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Supplementary Material

Article Title: Does Half-Life Matter After Antipsychotic Discontinuation? A Relapse Comparison in Schizophrenia With 3 Different Formulations of Paliperidone

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eAppendix 1

Paliperidone Dosing Regimens

The paliperidone dosing regimens used in the 3 studies are described in **Supplementary eTable 2**. The daily dose range in the ORAL paliperidone study was 3 mg to 15 mg once daily, and the starting dose was 9 mg once daily. ORAL paliperidone doses of stabilized patients ranged from 9 mg to 15 mg.[21]

Doses of paliperidone palmitate can be expressed both in terms of milligram equivalent (mg eq) of the pharmacologically active fraction, paliperidone, and in milligrams of paliperidone palmitate.[23] Thus, the doses expressed as 25, 50, 75, 100, and 150 mg eq of PP1M equate to 39, 78, 117, 156, and 234 mg, respectively, of PP1M. Similarly, 175, 263, 350, and 525 mg eq of PP3M correspond to 273, 410, 546, and 819 mg of PP3M.[23]

Supplementary eTable 3 shows doses of ORAL paliperidone, PP1M, and PP3M needed to attain similar steady-state paliperidone exposure during maintenance treatment.[15,23]

In the PP1M study, the PP1M dose range was 39–156 mg and the initial PP1M dose regimen was 78 mg on day 1 and day 8. Most stabilized patients received PP1M 156 mg.[22]

In the PP3M study, the PP1M dose range at the start of the study for most patients was 78 mg to 234 mg and the initial PP1M dose regimen was 234 mg (deltoid) on day 1 and 156 mg (deltoid) on day 8. Most patients received final PP1M doses of 156 mg or 234 mg. When they transitioned from PP1M to PP3M, patients received PP3M at a dose that was 3.5-fold that of the last PP1M dose. Therefore, most patients received a PP3M dose of 546 mg or 819 mg.[23]

Supplementary eTable 4 shows that the equivalent paliperidone dose ranges evaluated across the 3 studies were somewhat different. Dose ranges were 39 mg to 234 mg in the ORAL paliperidone study, 39 mg to 156 mg in the PP1M study, and 78 mg to 234 mg in the PP3M study. Thus, the range of evaluated doses was lower in the PP1M study than in the PP3M and ORAL paliperidone studies.[15,21-23]

Supplementary eTable 1. Doses (mg) of ORAL, PP1M, and PP3M Needed to Attain Similar Steady-State Paliperidone Exposure During Maintenance Treatment[15,23]

ORAL	PP1M	PP3M
3	39-78	273
6	117	410
9	156	546
12	234	819
15[a]	NA	NA

NA, not applicable; ORAL, daily extended-release oral paliperidone; PP1M, once-monthly long-acting injectable paliperidone palmitate; PP3M, once-every-3-months long-acting injectable paliperidone palmitate.

[a]Not an approved dose.

Supplementary eTable 2. Comparison of Paliperidone Dose Ranges (mg) in the ORAL, PP1M, and PP3M Studies[15,21,23]

Study 1		Study 2	Study 3
ORAL[a]	Comparable PP1M Dose[a]	PP1M	PP1M Dose Range Before Conversion to PP3M
3	39 or 78	39 or 78	78
6	117	NA	117
9	156	156	156
12	234	NA	234
15[b]	NA	NA	NA

NA, applicable; ORAL, daily extended-release oral paliperidone; PP1M, once-monthly long-acting injectable paliperidone palmitate; PP3M, once-every-3-months long-acting injectable paliperidone palmitate.

[a]PP1M dose needed to attain similar steady-state paliperidone exposure during maintenance treatment.

[b]Maintenance dose ranges currently approved by the US Food and Drug Administration for patients with schizophrenia are ORAL, 3–12 mg/day;[19] PP1M, 39–234 mg once per month;[15] and PP3M, 273–819 mg once every 3 months.[20]

Supplementary eTable 3. Paliperidone Dose Regimens in the ORAL, PP1M, and PP3M Studies[21-23]

Study Phase	Study		
	ORAL[21]	**PP1M[22]**	**PP3M[23]**
Stabilization	*Regimen:* ORAL started at 9 mg once daily and administered at a dose of 3–15 mg once daily *Results:* • 45% of patients received 9 mg/day • 47% of patients had dose increased to 12 or 15 mg dose, 8% were tapered to 6 or 3 mg dose	*Regimen:* Patients switched from previous antipsychotic and received once-monthly injections of flexibly dosed PP1M (39, 78, or 156 mg) after an initial regimen of PP1M 78 mg on days 1 and 8 *Results:* Almost all patients received PP1M 78 mg (53%) or 156 mg (46%) as their final dose	*Regimen:* All patients except those switching from other LAI antipsychotics or those receiving PP1M before study entry received PP1M for 120 days. Doses were: day 1, 234 mg (deltoid); day 8, 156 mg (deltoid); days 36 and 64: 78, 117, 156, or 234 mg flexible doses (deltoid or gluteal) *Results:* Final PP1M doses were 78 mg (2%), 117 mg (8%), 156 mg (48%), and 234 mg (42%)
Maintenance	*Regimen:* Patients were to remain on dose on which they were stabilized *Results:* Doses were 9 mg/day (33%), 12 mg/day (26%), and 15 mg/day (30%)	*Regimen:* Stable patients received flexibly dosed PP1M (39, 78, or 156 mg) for first 12 weeks, with dose adjustments based on clinical need; patients received PP1M treatment at established maintenance dose for 12 weeks *Results:* Final PP1M doses were 39 mg (2%), 78 mg (28%), and 156 mg (69%)	*Regimen:* Patients received a single dose of PP3M in the deltoid or gluteal muscle; dose of PP3M was 3.5-fold that of the final PP1M dose administered on day 92 *Results:* PP3M doses were 273 mg (2%), 410 mg (9%), 546 mg (49%), and 819 mg (39%)

LAI, long-acting injectable; ORAL, daily extended-release oral paliperidone; PP1M, once-monthly LAI paliperidone palmitate; PP3M, once-every-3-months LAI paliperidone palmitate.

Supplementary eTable 4. Inclusion and Exclusion Criteria in the ORAL, PP1M, and PP3M Studies[21-23]

	Study		
Variable	**ORAL**	**PP1M**	**PP3M**
Inclusion Criteria			
Male and female	X	X	X
Age 18–65 years	X	X	18–70 years
Diagnosis of schizophrenia[a]	X	X	X
PANSS score (total) <120 at screening and baseline	70–120	X	X
Exclusion Criteria			
DSM-IV diagnosis other than schizophrenia	X	X	X
Significant risk of suicide or aggressive behavior	X	X	X
History of substance dependency[b]	X	X	X
Involuntary admission to a psychiatric hospital	X[c]	X[d]	X[d]
Women pregnant, breastfeeding, or planning pregnancy	X	X	—
Recent use of any 4-week depot antipsychotic prior to screening	X[e]	X[e]	—
Presence of a medical condition that could alter the absorption, metabolism, or excretion of the study medication	X	—	—
Relevant history of significant unstable disease	X	—	—
Known allergic reaction to barbiturates, carbamazepine, lamotrigine, phenytoin, paliperidone, or risperidone	X	—	—
Previous lack of response to risperidone	X	—	—
Exposure to an experimental treatment within 90 days before screening	X	—	—
Electroconvulsive treatment within 3 months before screening	X	—	—
Treatment resistance[f]	—	X	—

Variable	Study		
	ORAL	PP1M	PP3M
Discontinued antiparkinsonian medications, antiepileptics, lithium, β-blockers,[g] and monoamine oxidase inhibitors before run-in	X	—	—
Use of risperidone LAI within 5 weeks before screening	—	X	—
Use of oral antipsychotics, mood stabilizers, or OTC drugs within 2 days before baseline	—	X	—
History of neuroleptic malignant syndrome, tardive dyskinesia, or any malignant neoplasm in the previous 5 years[h]	—	—	X

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; LAI, long-acting injectable; ORAL, daily extended-release oral paliperidone; OTC, over-the-counter; PANSS, Positive and Negative Syndrome Scale; PP1M, once-monthly LAI paliperidone palmitate; PP3M, once-every-3-months LAI paliperidone palmitate.

[a]Diagnosis per DSM-IV criteria, for ≥1 year before screening.

[b]Within 6 months of screening for ORAL and PP3M studies; within 3 months of screening for PP1M study.

[c]At screening.

[d]Any history.

[e]Within 28 days for PP1M study; within 120 days for ORAL study.

[f]Failure to respond to 2 trials; minimum of 4 weeks of antipsychotic medications.

[g]Except if for the treatment of hypertension in stabilized patients.

[h]Except basal cell carcinoma.

Supplementary eTable 5. Baseline Demographic and Clinical Characteristics of the Placebo Cohorts (final analysis set) in the Double-Blind Phases of the ORAL, PP1M, and PP3M Studies[21-23]

Characteristic	ORAL n=101	PP1M n=203	PP3M n=145	*P* Value[c]
Age, mean±SD, years	37.5±10.4	39.4±10.8	38.5±11.2	0.348
Male, n (%)	63 (62)	111 (55)	110 (76)	<0.001
Race, n (%)				<0.001
White	61 (60)	133 (66)	91 (63)	
Black	9 (9)	36 (18)	21 (14)	
Asian	0	30 (15)	15 (10)	
Other	31 (31)	4 (2)	18 (12)	
BMI, mean±SD, kg/m^2	26.5±7.9	27.2±6.0[a]	26.2±4.6	0.290
Age at schizophrenia diagnosis, mean±SD, years	25.8±9.4	28.1±9.1	27.7±9.0	0.116
PANSS total score, mean±SD	53.4±10.6	53.1±11.9	54.2±9.3	0.642
PSP score, mean±SD	72.6±10.4	72.8±10.8	68.6±9.0	<0.001
Previous hospitalizations for psychosis, n (%)				<0.001
0	27 (27)	21 (10)	51 (40)[b]	
1	14 (14)	42 (21)	44 (34)[b]	
≥2	60 (59)	140 (69)	33 (26)[b]	

BMI, body mass index; CGI-S, Clinical Global Impressions–Severity; ORAL, daily extended-release oral paliperidone; PANSS, Positive and Negative Syndrome Scale; PP1M, once-monthly long-acting injectable paliperidone palmitate; PP3M, once-every-3-months long-acting injectable paliperidone palmitate; PSP, Personal and Social Performance scale.

[a]Corresponds to transition baseline BMI calculated using transition baseline weight and height.

[b]Based on n-value of 128.

[c]Comparison of 3 groups.

Supplementary eTable 6. Baseline Demographics and Disposition of All Patients Who Entered the Double-Blind Phases of the 3 Studies

Characteristic	ORAL n=205	PP1M n=408	PP3M n=305	*P* Value[b]
Age (years), mean±SD	38.2±10.5	39.1±11.1	37.8±11.0	0.887
Sex (male), n (%)	121 (59.0)	220 (53.9)	228 (74.8)	<0.001
Race, n (%)				0.447
White	123 (60.0)	266 (65.2)	195 (63.9)	
Other	82 (40.0)	142 (34.8)	110 (36.1)	
Age at schizophrenia diagnosis (years), mean±SD	26.5±9.3	27.3±9.2	26.9±8.6	0.596
Baseline (DB) PANSS score (total), mean±SD	52.2±11.0	52.6±11.8	54.5±9.7	0.022
Baseline (DB) PSP score (total), mean±SD	71.7±10.7	72.4±10.7	68.7±9.1	<0.001
Prior hospitalizations for psychosis,[a] n	n=205	n=408	n=274	<0.001
(%)	53 (25.9)	43 (10.5)	99 (36.1)	
0	29 (14.2)	88 (21.6)	92 (33.6)	
1	26 (12.7)	86 (21.1)	43 (15.7)	
2	28 (13.7)	67 (16.4)	21 (7.7)	
3	69 (33.7)	124 (30.4)	19 (6.9)	
≥4				

DB, double-blind; PANSS, Positive and Negative Syndrome Scale; ORAL, daily extended-release oral paliperidone; PP1M, once-monthly long-acting injectable paliperidone palmitate; PP3M, once-every-3-months long-acting injectable paliperidone palmitate; PSP, Personal and Social Performance Scale; SD, standard deviation.

[a]For the PP3M cohort, this is the number of hospitalizations within 24 months before the start of the study.

[b]Comparison of 3 groups.

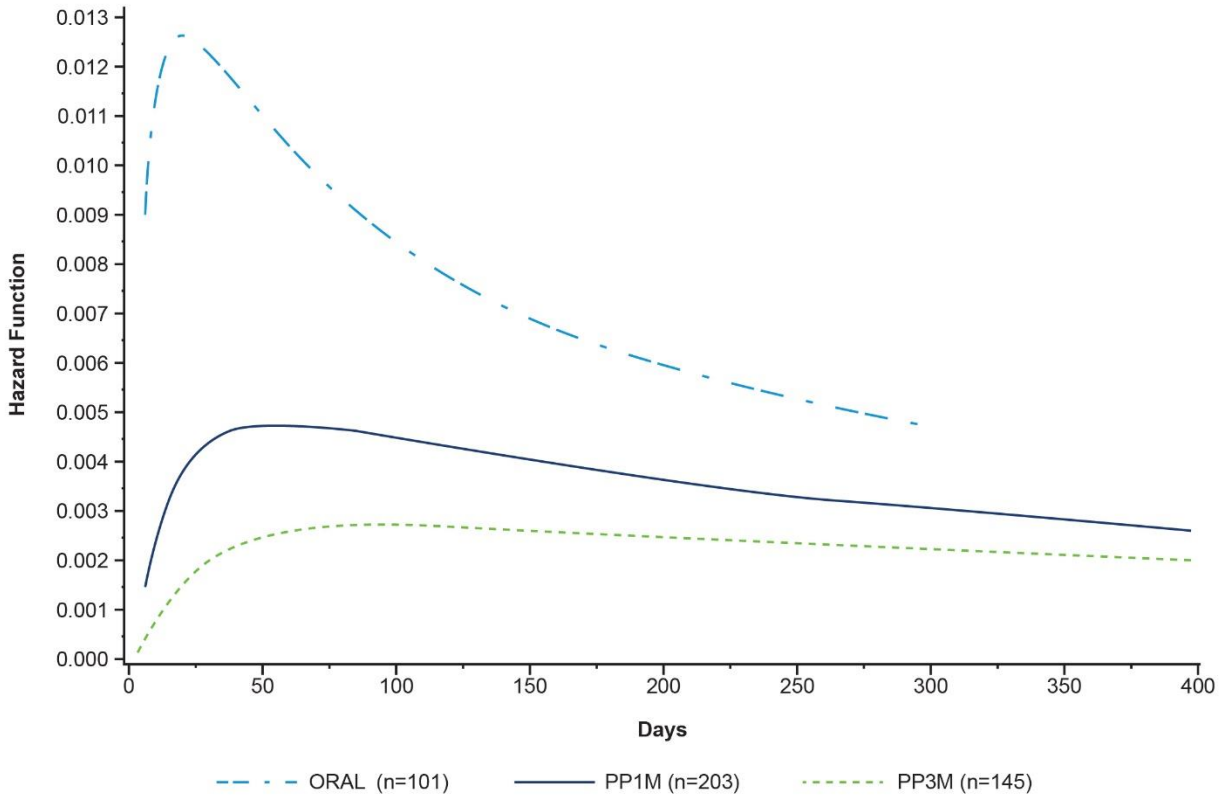
Supplementary eTable 7. Multiple Cox Proportional Model on Time to Relapse for the Placebo Arms of the ORAL, PP1M, and PP3M Studies (double-blind intent-to-treat populations)

Predictors	Maximum Likelihood Estimates			
	Estimate	**SE**	**95% CI**	***P* Value**
Baseline (DB) PSP	0.018	0.007	0.003, 0.032	0.016
Trial				<0.001
PP1M vs ORAL	0.808	0.176	0.462, 1.154	<0.001
PP3M vs ORAL	1.322	0.234	0.864, 1.781	<0.001
Prior hospitalizations for psychosis[a]				0.370
1 vs 0	–0.390	0.255	–0.889, 0.110	0.126
2 vs 0	–0.265	0.276	–0.806, 0.276	0.337
3 vs 0	–0.420	0.299	–1.006, 0.165	0.159
≥4 vs 0	–0.505	0.259	–1.013, 0.003	0.051

CI, confidence interval; DB, double-blind; PP1M, once-monthly long-acting injectable paliperidone palmitate; ORAL, daily extended-release oral paliperidone; PP3M, once-every-3-months long-acting injectable paliperidone palmitate; PSP, Personal and Social Performance Scale; SE, standard error.

[a]For the PP3M cohort, this is the number of hospitalizations within 24 months before the start of the study.

Supplementary eFigure 1. Hazard function of a parametric log-normal model* on time to relapse for the intent-to-treat placebo double-blind (DB) populations from the ORAL, PP1M, and PP3M studies, with predictors: trials, baseline (DB) Personal and Social Performance Scale, and prior hospitalizations for psychosis.



*The exponential, Weibull, and log-logistic parametric models were also evaluated for model fit, and likelihood-ratio statistics were considered in choosing the log-normal model.
ORAL, daily extended-release oral paliperidone; PP1M, once-monthly long-acting injectable paliperidone palmitate; PP3M, once-every-3-months long-acting injectable paliperidone palmitate.