

# Effects of Discontinuation of Paliperidone Long-Acting Injectable After Switching from Risperidone Long-Acting Injectable Switching

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**ABSTRACT ~ Background:** Risperidone long-acting injection (RLAI) is increasingly being switched to paliperidone palmitate (PP) because of several benefits. However, this switching is not always successful. **Methods:** We examined patient profiles following discontinuation of PP after switching from RLAI. We collected the electronic records of 24 patients with schizophrenia who had switched from RLAI to PP treatment at our hospital between November 2013 and March 2014. Twelve patients continued PP injection for over 1 year (PP-continuers), the other 12 patients discontinued within 1 year (PP-discontinuers), and both groups were followed up until December 31, 2014. **Results:** PP-discontinuers had significantly shorter RLAI-administration period (mean  $73.1 \pm 59.0$  weeks versus  $148.5 \pm 75.0$  weeks), and lower chlorpromazine (CP) equivalent mean doses (mean  $553.5 \pm 251.0$  mg versus  $1002.5 \pm 529.3$  mg) compared with PP-continuers. The CP equivalent mean dose of PP-discontinuers had increased at the time of discontinuation and their social status became significantly worse. Six PP-discontinuers (50%) re-switched to RLAI, and their social status was not significantly worse at the end of the observation period. **Conclusions:** On switching from RLAI to PP, we need to consider that some patients have had a shorter RLAI-administration period and may require lower amounts of antipsychotics. *Psychopharmacology Bulletin.* 2016;46(2):42–52.

## INTRODUCTION

Paliperidone Palmitate (PP) has been developed as a long acting injectable second-generation antipsychotic that is a suspension of nanocrystals in an aqueous formulation administered monthly by intramuscular injection. The non-inferiority of PP to risperidone long acting injection (RLAI) has been demonstrated in adult patients with schizophrenia.<sup>1–4</sup> PP has several benefits over RLAI, which include minimal hepatic metabolism and a consequent reduction in potential drug

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interactions, fewer concerns about post-injection syndrome, no requirements for refrigeration, and the option of deltoid or gluteal administration. Furthermore, PP is administered every four weeks, which is less burdensome than the fortnightly administration of RLAI.<sup>5</sup> If RLAI is to be switched to PP, the manufacturer's instructions advise using a simple method. Each 25, 37.5, and 50 mg dose of RLAI is switched to 50, 75, and 100 mg dose of PP, and thereafter, PP is administered at four-weekly intervals.

In an analysis of a Medicaid claims database, more than a quarter of the patients who were being treated with PP had been switched from RLAI.<sup>6</sup> Some risk factors for discontinuing PP after switching from other antipsychotics have been reported.<sup>5,7</sup> Switching from oral risperidone or RLAI to PP has been shown to be a favorable predictor for continuing PP injection for more than 1 year after switching. Other factors, such as initiation as an outpatient, correct initiation, absence of positive psychotic symptoms at the initiation of treatment, and starting on a lower PP dose may also contribute to the success. To our knowledge, no study has yet directly explored the risk factors for discontinuing PP injection after switching from RLAI.

The purpose of this study was to examine the differences in patient profiles between those who successfully switched from RLAI to PP and those who did not. We retrospectively compared the baseline characteristics of PP-continuers with PP-discontinuers within 1 year of switching from RLAI.

## METHODS

### *Subjects*

This descriptive and exploratory study was conducted by consecutively compiling the electronic records of patients with a diagnosis of schizophrenia who had switched from RLAI to PP injection at our hospital between November 2013 and March 2014. The patients were divided into two groups: those who continued PP injection for more than 1 year (PP-continuers) and those who discontinued it within 1 year (PP-discontinuers). Both groups were followed up until December 31, 2014.

Data pertaining to the characteristics of subjects, such as age, sex, illness duration, indications for prescribing RLAI and for switching to PP (whether that was performed with adequate consensus or poor consensus), RLAI-administration period, number of admissions, care setting (in-patient or out-patient status), administered dose of depot antipsychotics, chlorpromazine (CP) equivalent doses of depot and

combined oral antipsychotics, content of combined oral antipsychotics and other psychotropic agents, and social status were collected. Adequate consensus means that the informed consent of the patients was described in the electronic records. Furthermore we verified the PP-administration period, reason for cessation of PP, administered dose of depot antipsychotics, CP equivalent doses of depot and combined oral antipsychotics, content of combined oral antipsychotics and other psychotropic agents, and social status at the time of discontinuation and the end of the follow up (that is, 31st December 2014).

Finally, we compared the characteristics of PP-continuers versus PP-discontinuers at the end of follow up.

### *Statistical Analysis*

Patient characteristics were summarized using descriptive statistics. For categorical variables, the differences in the distribution of variables between the groups were compared using chi-square tests. For continuous variables, differences in the means and medians between groups were compared using *t*-tests, and Mann-Whitney *U*-tests or non-parametric Wilcoxon signed-rank tests for paired data. Statistical significance was accepted for *P* values less than 0.05. All tests were performed using Statcel version 3 (OMS Publishing Inc, Saitama, Japan).

### *Ethical Considerations*

This study was conducted with the approval of the Ethics Review Committee of Gifu Hospital, Japan, on July 9, 2015.

## **RESULTS**

### *Discontinuation*

Twenty-four patients had been directly switched from RLAI to PP injection between November 2013 and March 2014. All patients had a diagnosis of schizophrenia, and had been switched in the correct manner according to the manufacturer's instructions. Twelve (50%) of the 24 patients discontinued PP within 1 year during the study period—one at the request of the patient, three due to adverse physical events (of whom one had akathisia, one had tremor, and one had pain at the site of injection), five due to deterioration in their mental states (two of whom required acute admission), two were lost to follow up during the observation period (and required acute admission after the study period), and one who died during the observation period. PP injection

TABLE 1

**ANTIPSYCHOTIC SWITCHED TO AFTER DISCONTINUING PP AT END OF FOLLOWING UP**

DRUG SWITCHED TO (N = 12)	n	%
Aripiprazole	1	8.3
Blonanserin	1	8.3
Paliperidone	1	8.3
Risperidone	1	8.3
Risperidone LAI	6	50
None (refused all medication)*	3	25

**Note:** \*One died, and 2 missed at the end of observation.

**Abbreviations:** PP, Paliperidone palmitate; LAI, long acting injection.

was discontinued after 3.9 months on average (between 1 month and 11 months). Of those who discontinued treatment within 1 year, nine discontinued within 3 months, one discontinued between 3 and 6 months, and two discontinued between 6 and 12 months. On cessation, six patients (50%) re-switched to RLAI at the end of the observation period (five patients were administered 50 mg RLAI and one patient was administered 37.5 mg RLAI) (Table 1).

*Baseline Patient Characteristics at the Time of Switching*

We compared the baseline characteristics of PP-discontinuers and PP-continuers at the time of switching (Table 2). A significant difference in the length of the RLAI-administration period was seen between the PP-discontinuers and PP-continuers. RLAI had been administered to the PP-discontinuers for 73.1 weeks on average, compared with an average of 148.5 weeks for the PP-continuers. The age and gender distributions appeared similar in both groups. No significant differences in mean values were found with regard to illness duration and number of admissions.

In most patients, adequate consensus was obtained when switching to PP, although there was poor consensus for 10 patients (41.7%) of those prescribed RLAI previously. Many patients were switched to PP injection in an outpatient setting. No significant differences in the distributions were apparent with regard to the initiation of RLAI, initiation of the switch to PP, and the care setting between PP-discontinuers and PP-continuers.

The oral antipsychotics that were combined with PP included aripiprazole, blonanserin, chrolpromazine, levomepromazine, risperidone, olanzapine, paliperidone, and quetiapine, and no significant differences in the distributions were found between the patient groups (Table 3).

TABLE 2

## BASELINE CHARACTERISTICS

PARAMETERS	DISCONTINUED n = 12	CONTINUED n = 12	P
Age			
Mean (SD)	47.4 (16.4)	48.8 (14)	0.410
Illness duration			
Mean (SD) weeks	738.6 (382.4)	1084.8 (920.5)	0.248
RLAI-administered period			
Mean (SD) weeks	73.1 (59.1)	148.5 (75.0)	0.012
Number of admission			
Mean (SD)	4.08 (4.48)	9.33 (8.36)	0.072
Gender			
Male	5 (41.7%)	7 (58.3%)	0.414
Initiation for prescribing RLAI			
With adequate consensus	6 (50%)	8 (66.7%)	0.407
With poor consensus	6 (50%)	4 (33.3%)	
Initiation for switching to PP			
With adequate consensus	11 (91.7%)	9 (75%)	0.273
With poor consensus	1 (8.3%)	3 (25%)	
Care setting			
In-patient	2 (16.7%)	5 (41.7%)	0.177
Out-patient	10 (83.3%)	7 (58.3%)	

**Abbreviations:** PP, Paliperidone palmitate; RLAI, risperidone long acting injection; SD, standard deviation.

There were also no significant differences between the groups for psychotropic agents other than antipsychotics (Table 4).

*Dose of PP and Other antipsychotics*

No significant differences were found in the median values for the starting dose of PP and maintenance dose of PP (Table 5) between

TABLE 3

## COMBINED ORAL ANTIPSYCHOTICS AT THE TIME OF SWITCHING

COMBINED ORAL ANTIPSYCHOTICS	NUMBER DISCONTINUED (n = 12)		NUMBER CONTINUED (n = 12)	
		%		%
Aripiprazole	0	0	4	33.3
Blonanserin	0	0	1	8.3
Chlorpromazine	0	0	1	8.3
Levomepromazine	2	16.7	0	0
Risperidone	1	8.3	3	25
Olanzapine	0	0	3	25
Paliperidone	1	8.3	0	0
Quetiapine	0	0	1	8.3
None	8	75	4	33.3

TABLE 4

## OTHER PSYCHOTROPIC AGENTS AT THE TIME OF SWITCHING

PSYCHOTROPIC AGENTS		NUMBER DISCONTINUED		NUMBER CONTINUED	
		(N = 12)	%	(N = 12)	%
Anticholinergic agent	Biperiden	1	8.3	2	16.7
	Trihexyphenidyl	0	0	2	16.7
	None	11	91.7	8	66.6
Benzodiazepines or Z drugs	Clonazepam	0	0	2	16.7
	Estazolam	0	0	1	8.3
	Flunitrazepam	1	8.3	1	8.3
	Lorazepam	0	0	1	8.3
	Nitrazepam	1	8.3	1	8.3
	Quazepam	0	0	1	8.3
	Zolpidem	1	8.3	1	8.3
	None	9	75	7	58.3
	Carbamazepine	0	0	1	8.3
Others	Gabapentin	0	0	1	8.3
	Paroxetine	1	8.3	0	0
	Valproate	1	8.3	0	0
	None	10	83.3	10	83.3

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the PP-discontinuers and PP-continuers. The median value of the PP maintenance dose was significantly increased compared with the median value of the PP starting dose among the PP-discontinuers, but not among the PP-continuers.

The chlorpromazine equivalent mean doses of depot and combined oral antipsychotics were calculated (Figure 1). At the time of switching to PP, the chlorpromazine equivalent mean dose for PP-discontinuers was 553.5 mg, and this was significantly lower than the mean dose of

TABLE 5

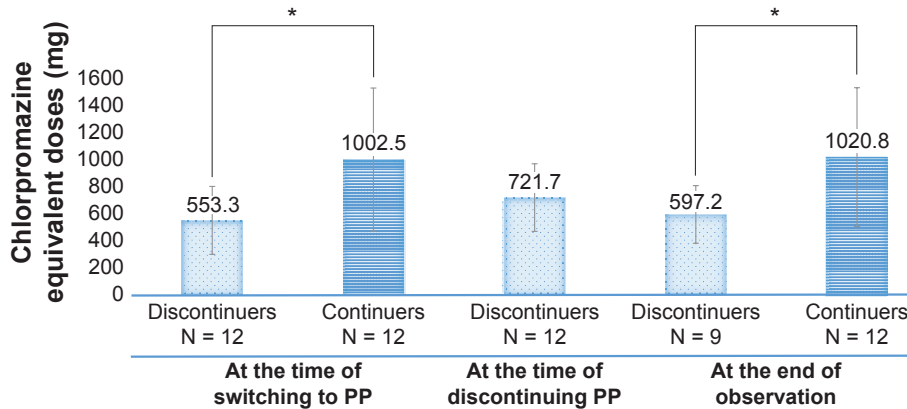
## STARTING AND MAINTENANCE DOSE OF PP PRESCRIBED

	NUMBER DISCONTINUED		NUMBER CONTINUED		TOTAL	%
		%		%		
Starting dose (mg)						
50	0	0	0	0	0	0
75	3	25	0	0	3	12.5
100	9	75	12	100	21	87.5
Maintenance dose (mg)						
50	0	0	0	0	0	0
75	2	16.7	0	0	2	16.7
100	3	25	9	75	12	50
150	7	58.3	3	25	10	83.3

Abbreviation: PP, Paliperidone palmitate.

FIGURE 1

## CHLORPROMAZINE EQUIVALENT MEAN DOSES OF DEPOT AND COMBINED ORAL ANTIPSYCHOTICS



Abbreviation: PP, Paliperidone palmitate.

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1002.5 mg for PP-continuers. For PP-discontinuers, the chlorpromazine equivalent mean dose had increased to 721.7 mg at the time of discontinuation. At the end of the observation period, the chlorpromazine equivalent mean dose for PP-discontinuers decreased to 633.3 mg, and was significantly lower than the mean dose of 1041.7 mg for PP-continuers.

### Social Status

The distribution of social status was not significantly different between the PP-discontinuers and PP-continuers at the time of switching (Table 6). The median value for the social status of the PP-discontinuers was significantly worse at the time of discontinuation compared with the value at time of switching, but had recovered by the end of the observation period. No significant change to the median value for social status was observed for the PP-continuers between the time of switching and the end of the observation period.

### DISCUSSION

In this study, fifty percent of the 24 patients who had switched from RLAI to PP injection continued on PP for at least 1 year, and more patients discontinued than expected. In the present comparison of baseline patient characteristics between the PP-discontinuers and PP-continuers, a significantly shorter mean period of RLAI administration and smaller CP equivalent mean dose were observed among



TABLE 6

## SOCIAL STATUS

	NUMBER DISCONTINUED (%)			NUMBER CONTINUED (%)	
	AT THE TIME OF SWITCHING	AT THE TIME OF DISCONTINUATION*	AT THE END OF OBSERVATION	AT THE TIME OF SWITCHING	AT THE END OF OBSERVATION
Employed	0 (0)	0 (0)	3 (25)	2 (16.7)	3 (25)
Psychiatric daycare	0 (0)	0 (0)	0 (0)	1 (8.3)	1 (8.3)
Unemployed	10 (83.3)	6 (50)	5 (41.7)	4 (33.3)	4 (33.3)
Admitted	2 (16.7)	3 (25)	1 (8.3)	5 (41.7)	4 (33.3)
Missed	0 (0)	2 (16.7)	2 (16.7)	0 (0)	0 (0)
Died	0 (0)	1 (8.3)	1 (8.3)	0 (0)	0 (0)

**Note:** \*The distribution of social status was significantly deteriorate at the time of discontinuation compared with the time of switching (using non-parametric Wilcoxon signed-rank tests for paired data,  $P = 0.043$ ).

the PP-discontinuers than among the PP-continuers. This result was surprising because we expected that the PP-discontinuers would have been administered RLAI for a longer period and would need a higher amount of PP and other antipsychotics because more severely ill patients would be more likely to discontinue PP.

Several possibilities might explain the present findings. The first possibility is that many of the PP-discontinuers were skeptical about pharmacotherapy and responded negatively to the increased dose of antipsychotics. This possibility might be supported by the finding that six PP-discontinuers (50%) were prescribed RLAI unwillingly. Furthermore, this might partly explain why the CP equivalent mean dose was lower among the PP-discontinuers than among PP-continuers at the time of switching and at the end of the observation period, and the mean period of RLAI administered before switching was shorter among the PP-discontinuers than among the PP-continuers. The duration of RLAI administration might not be long enough for them to be familiar with pharmacotherapy.

The second possibility is that the PP-discontinuers were the patients who responded to RLAI, but not to PP for reasons that are unknown. The PP-discontinuers did not require as high a CP equivalent dose as the PP-continuers did, for maintenance at the end of the observation period. Furthermore, six of the PP-discontinuers (50%) were re-administered RLAI at the end of the study period. The non-inferiority of PP to RLAI has been demonstrated,<sup>4</sup> and the superiority of PP also has been suggested because of its minimal hepatic metabolism and a consequent reduction in potential drug interactions, fewer concerns about post injection syndrome, no requirements for refrigeration, and the option of deltoid or gluteal administration.<sup>5</sup> In contrast, Singh *et al.*



reported a case where the change from RLAI to PP resulted in a poor clinical outcome, and suggested that the two medications may not be equally efficacious for all individuals, although the mechanism for this was unknown.<sup>8</sup> The present results suggest that PP was inferior to RLAI in a larger number of patients than expected. RLAI might be more suitable than PP for some patients, who were more skeptical to pharmacotherapy and/or were not familiar with depot antipsychotics.

The third possibility is that the PP-discontinuers were highly sensitive to the adverse effects of PP. This possibility might be difficult to substantiate because only three PP-discontinuers (25%) stopped taking PP due to adverse physical effects.

Finally, it is possible that the lower dose of PP caused the psychiatric deterioration. However, seven PP-discontinuers (60%) required the maximum dose of PP (150 mg) for maintenance before discontinuation, in contrast to only three PP-continuers (25%) (Table 5).

The discontinuation rate for PP after one year has been reported to be 35% to 60% in several studies, which was lower than the discontinuation rate for RLAI after one year (about 70%).<sup>5,7,9,10</sup> The relatively higher discontinuation rate in this study might reflect that the study included those who were lost to follow up or had died, and that this study included relatively more severe cases, because the main reason for discontinuation was the deterioration in mental state of the patient (the two missing cases also deteriorated and were admitted to our hospital after the observation period). Hamer *et al.* also demonstrated a relatively high rate of discontinuation for PP within one year, with the main reason for discontinuation being deterioration in the mental state of the patient.<sup>7</sup> They suggested that more severely ill patients with an incomplete response to their previous antipsychotic were more likely to experience deterioration in their mental state after a switch to PP and subsequently discontinue treatment. In our study, those with an incomplete response to the previous antipsychotic (RLAI) were not more likely to experience deterioration in their mental state after a switch to PP because no significant differences in the distributions appeared in either the initiation of the switch to PP or the care setting between the PP-discontinuers and PP-continuers. It is possible that our study could not detect a significant difference because only four patients had been switched to PP injection with poor consensus and only seven patients had been switched to PP injection in an in-patient setting, although correct initiation and an out-patient setting have been shown to be favorable factors in several studies when switching to PP from other antipsychotics.<sup>5,7</sup> Nevertheless, a longer period of RLAI administration and a higher CP equivalent dose might be more favorable factors when switching to PP.

Our results should be treated with caution because there are a number of limitations to this study. As a retrospective observational study, it is likely that the data concerning the mental state of patients (at initiation and discontinuation of treatment) were not as reliable as those collected in a prospective study using validated rating scales. The sample size was small and limited the likelihood of finding significant associations between patients or treatment factors and discontinuation. We cannot exclude selection bias when administrators decide to switch to PP. It is possible that the patients had more severe symptoms than those in other studies because poor consensus was frequent at the commencement of RLAI in this study.

Because several advantages have been reported that favor the superiority of PP over RLAI, as mentioned above, there might be many requests to switch from RLAI to PP. However, even after receiving requests from patients, switching from RLAI to PP should be conducted cautiously, particularly when patients who are skeptical about pharmacotherapy are being treated stably with a comparatively smaller CP equivalent dose of RLAI for a shorter period. Further long-term prospective and pharmaco-biological studies are required to determine which patients are more suitable for treatment with RLAI than with PP and to clarify the differences in the mechanisms of action between PP and RLAI.

## CONCLUSION

Even if RLAI has been administered, a cautious approach is recommended when deciding whether to switch to PP injection in some patients, especially in those who have been administered RLAI for a shorter period and are being prescribed relatively lower amounts of antipsychotics. ♣

## CONFLICTS OF INTEREST AND SOURCE OF FUNDING

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