination with QUE (Table 1). A total of 13 studies utilized propensity score matching, of which two were based on inverse probability of treatment weighing, and one based on standardized mortality

Table 1. Summary of real-world evidence studies to support the value of pimavanserin post-launch.

Study	Primary author, year	Matching method	Medications	Data source	Outcomes	Setting
1	Moreno GM, 2018	N/A	PIM vs QUE PIM + QUE	UCSD EMR Database	Clinical characteristics and mortality	Community
2	Hwang YJ, 2021	IPTW	PIM vs Non-User	100% Medicare Beneficiaries	All-cause hospitalizations and mortality	LTC
3	Pham Nguyen TP, 2021	N/A	PIM vs other-AAPs	Commercial Optum Database	Adherence: continuation vs discontinuation	Community
4	Mosholder AD, 2022	IPTW	PIM vs other-AAPs	100% Medicare Beneficiaries	All-cause mortality	Community
5	Layton JB, 2022	1:1	PIM vs other-AAPs	100% Medicare Beneficiaries	Incidence rates of falls or fractures or falls/fractures	Community & NH/LTC
6	Pham Nguyen TP, 2022	1:1 or 1:5 [†]	PIM vs other-AAPs (DRB-AAPs)	Commercial Optum Database	All-cause mortality	Community
7	Alipour-Haris G, 2023	SMWR	PIM vs QUE	15% Medicare Beneficiaries	All-cause hospitalizations and all-cause mortality	Community
8	Layton JB, 2023	1:1	PIM vs other-AAPs	100% Medicare Beneficiaries	All-cause mortality	Community & NH/LTC
9	Longardner K, 2023	N/A	PIM vs Untreated; PIM vs QUE	UCSD EMR Database	Clinical characteristics and all-cause mortality	Community
10	Rajagopalan K, 2023	1:1	PIM vs other-AAPs	100% Medicare Beneficiaries	All-cause and psych-related HCRU [†]	Community
11	Rajagopalan K, 2023	1:1	PIM vs QUE	100% Medicare Beneficiaries	All-cause and psych-related HCRU [†]	Community
12	Rajagopalan K, 2024	1:1	PIM vs QUE	100% Medicare Beneficiaries	Rates/risk/time to NH/LTCA	Community to NH/LTC
13	Rajagopalan K, 2024	1:1	PIM vs QUE; PIM vs other-AAPs	100% Medicare Beneficiaries	Risk of falls or fractures or falls/fractures	NH/LTC
14	Rajagopalan K, 2024	1:1	PIM vs QUE; PIM vs other-AAPs	100% Medicare Beneficiaries	All-cause and psych-related HCRU [†]	NH/LTC
15	Rajagopalan K, 2024	1:1	PIM vs QUE; PIM vs other-AAPs	100% Medicare Beneficiaries	Costs associated with SNF-stay and LTCA	NH/LTC
16	Rao S, 2025	1:1	PIM vs other-AAPs	100% Medicare Beneficiaries	All-cause mortality	Community & NH/LTC

[†]Inpatient, short-term stay, long-term care stay, skilled nursing facility stay, outpatient, office visits, emergency room visits; greedy matching.

AAP: Atypical antipsychotic; DRB-AAPs: Dopamine receptor blocking atypical antipsychotic; EMR: Electronic medical record; HCRU: Healthcare resource utilization; IPTW: Inverse probability of treatment weighing; LTCA: Long-term care admission; N/A: Not applicable; NH/LTC: Nursing home/long-term care; PIM: Pimavanserin; Psych: Psychiatric; QUE: Quetiapine; SMWR: Standardized mortality weighting ratio.

**Figure 2. Real world evidence study outcomes and number of studies.**

HCRU: Healthcare resource utilization; NH/LTCA: Nursing home/Long-term care admission; Psych: Psychiatric.

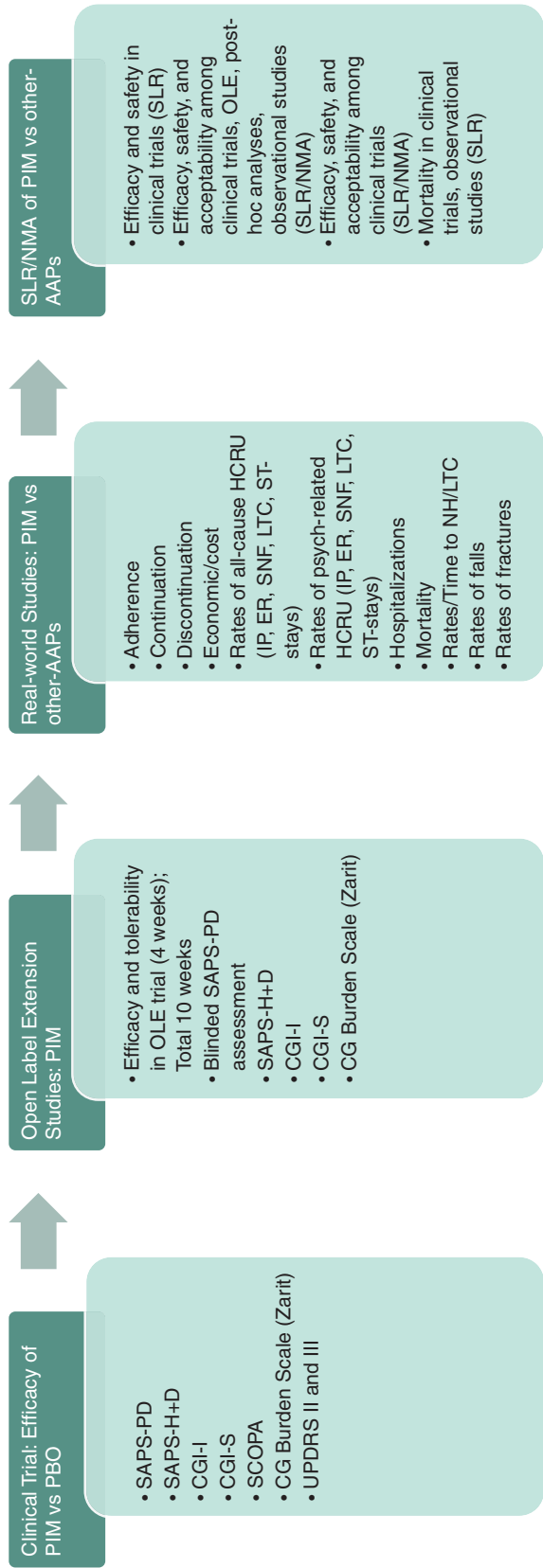


Figure 3. The evolution of data generation for the journey of pimavanserin from US FDA approval to post-launch.
AAP: Atypical antipsychotic; CG: Caregiver; CGI-I: Clinical global impression – improvement; CGI-S: Clinical global impression – severity; ER: Emergency room visit; H + D: Hallucinations and delusion; HCRU: Healthcare resource utilization; IP: Inpatient; LTC: Long-term care stay; NH: Nursing home; SNF: Skilled nursing facility stay; ST: Short-term stay; NMA: Network meta-analysis; OLE: Open label extension; PBO: Placebo; PIM: Pimavanserin; Psych: Psychiatric; SAPS: Scale for the assessment of positive symptom; SAPS-PD: Sum of nine item Parkinson’s disease-adapted SAPS; SCOPA: Scale for outcomes of Parkinson’s disease; SLR: Systematic literature review; UPDRS: Unified Parkinson’s disease rating scale.

Table 2. All-cause and psychiatric-related hospitalizations across different RWE studies (6 months and 12 months follow-up.).

Study, year [setting]	Medication (total n)	Follow-up time	Outcomes measured		
All cause hospitalizations			n (%)	aHR RR (95% CI)	Ref.
Alipour-Haris G, 2023 [community]	PIM (844)	6 months	177 (21.0)	aHR: 0.63 (0.52–0.77)	[15]
	QUE (2505)	6 months	894 (35.7)	REF	
	PIM (844)	12 months	258 (30.6)	aHR: 0.70 (0.60–0.83) [†]	
	QUE (2505)	12 months	1148 (45.8)	REF	
Rajagopalan K, 2023 [community]	PIM (842)	12 months	319 (37.8)	–	[16]
	Other-AAPs (842)	12 months	420 (49.8%) [†]	–	
Rajagopalan K, 2023 [community]	PIM (842)	12 months	319 (37.8)	RR: 0.78 (0.70–0.87) [†]	[17]
	QUE (842)	12 months	410 (48.6) [†]	REF	
Rajagopalan K, 2024 [NH/LTC]	PIM (1827)	6 months	29.8%	RR: 0.82 (0.75–0.90) [†]	[18]
	QUE (1827)	6 months	36.7% [†]	REF	
	PIM (1827)	6 months	29.8%	RR: 0.78 (0.71–0.86) [†]	
	Other-AAPs (1827)	6 months	37.7% [†]	REF	
Psychiatric-related hospitalizations					
Rajagopalan K, 2023 [community]	PIM (842)	6 months	81 (9.6%)	–	[16]
	Other-AAPs (842)	6 months	123 (14.6%) [†]	–	
Rajagopalan K, 2023 [community]	PIM (842)	12 months	81 (9.6%)	RR: 0.63 (0.48–0.82) [†]	[17]
	QUE (842)	12 months	129 (15.4%) [†]	REF	
Rajagopalan K, 2024 [NH/LTC]	PIM (1827)	6 months	8.8% [†]	RR: 0.71 (0.58–0.85) [†]	[18]
	QUE (1827)	6 months	12.6%	REF	
	PIM (1827)	6 months	8.8% [†]	RR: 0.67 (0.56–0.81) [†]	
	Other-AAPs (1827)	6 months	12.9%	REF	

[†] p < 0.05, statistically significant.
AAP: Atypical Antipsychotic; aHR: Adjusted hazard ratio; NH/LTC: Nursing home/Long-term care; PIM: Pimavanserin; QUE: Quetiapine; REF: Reference; RR: Relative risk.

[†]p < 0.05, statistically significant.

AAP: Atypical Antipsychotic; aHR: Adjusted hazard ratio; NH/LTC: Nursing home/Long-term care; PIM: Pimavanserin; QUE: Quetiapine; REF: Reference; RR: Relative risk.

ratio weighing. Majority of the studies utilized Medicare data from CMS, the federal insurance program for all individuals ≥ 65 years in the US. The Medicare data is likely to be representative of patients with PDP in the US since the median age of PD is 79.4 years [13], and approximately 50% of PD patients may be at risk of developing PDP during the course of their disease [14].

Outcomes & settings

Real-world outcomes of interest that were reviewed and evaluated among the sixteen studies were: clinical events (e.g., falls/fractures), treatment patterns (e.g., adherence), HCRU (e.g., all-cause and psychiatric hospitalizations, ER visits, etc.), length of stay (LOS) for HCRU, as well as rates or risk for SNF-stay, LTC-stay, LTCA (composite LTC + SNF), mortality; cost of SNF-stay, cost of LTC-stay and cost of LTCA (Table 1 & Figure 2). Overall, eight studies evaluated PDP patients within the community setting, four studies evaluated PDP patients within the NH/LTC setting and the remaining four studies evaluated PDP patients among both settings.

Healthcare resource utilization

Rates & risk of all-cause & psychiatric-related hospitalizations

Among the four studies that included all-cause and psychiatric-related hospitalizations, PDP patients on PIM had fewer hospitalizations versus other-AAPs and QUE in community and NH/LTC setting during 6 months and 12 months of follow-up, respectively (Table 2). Alipour-Haris *et al.* reported all-cause hospitalization rates to be lower for PIM versus QUE by 14.7% at 6 months and 15.2% at 12 months, respectively. Adjusted hazard ratios (aHR) for the risk of all-cause hospitalizations was 37% lower (aHR: 0.63, 95% CI: 0.52–0.77) and 30% lower (aHR: 0.70, 95% CI: 0.60–0.83) for PIM versus QUE at 6-months and 12-months follow-up, respectively [15]. Two studies by Rajagopalan *et al.* also showed PIM to have 12% and 11% lower rates of all-cause hospitalizations versus other-AAPs and versus QUE, respectively. PIM showed 22% lower risk of all-cause hospitalization versus QUE [16,17]. Similar results were also observed among PDP patients residing in the NH/LTC setting where PIM

Table 3. Rates and risk of other healthcare resource utilization outcomes for Medicare studies with 100% beneficiaries.

Study outcomes	Rajagopalan K, 2023 [16]		Rajagopalan K, 2023 [17] Rajagopalan K, 2024 [‡] [19]		Rajagopalan K, 2024 [18]		
All cause visits	PIM	Other-AAPs	PIM	QUE	PIM	Other-AAPs	QUE
n	842	842	842	842	1827	1827	1827
Emergency room visits, n (%)	519 (61.6%)	584 (69.4%) [†]	519 (61.6%)	572 (68.0%) [†]	864 (47.3%)	1013 (55.5%) [†]	1020 (55.8%) [†]
LTCA [composite LTC + SNF], n (%)	–	–	196 (23.2%)	285 (33.8%) [†]	–	–	–
Time to first LTCA, mean days (SD) [‡]	–	–	161 (113) [‡]	141 (111) [‡]	–	–	–
Hazard ratio (95% CI) of LTCA [‡]	–	–	0.80 (0.66–0.97)	REF	–	–	–
LTC-stay, n (%)	52 (6.2%)	57 (6.8%)	52 (6.2%)	47 (5.6%)	81 (4.4%)	120 (6.6%) [†]	113 (6.2%) [†]
Time to first LTC-stay, mean days (SD) [‡]	–	–	157 (111) [‡]	143 (102) [‡]	–	–	–
LTC-stay, LOS, median days (IQR)	9.93 ± 6.59	10.69 ± 8.42	9.93 ± 6.59	11.49 ± 7.23	–	–	–
Office visits, n (%)	814 (96.6%)	783 (93.0%) [†]	814 (96.6%)	793 (94.2%) [†]	–	–	–
Outpatient visits, n (%)	777 (92.2%)	776 (92.2%)	777 (92.2%)	766 (91.0%)	–	–	–
SNF-stay, n (%)	170 (20.2%)	267 (31.8%) [†]	170 (20.2%) [‡]	265 (31.4%) ^{‡,†}	316 (17.3%)	421 (23.0%)	413 (22.6%)
SNF-stay, LOS, mean days ± SD	36.27 ± 44.20	41.96 ± 64.89	36.27 ± 44.20	45.51 ± 67.59 [†]	–	–	–
Time to first SNF-stay, mean days (SD) [‡]	–	–	165 (113) [‡]	140 (111) [‡]	–	–	–
ST-stay, n (%)	286 (34.0%)	389 (46.2%) [†]	286 (34.0%)	383 (45.5%) [†]	466 (25.5%)	587 (32.1%)	590 (32.3%)
ST-stay, LOS, mean days ± SD	5.43 ± 5.45	6.48 ± 6.65 [†]	5.43 ± 5.45	6.37 ± 7.02 [†]	–	–	–
Psychiatric-related visits							
Emergency room visits, n (%)	43 (5.2%)	86 (10.2%) [†]	43 (5.2%)	81 (9.6%) [†]	74 (4.1%)	146 (8.0%)	142 (7.8%)
LTC-stay, n (%)	11 (1.4%)	11 (1.4%)	11 (1.4%)	11 (1.4%)	19 (1.0%)	34 (1.8%)	30 (1.6%)
Office visits, n (%)	494 (58.6%)	269 (32.0%) [†]	494 (58.6%)	285 (33.8%) [†]	–	–	–
Outpatient visits, n (%)	154 (18.2%)	182 (21.6%)	154 (18.2%)	186 (22.0%)	–	–	–
SNF-stay, n (%)	40 (4.8%)	52 (6.2%)	40 (4.8%)	58 (6.8%)	91 (4.9%)	109 (5.9%)	113 (6.2%)
ST-stay, n (%)	46 (5.4%)	80 (9.6%) [†]	46 (5.4%)	76 (9.0%) [†]	76 (4.2%)	125 (6.8%)	122 (6.7%)

† p < 0.05.

[‡] Rajagopalan K, 2024 is the study that has time to LTCA, time to LTC-stay, or time to SNF-stay.

AAP: Atypical Antipsychotic; IQR, Inter-quartile range; LTC-stay: Long-term care stay; LTCA: Long-term care admission; LOS: Length of stay; PIM: Pimavanserin; QUE: Quetiapine; SD: Standard deviation; SNF-stay: Skilled nursing facility stay; ST-stay: Short-term stay.

showed approximately 8% lower rates of all-cause hospitalization versus QUE and versus other-AAPs within 6 months. The risk for all-cause hospitalizations was lower for PIM versus QUE by 18% (RR: 0.82, 95% CI: 0.75–0.90) and PIM versus other-AAPs by 22% (RR: 0.78, 95% CI: 0.71–0.86) [18]. Results for psychiatric-related hospitalizations trended the same for PIM versus other-AAPs and QUE. Across all the studies mentioned in Table 2, PIM exhibited that the risk of all-cause and psychiatric-related hospitalizations were significantly lower versus other-AAPs and versus QUE among community and NH/LTC settings [15–18].

Rates, risk, time & LOS of other HCRU outcomes

Four studies examined the rates, risk of LTCA, time to LTCA/LTC/SNF, and LOS among PDP patients on PIM versus other-AAPs or versus QUE (Table 3). Of these, three studies evaluated PDP patients in the community setting and one among NH/LTC setting [16–19]. Comparatively, PIM had lower all-cause rates of ER visits, SNF-stay, and ST-stay, LTC-stay and LTCA across all the studies versus other-AAPs and versus QUE. There was a 20% lower risk for LTCA for PDP patients on PIM versus QUE. A delay in being admitted to LTCA, LTC-stay, SNF-stay and ST-stay for PDP patients on PIM versus QUE was also observed. Additionally, the mean LOS for these stay types was lower for PIM versus other-AAPs and versus QUE. Furthermore, psychiatric-related ER visits, IP visits (including ST-stay, SNF-stay and LTC-stay) and outpatient visits were lower for PIM versus other-AAPs and versus QUE (Table 3). However, higher all-cause office visits and psychiatric-related office visits were seen with PIM versus other-AAPs (or versus QUE), which could be suggestive with closer management of psychosis associated with PD [17]; this is aligned with usual care practices.

Table 4. Real-world clinical outcomes (adherence, falls and fractures).

Study, year [setting]	Medication (total n)	Adherence outcomes					
		DC within 6 months, n (%)	Median time to DC, Days (min, max)	Adjusted HR (95% CI)			
Pham Nguyen TP, 2021 [community] [20]	Overall (3566)	1376 (38.58)	–	–			
	PIM (153)	35 (22.90%)	168 (71–213)	REF			
	QUE (2452)	960 (39.20%)	96.5 (44–203)	1.76 (1.40–2.20)			
	Aripiprazole (169)	69 (40.80%)	85 (44–190)	2.15 (1.61–2.86)			
	Risperidone (462)	195 (42.20%)	72 (44–186)	2.12 (1.66–2.72)			
	Olanzapine (304)	111 (36.50%)	78 (44–193.5)	2.07 (1.60–2.67)			
Study, year [setting]	Medication (total n)	Falls /fractures outcomes					
		Falls		Fractures		Composite (fall and/or fractures)	
		n (%)	IRR (95% CI) RR (95% CI)	n (%)	IRR (95% CI) RR (95% CI)	n (%)	IRR (95% CI) RR (95% CI)
Layton JB, 2022 [community and NH/LTC] [21]	PIM (108)	8 (7.41%)	IRR:0.88 (0.33–2.15)	1 (0.92%)	IRR: 0.31 (0.01–2.56)	8 (7.41%)	IRR: 0.71 (0.27–1.67)
	Other-AAPs (216)	17 (7.87%)	REF	6 (2.78%)	REF	21 (9.72%)	REF
Rajagopalan K, 2024 [NH/LTC] [22]	PIM (1005)	46 (4.58%)	RR: 0.55 (0.39–0.79)	14 (1.39%)	RR: 0.74 (0.37–1.46)	57 (5.67%)	RR: 0.59 (0.43–0.81)
	QUE (1005)	83 (8.26%)	REF	19 (1.89%)	REF	96 (9.55%)	REF
	PIM (1005)	46 (4.58%)	RR: 0.60 (0.42–0.85)	14 (1.39%)	RR: 0.67 (0.34–1.30)	57 (5.67%)	RR: 0.63 (0.46–0.86)
	Other-AAPs (1005)	77 (7.66%)	REF	21 (2.09%)	REF	91 (9.05%)	REF

AAP: Atypical antipsychotic; CI: Confidence interval; DC: Discontinuation; HR: Hazard ratio; IRR: Incident rate ratio; NH/LTC: Nursing home/long-term care; PIM: Pimavanserin; QUE: Quetiapine; RR: Relative risk; REF: Reference.

Adherence rates

One retrospective cohort study utilizing data from commercially insured individuals (Optum 2001–2019) in the US evaluated AAPs discontinuation rates among patients ($n = 3566$) with PDP. Approximately 61.4% continued their first AAPs treatment (i.e., QUE, aripiprazole, risperidone, olanzapine, clozapine and PIM) versus 38.6% discontinued treatment within the first 6 month (Table 4). The aHR indicated increased risk of discontinuation for QUE (aHR: 1.76, 95% CI: 1.40–2.20), aripiprazole (aHR: 2.15, 95% CI: 1.61–2.86), risperidone (aHR: 2.12, 95% CI: 1.66–2.72) and olanzapine (aHR: 2.07, 95% CI: 1.60–2.67) compared with PIM (Table 4) [20].

Falls & fractures

The incidence of falls and fractures outcomes were reviewed among two studies [21,22]. Layton *et al.* (2022) evaluated the incident rate ratio (IRR) for those with falls, fractures and as a composite outcome (fall and/or fractures) in patients with PDP residing in the community and NH/LTC setting, while Rajagopalan *et al.* (2024), evaluated patients with PDP in the NH/LTC setting. The matched IRR across all three outcomes in Layton *et al.*, (2022) study showed that PIM had lower rates of falls (IRR: 0.88, 95% CI: 0.33–2.15), fractures (IRR: 0.31, 95% CI: 0.01–2.56) or composite (IRR: 0.71, 95% CI: 0.27–1.67). This result suggests that PIM does not increase falls or fractures among PDP patients when compared with other-AAPs [21]. Among residents in NH/LTC setting, PDP patients on PIM versus QUE or versus other-AAPs reported 45% and 40% lower observed risk of falls, respectively. Similar results were seen for fractures where lower risk of fractures for PIM versus QUE versus other-AAPs were 26% and 33%, respectively. Lastly, the risk of composite fall or fracture was 41% lower for PIM versus QUE and 37% lower for PIM versus other-AAPs (Table 4) [22].

Mortality

Over the last two decades, all FDA-approved AAPs including PIM carry a product black box warning for increased mortality in elderly patients with dementia related psychosis. Notwithstanding the black-box warning, literature suggests that PIM may carry a lower observed risk of mortality compared with other-AAPs. In this review of the real-world literature, a total of eight studies examined mortality outcomes with PIM versus various comparators (QUE, other-AAPs, untreated). We found that seven out of eight studies [15,21,23–28] reported significantly lower

mortality risk versus other-AAPs while mortality risk was numerically lower in some instances (Table 1). However, one study by Hwang *et al.* (2021) reported higher mortality risk among PIM users versus non-PIM users in LTC setting [23]. The Hwang *et al.* (2021) analyses compared a control group of non-PIM users with PD which included untreated patients and did not adjust for several confounding factors that were established contributors to increased mortality risk (e.g., underlying psychosis, disease duration, disease severity and age at onset of symptoms). Additionally, the PIM user group were allowed to be on concomitant AAPs treatment, potentially biasing the results. Notwithstanding this, findings from these retrospective studies of mortality should be interpreted with caution since they were not designed or powered to make direct safety comparisons between AAPs. Additionally, they were not intended to show an independent treatment effect of product on survival. Overall, it is found that PIM did not increase the mortality risk in PDP, and the mortality risk appeared to be comparable to or lower than other-AAPs prescribed for PDP, including QUE.

Cost avoidance

In total, one study examined cost-savings of PIM versus QUE or versus other-AAPs due to fewer SNF-stay or LTCA among patients with PDP. Prior data showed lower rates of HCRU outcomes that helped to quantify the cost-savings within the healthcare system. This cost-offset analysis found the mean per patient per year costs savings due to lower SNF-stay rehabilitation and resident-related expenses with PIM versus QUE and versus other-AAPs were \$23,364 and \$23,856, respectively. Similarly, mean per patient per year cost savings due to lower LTCA rehabilitation and resident-related expenses with PIM versus QUE and versus other-AAPs were \$22,134 and \$23,609, respectively [29].

Discussion

Traditionally, RCTs have been the gold standard for establishing the safety and efficacy, and to obtain the FDA approval of drugs and technologies. However, the US FDA and regulators around the world have become open to the idea of utilizing RWD in drug applications where it can complement clinical data and accelerate the drug process. This evolution in regulatory thinking potentially occurred due to the confluence of several factors: difficulty in RCT patient recruitment, increased availability of secondary data, and innovations in study designs that allow indirect comparisons of secondary data either as historical or synthetic control arms, etc. As a result, the Cures Act was codified into law in December 2016 requiring the FDA to provide guidance to the industry to help bring new and innovative medical products to market faster using RWE.

There are several important insights from this review we would like to highlight. First, this review of RWE studies of PIM is a great example of how real-world studies can complement clinical trial evidence and augment our understanding of treatment patterns and long-term outcomes in clinical practice. To date, PIM is the only FDA-approved therapy for patients with PDP in the US based on demonstrated efficacy in treating symptoms of hallucinations and delusions from a clinical trial [1]. A few years after launch of PIM, two studies published by Isaacson *et al.* [3,4] added new trial data to support the use of PIM with longer follow-up with an additional 10 weeks of PIM in an open label study. The first real-world study of PIM was published by Moreno *et al.* (2018), approximately 2 years post-launch of PIM [24]. Second, the real-world analyses in this review of PDP patients highlighted multiple advantages of PIM versus off-label AAPs (i.e., QUE) in usual care noncontrolled settings. Overall, the key message from these studies have a consistent trend in results where PIM exhibited longer time to NH/LTC placement and had lower reported risk of NH/LTC placement, lower all-cause HCRU outcomes and lower psychiatric-related HCRU outcomes. Additionally, when compared with other-AAPs including QUE, PIM reported fewer falls and fractures, better adherence measures, and lower risk of mortality among PDP patients residing in the community and NH/LTC setting. These long-term findings cannot be studied in short-term and highly controlled designs, such as clinical trials, thus the need for RWE studies is essential. Third, PIM treatment among patients with PDP consistently resulted in greater benefits compared with other-AAPs such as QUE across a range of outcomes (e.g., adherence, falls/fractures, HCRU, mortality, etc.) despite differences in the setting (e.g., community, NH/LTC) and data sources (e.g., Medicare, commercial). While this review focused on data from real-world comparative database studies, evidence generated from other research involving systematic literature reviews, meta-analysis or network meta-analysis is increasingly being incorporated with observational data alongside clinical trials (Figure 2) [30–32]. All these studies are valuable for clinical and formulary decision-making by enabling comparative effectiveness analysis of various drug treatments.

Another important highlight to discuss is PIM's unique mechanism of action and how there could be a potential linkage to observed outcomes in this review. For example, PIM's lack of D2 antagonism likely contributes to

preserved motor function and reduced fall risk, while its selective serotonergic activity appears sufficient for managing psychosis without impairing mobility or cognition. This pharmacological distinction is especially important in PDP, where baseline motor function is already compromised. Real-world studies consistently report reduced healthcare utilization, lower rates of institutionalization, and decreased mortality among individuals receiving PIM. These outcomes align with its mechanism of action and reinforce the biological plausibility of its clinical benefits. Collectively, the evidence suggests that PIM may support functional independence and help individuals with PDP remain in community settings.

This targeted review also indicates that most studies included the Medicare population, thereby increasing the generalizability of findings to the PDP population. It should be noted that over 90% of the patients diagnosed with PD are over 65 years of age, the age at which Medicare becomes the primary insurer [33]. The median age of PDP onset is estimated to be approximately 79 years [13,34], whereas the average time of progression from PD to PDP occurs nearly a decade later [13,34,35]. Therefore, the authors believe this analysis of patients ≥ 65 years of age from Medicare claims is generalizable to the overall PDP population in the US. Another database identified in this review, was Optum's de-identified Clinformatics® Data Mart data. Optum is a large-scale commercially insured healthcare claims data from persons across the United States and represents a diverse pool of PDP patients to evaluate treatment adherence and mortality [20,25]. Lastly, data from the two studies conducted using the USCD, a medical center database with an EMR system with chart notes, allowed researchers to further confirm the findings from other claims database studies [24,26]. While the clinical trials of PIM increased the internal validity of findings in establishing treatment effects, these RWE studies support the use of PIM in broader and generalizable populations seen in usual clinical care settings.

Healthcare providers, population health decision makers and payors often utilize patient health status assessments in their daily practices that are different from efficacy end points in clinical trials. Thus, surrogate markers of clinical trial end points are often identified as a proxy measure of effectiveness in real-world database studies. One key example is how hallucinations and delusions are assessed differently in clinical trials versus real-world settings. In trials, the Scale for the Assessment of Positive Symptoms-Hallucinations and Delusions (SAPS-H + D) is often used as a standardized end point. However, in real-world studies, outcomes such as psychiatric-related visits identified using diagnosis codes may be used as a surrogate marker to show the effect of improved symptoms. Both types of outcomes measure symptom improvements and associated benefits of PIM in different ways, one focusing on direct symptom assessment to establish treatment efficacy while the other focuses on healthcare burden, potentially because of the potential impact on symptoms.

Limitations

This targeted review of observational studies also carries the inherent limitations of RWE using data sources with intrinsic limitations. Thus, the limitations of the targeted review also must be addressed in the context of the underlying limitations of the RWE studies that comprised it when interpreting the findings. RWE/observational claims studies (i.e., Medicare, commercial insurance), are subject to limitations related to claims data quality (i.e., miscoding or under coding) and the potential for confounding factors that are not observable in such data. As acknowledged in the individual publications, residual confounding may exist due to potentially unobservable variables. For example, it is possible that patients initiating PIM may be more likely to be managed by movement-disorders or dementia specialists, have better care coordination, and face fewer access barriers (e.g., prior authorization support, formulary navigation). It is also possible that these factors can independently reduce hospitalizations, emergency visits and long-term care placement and may not be fully captured by claims-based covariates.

While we conducted a targeted literature review of comparative RWE studies of PIM, pooled quantitative analysis (e.g., network meta-analysis) was not considered given variability in the type of comparators, outcomes and follow-up period. Furthermore, this qualitative review may include overlapping cohorts; therefore, quantitative indirect treatment comparisons were not conducted. It is also possible that selection bias due to the non-inclusion of published abstracts may exist in this review of the literature. However, we believe that the selection bias will be minimal since most of the publications in this review include information presented in published abstracts. Notwithstanding the potential limitations mentioned above, this descriptive synthesis of the RWE studies of PIM provides greater insights about the potential benefits of PIM as a treatment for PDP among various care settings.

RWE observational studies are more prone to biases as data from EMRs or insurance claims may be incomplete or inaccurate, and the lack of randomization makes it challenging to establish causality. While most studies included in this review are the Medicare population, it should be acknowledged that the results may not be fully applicable to

younger individuals, under-insured or other groups with different demographic and socioeconomic characteristics. Additionally, RWE studies often rely on retrospective data, which may not capture all relevant clinical details. Lastly, findings related to potential cost savings should be interpreted with caution, as they are derived from a single cost-offset model and represent modeled savings rather than findings from a formal cost analysis. Despite these limitations, RWE offers understanding of PIM's impact among PDP patients in usual clinical practice.

Conclusion

Across various real-world studies evaluating PIM as a treatment for PDP, findings suggest that PIM is consistently associated with lower rates of hospitalization, institutionalization (LTCA), falls, fractures and mortality, along with improved treatment compliance compared with off-label AAPs, including QUE. These differences may also be associated with cost savings to the healthcare system since fewer PDP patients on PIM may be admitted to LTC or SNF, resulting in a calculated cost-offset with PIM versus other-AAPs. Overall, these findings suggest that PIM's benefits are consistent with the findings of the clinical trials and may also translate into HCRU and economic benefits in real-world settings. These findings may further help reinforce the symptom-related efficacy demonstrated in clinical trials and underscore the importance of RWE studies to guide treatment strategies among patients with PDP.

Summary points

- Pimavanserin (PIM) is the only US FDA-approved medication for treating hallucinations and delusions in people with Parkinson's disease psychosis (PDP).
- Other antipsychotic drugs, such as quetiapine, are often used off-label, but may worsen Parkinson's motor symptoms.
- This article reviews 16 real-world evidence studies that compare PIM to these other off-label medications.
- RWE studies use data from routine clinical practice, like insurance claims and electronic health records, to provide insights not captured in clinical trials.
- The review found that PIM was associated with fewer hospitalizations and emergency room visits compared with other treatments.
- Patients on PIM also had a lower risk of falls and fractures, which is a significant concern for people with Parkinson's.
- The studies showed that patients were more likely to remain on PIM, suggesting better treatment adherence.
- Treatment with PIM was linked to a lower risk of mortality compared with other antipsychotics.
- These positive health outcomes translated into significant cost savings for the healthcare system, primarily by reducing the need for long-term care and hospital stays.
- The findings from these real-world studies reinforce the benefits of PIM seen in clinical trials and are a valuable resource for guiding treatment decisions.

Author contributions

Authors N Rashid, I Yunusa, D Doshi, V Yakkala and K Rajagopalan were responsible for study conception and design; authors N Rashid, I Yunusa, D Doshi, V Yakkala, D Gopal, V Abler and K Rajagopalan were responsible for analysis and interpretation of the data. All authors contributed to drafting or critically reviewing the manuscript, approved the final version and accepted accountability for all aspects of the work.

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Competing interests disclosure

N Rashid, D Doshi and V Abler are employees of Acadia Pharmaceuticals. I Yunusa is an Assistant Professor at the College of Pharmacy, University of South Carolina, Columbia, SC, USA. V Yakkala, D Gopal and K Rajagopalan are employees of Anlitiks Inc., a company that received funding from Acadia Pharmaceuticals to conduct this study. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

No funded writing assistance was utilized in the production of this manuscript.

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