MICRO REPORT

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Baseline risk characterization of early versus later adopters of long-acting paliperidone palmitate formulations

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Abstract

Early Post-Marketing Phase Vigilance (EPPV) is a unique system that encourages reporting of serious adverse reactions for medications newly introduced to Japan. When a once-monthly paliperidone palmitate formulation (PP1M) was introduced in Japan in 2013, EPPV detected a signal of increased mortality, but this signal was not subsequently confirmed. To clarify whether that signal reflected increased adverse event reporting or an atypically high baseline mortality risk among early adopters of PP1M, we evaluated the baseline risk characteristics of early, mid, and later adopters of PP1M in a Japanese database and did a similar evaluation of PP1M and the three-monthly formulation (PP3M) in two US databases. In Japan, early adopters compared with later adopters were older (mean 39.16 vs 33.70 years) but had a lower proportion of male patients (32.0% vs 44.44%), and a lower mean number of antipsychotic medications (distinct active medical substances) other than paliperidone (2.62 vs 2.85). In the United States, the baseline characteristics of early adopters of PP1M and PP3M did not suggest higher mortality risk than later adopters. These results offer no convincing evidence that the unconfirmed early signal of increased mortality with PP1M was due to increased baseline mortality risk among early adopters.

KEYWORDS
baseline characteristics, differences, early adopters, long-acting paliperidone

1 | INTRODUCTION

Early Post-Marketing Phase Vigilance (EPPV) is a unique system that encourages reporting of serious adverse reactions for medications newly introduced to Japan among patients who took these medications within 6 months of their introduction in Japan. Following the introduction in Japan of once-monthly paliperidone palmitate (PP1M) for the treatment of schizophrenia,[1,2] the

EPPV identified 32 deaths among an estimated 11000 exposed patients.[3] Although this reporting rate (5.84/1000 person years) was consistent with mortality rates observed during clinical studies and in population-based observational cohorts (10.2/1000 person-years),[3] it represented a safety signal as it was higher than the reporting rates found after PP1M was introduced globally and in the United States (0.38 and 0.43 cases/1000 person-years, respectively).[3] However, this signal was not confirmed and thus was

attributed to a combination of increased reporting and adverse mortality risk characteristics that were observed among the reported fatalities. These included increased age, cardiovascular risks, and antipsychotic polypharmacy of the fatalities among the early adopters of PP1M.[3] The relative importance of increased reporting and adverse risk characteristics among all early adopters (rather than only those who died) was not ascertained. Therefore, the current study compared the baseline characteristics of early, mid, and later adopters of PP1M in Japan. To determine whether similar findings, that is, baseline differences in mortality risk between early and later adopters of this medication were observed outside of Japan with another long-acting paliperidone formulation, PP3M (paliperidone palmitate for administration every 3 months), similar comparisons were done for early, mid, and later adopters of PP1M and PP3M in two US databases.

2 | METHODS

Early, mid, and later adopters were defined as patients who began using the long-acting formulations within 6, 7–12, or 13–24 months of introduction of those formulations to the market, respectively. We used data from the Japan Medical Data Center (JMDC), a payer-based database that has collected claims from more than 250 payers and covers workers and their dependents and from two US databases: The IBM MarketScan® Multi-State Medicaid (MDCD) database representing Medicaid programs in numerous geographically dispersed states and the Optum® De-Identified Clinformatics® Data Mart Database – Date of Death (Optum), representing administrative health claims for members of large commercial and Medicare Advantage health plans. All databases were standardized to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM), version 5.3.1.[4-6] PP3M was introduced in Japan in September 2020 and those data in JMDC were not yet available for the current study.

For each paliperidone formulation and database, patients entered the study cohort when first dispensed either PP1M or PP3M. That dispensing date was the patient's index date. Patients were excluded if they had no diagnosis of schizophrenia before or on their index date, did not have 180 days of observable time prior to their index date, or had an index date >24 months after the formulation became available. Data collected for the 180 days before the index date included age, sex, hospitalizations, antipsychotic medications dispensed, and, for the entire medical history, the Charlson Comorbidity Index (CCI, Romano adaptation; Table 1).[7] Balance between early and mid-adopters and between early and later adopters was assessed using standardized mean differences (SMDs). An SMD >0.1 was used as an ad hoc criterion for a substantial difference.[8,9] The data that support the findings of this study are available for licensing from IBM at https://www.ibm.com/products/marketscan-research-databases, from Optum at https://www.optum.com/business/solutions/life-sciences/real-world-data.html and from JMDC at https://www.jmdc.co.jp/en/jmdc-claims-database. The

New England Institutional Review Board determined that studies conducted in MDCD and OPTUM_DOD were exempt from study-specific Institutional Review Board review, as these studies do not qualify as human subject research. For JMDC, the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects, Part 3, Scope of Application (Chapter 1) state that the guidelines do not apply to studies conducted using only "anonymously processed information or unidentifiably-processed personal information which has already been created."[10]

Though mid-adopters were included for completeness, this report focuses on the contrast between early and later adopters because later adopters are more representative of the patients who use the medication throughout its history.

3 | RESULTS

3.1 | PP1M

Among patients qualifying for the study in JMDC (n = 87), the substantial baseline differences, that is, the differences with an SMD >0.10 when comparing early adopters to later adopters of PP1M were: The early adopters had a lower proportion of males (32.00% vs 44.44%), and a lower mean number of antipsychotic medications (distinct active medical substances) other than paliperidone (2.62 vs 2.85) dispensed in the 180 days before their index date, that is, recent antipsychotic medications, but were older (mean age 39.16 vs 33.70 years). The first two of these favored a lower mortality among early adopters and the third favored the opposite. Compared with later adopters, early adopters also had a lower proportion hospitalized during the 180 days before their index date and slightly lower mean CCI, but the SMDs for these variables were ≤0.1 (Table 1).

Among patients qualifying for the study in MDCD, there were no substantial differences between early and later adopters. Among those in Optum the substantial baseline differences when comparing early adopters to later adopters of PP1M were lower CCI (1.44 vs 2.10, lower mean age (46.59 vs 48.94 years), lower proportion with recent hospitalizations (26.47% vs 59.30%), but a higher mean number of recent antipsychotic medications (2.09 vs 1.80). The first three of these differences favored lower mortality among early adopters and the last favored the opposite.

Comparing early adopters to mid adopters, in JMDC, the number of mid adopters was small (N = 10) and the substantial differences were that the early adopters had: A lower mean CCI (0.78 vs 1.30), a lower proportion with recent hospitalizations (32.00% vs 50.00%), a higher proportion of men (32.00% vs 20.00%), and a higher mean number of recent antipsychotic medications (2.62 vs 1.80). The first two of these differences favored a lower mortality among early adopters and the last two favored the opposite. In MDCD, there were no substantial differences between the early adopters and the mid-adopters and most of the small differences favored lower mortality in the early adopters. In Optum,

TABLE 1 Selected baseline characteristics of the study patients

Database	Covariate[a]	Early adopters Mean or %	Mid adopters Mean or %	Early vs mid SMD	Later adopters Mean or %	Early vs later SMD
PP1M						
JMDC	N	50	10		27	
	CCI (SD)	0.78 (1.23)	1.30 (1.52)	**0.2661**	0.93 (1.19)	0.0853
	Age (years)	39.16 (11.48)	39.60 (11.04)	0.0276	33.70 (9.52)	**0.3658**
	Men (%)	32.00%	20.00%	**0.1623**	44.44%	**0.1403**
	Hospitalization (%)	32.00%	50.00%	**0.1923**	37.04%	0.0600
	Antipsychotics[b] (SD)	2.62 (1.56)	1.80 (0.79)	**0.4682**	2.85 (1.32)	**0.1133**
MDCD	N	500	493		770	
	CCI (SD)	1.34 (2.06)	1.49 (2.20)	0.0488	1.65 (2.36)	0.0981
	Age (years)	39.30 (12.64)	40.12 (2.58)	0.0461	40.54 (13.07)	0.0684
	Men (%)	59.40%	62.47%	0.0278	57.66%	0.0160
	Hospitalization (%)	31.80%	27.99%	0.0492	38.31%	0.0777
	Antipsychotics (SD)	1.70 (1.10)	1.71 (1.04)	0.0039	1.62 (1.13)	0.0525
Optum	N	34	42		86	
	CCI (SD)	1.44 (1.25)	2.48 (2.71)	**0.3463**	2.10 (2.16)	**0.2652**
	Age (years)	46.59 (12.31)	48.21 (13.96)	0.0873	48.94 (13.16)	**0.1306**
	Men (%)	52.94%	52.38%	0.0054	51.16%	0.0173
	Hospitalization (%)	26.47%	42.86%	**0.1943**	59.30%	**0.3515**
	Antipsychotics (SD)	2.09 (0.97)	1.79 (1.12)	**0.2050**	1.80 (1.18)	**0.1879**
PP3M						
MDCD	N	377	540		715	
	CCI (SD)	1.75 (2.32)	1.79 (2.54)	0.0108	1.82 (2.39)	0.0211
	Age (years)	40.33 (13.07)	41.25 (12.57)	0.0508	41.19 (13.45)	0.0462
	Male (%)	67.64%	68.15%	0.0044	63.36%	0.0374
	Hospitalization (%)	16.98%	11.85%	0.0953	13.99%	0.0537
	Antipsychotics (SD)	1.55 (0.85)	1.35 (0.94)	**0.1640**	1.38 (0.86)	**0.1474**
Optum	N	62	49		51	
	CCI (SD)	2.27 (2.43)	2.10 (2.29)	0.0515	2.84 (2.49)	**0.1635**
	Age (years)	48.39 (12.43)	47.02 (13.60)	0.0742	48.82 (14.04)	0.0233
	Men (%)	62.90%	67.35%	0.0386	54.90%	0.0731
	Hospitalization (%)	16.13%	14.29%	0.0331	17.65%	0.0259
	Antipsychotics (SD)	1.66 (0.85)	1.78 (0.80)	0.0981	1.67 (0.95)	0.0042

Note: Values expressed as mean (SD) unless mentioned otherwise; SMD >0.1 are denoted in bold.

Abbreviations: CNS, central nervous system; CCI, Charlson Comorbidity Index; JMDC, Japan Medical Data Center; MDCD, IBM MarketScan® Multi-State Medicaid; N: counts of subjects; PP1M, once-monthly paliperidone palmitate; PP3M, three-monthly paliperidone palmitate; SD, standard deviation; SMD, standardized mean difference.

[a]Covariates other than the CCI were assessed for the 180 days prior to (≤) cohort entry. The CCI was assessed for all time prior to cohort entry. The mean number of antipsychotics was calculated without the inclusion of paliperidone.

[b]The number of antipsychotics is the number of antipsychotic ingredients other than paliperidone that the patient received in the 180 days prior to (≤) cohort entry.

the substantial differences between early and mid-adopters were lower CCI (1.44 vs 2.48) and a lower proportion with recent hospitalizations (26.47% vs 42.86%), but a higher mean number of recent antipsychotic medications (2.09 vs 1.79). The first two of these differences favored a lower mortality among early adopters and the last one favored the opposite.

3.2 | PP3M

Among patients in MDCD, the only substantial differences between early adopters of PP3M and mid adopters or later adopters were that the mean number of antipsychotics used in the 180 days before the index date was higher among the early adopters (1.55 vs 1.35

and 1.55 vs 1.38, respectively). In Optum, the only substantial differences between early adopters and mid adopters or later adopters of PP3M was that early adopters and mid adopters had a lower mean CCI than later adopters.

4 | DISCUSSION

As suggested by Pierce et al. based on the fatal cases, the early adopters of PP1M in JMDC were substantially older than the later adopters.[3] However, the proportion of men among early adopters was substantially lower than the proportion of men among the later adopters and this partially offset the increased mortality risk due to age (Japan Ministry of Health, Labour and Welfare)[11] as did the substantially lower mean number of antipsychotic medications and, though they carried an SMD <0.1, the slightly lower mean CCI and the slightly lower proportion hospitalized. Thus, the findings from JMDC do not provide compelling evidence for a difference in baseline mortality risk. For the US databases, there were no substantial differences in patient baseline characteristics between early and later adopters in MDCD and of the three baseline characteristics with SMDs >0.10 in Optum, three (lower mean CCI, lower mean age, and lower proportion recently hospitalized) suggested lower mortality risk among the early adopters.

A major limitation of the present study was the modest number of exposed subjects. Thus, it would be useful for a future study to do a similar comparison of early vs later adopters in a database where the number of exposed subjects is larger.

In conclusion, the results of the present study do not support the view that early adopters of PP1M in Japan or early adopters of PP1M or PP3M in the United States had a higher baseline mortality risk than later adopters.

https://www.jmdc.co.jp/en/jmdc-claims-database. The New England Institutional Review Board determined that studies conducted in MDCD and OPTUM_DOD were exempt from study-specific Institutional Review Board review, as these studies do not qualify as human subject research. For JMDC, the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects, Part 3, Scope of Application (Chapter 1) state that the guidelines do not apply to studies conducted using only "anonymously processed information or unidentifiably-processed personal information which has already been created"

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