mhc MENTAL HEALTH CLINICIAN

ORIGINAL RESEARCH Open Access

Impact of traditional versus nontraditional initiation dosing schedule of paliperidone palmitate on 30-day readmission and safety

Erika Kim, PharmD, BCPP[1]; Andrew Williams, PharmD, BCPP[2]; Justin Chang, PharmD[3]; Niyati Butala, PharmD, BCPP[4]; Matthew Firek[5]

How to cite: Kim E, Williams A, Chang J, Butala N, Firek M. Impact of traditional vs nontraditional initiation dosing schedule of paliperidone palmitate on 30-day readmission and safety. Ment Health Clin [Internet]. 2023;13(6):311-316. DOI: 10.9740/mhc.2023.12.311.

Submitted for Publication: March 11, 2023; **Accepted for Publication:** September 2, 2023

Abstract

Introduction: Paliperidone palmitate (PP), a second-generation long-acting injectable antipsychotic, requires 2 injections upon initiation. Due to the fast-paced nature of the inpatient setting, the second dose may be administered earlier than recommended by labeled use despite the lack of evidence that evaluates this practice.

Methods: This was a retrospective chart review that investigated the outcomes associated with the timing of the second PP initiation dose with the aim of comparing patients who received the second PP dose fewer than 3 days after the first injection with those who received it between 3 and 11 days after the first injection. The primary outcomes included 30-day psychiatric readmission, index hospitalization length of stay, and time until the next psychiatric hospitalization. Secondary outcomes included 6-month readmission and the percentage of patients who experienced an adverse event after the second injection.

Results: No statistically significant differences were observed between groups for 30-day readmission. There was a statistically significant shortened index length of hospitalization (median, 2 vs 4 days; $P < 0.001$) and a non-statistically significant trend for time until the next psychiatric hospitalization (median, 25 vs 47 days) when comparing those who received the nontraditional loading regimen to those who received the traditional labeled loading regimen. No differences were observed in the secondary outcomes or safety/tolerability.

Discussion: The results of the study indicate that there are no significant differences in readmission rates and adverse drug reactions in those who received the second PP dose earlier than recommended per labeled use. Larger, controlled studies are needed to further investigate clinical and safety outcomes.

Keywords: paliperidone palmitate, long-acting injectable antipsychotic, adherence, readmission, discharge

[1] Clinical Pharmacist, Riverside University Health System, Riverside, California, ORCID: https://orcid.org/0000-0002-5871-9590; [2] (Corresponding author) Supervising Clinical Pharmacist, Riverside University Health System, Riverside, California, Andrewmwilliams626@gmail.com, ORCID: https://orcid.org/0000-0003-3140-414X; [3] Clinical Pharmacist, Riverside University Health System, Riverside, California, ORCID: https://orcid.org/0000-0002-4462-0995; [4] Clinical Pharmacist, Riverside University Health System, Riverside, California, ORCID: https://orcid.org/0000-0003-0383-6068; [5] Research Specialist, Comparative Effectiveness and Clinical Outcomes Research Center, Riverside University Health System, Moreno Valley, California, ORCID: https://orcid.org/0009-0009-7232-4104

Introduction

Paliperidone palmitate (PP) is a second-generation long-acting injectable antipsychotic that was approved for the treatment of schizophrenia and schizoaffective disorder.[1] Upon initiation of PP, the product labeling recommends the administration of 2 intramuscular injections into the deltoid muscle. The first injection (234 mg) is considered day 1 of the regimen and is followed by a second injection (156 mg) that is administered 7 days later (ie, on day 8).[1] These recommendations stem from pharmacokinetic population modeling studies that have shown that this regimen achieves target paliperidone plasma concentrations in 84% of patients less than 1 week after the first

dose as well as therapeutic plasma concentrations in 90% of patients on days 8 and 36 after regimen completion.[2] Furthermore, pharmacokinetic simulation studies suggest minimal differences in paliperidone exposure and concern for adverse events when the second dose of PP is given 4 days before or after the recommended 1-week time point.[3] Consequently, per labeled use, the second PP injection may be given between 3 and 11 days after the first dose to prevent missed doses and allow for dosing flexibility.[1]

Due to the fast-paced nature of the acute inpatient setting, goals of treatment often include rapid stabilization and preparation for discharge.[4] As a result, at our institution, the second injection has been given sooner than package insert recommendations. To our knowledge, there are currently no studies that have investigated the administration of the second PP dose less than 3 days after the first injection. Given the absence of knowledge of this practice, this study will be the first to examine and assess the clinical and safety outcomes associated with differences in administering the second PP injection earlier than recommended per labeled use in an inpatient psychiatric county facility.

Methods

This study was a single-site retrospective chart review performed at a 77-bed academic inpatient safety-net psychiatric hospital. IRB approval was obtained prior to data collection. It included patients over 18 years old who received the 2-dose PP initiation regimen of 234 mg followed by 156 mg while admitted to the facility between January 1, 2016, and August 3, 2020. Exclusion criteria included being <18 years old, previously receiving a PP injection(s) in the past 12 months, and receiving the study medication(s) in the psychiatric emergency department or medical center without subsequent inpatient psychiatric admission. Furthermore, patients were excluded if they received the study medication <30 days before the study end date, were discharged after >30 days from regimen completion, or received modified dosing due to renal impairment.

Patients were first selected using the computerized pharmacy surveillance software Vigilanz® to identify all patients who had medication orders for PP. Selected patients were screened for inclusion criteria and separated into 2 groups based on the number of days between PP injections. The traditional PP group consisted of those who received the second injection 3 to 11 days after the first (as per FDA-approved labeled use), while the nontraditional group consisted of patients who received the second injection 1 to 2 days after the first dose. All data were collected using the electronic health record system EPIC®.

Baseline characteristics included age, sex identified at birth, ethnicity, discharge diagnosis, previous number of antipsychotic trials, and placement after discharge. Data from urine drug screening at admission were also collected to further account for another confounding factor that could contribute to readmission. An antipsychotic trial was defined as evidence of at least 7 days of therapy in the patient's chart, which included all available encounters (ie, current and previous admissions) and was confirmed by the medication administration record and/or provider documentation. Overlap with oral risperidone, paliperidone, or another antipsychotic at discharge was also noted. Additionally, investigators recorded whether patients received a trial of oral risperidone or paliperidone prior to PP initiation, which was defined as at least 5 days of oral medication prior to the first PP injection confirmed via the medication administration record and/or provider documentation. Injection data collected included the number of days between the first and second PP injections and administration location (deltoid vs gluteal muscle). Safety data were collected using provider and nursing documentation as well as the record of medications administered to treat extrapyramidal symptoms (EPSs) after the second PP injection (ie, propranolol, benztropine, trihexyphenidyl, amantadine).

The primary outcome of the study included 30-day readmission, index hospitalization length of stay (LOS), and time (days) until the next psychiatric hospitalization. Secondary outcomes included 6-month readmission and safety/tolerability upon regimen completion.

Statistical Analysis

Categorical variables were compared using either the chi-squared test or Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test. Survival analysis was performed by analyzing a Cox proportional hazard model as well as a Kaplan-Meier estimator. All statistical analyses were performed using the R statistical programming language, version 4.3.0 (R Foundation for Statistical Computing).

Results

Initially, Vigilanz® identified 862 PP orders, from which a total of 363 patients met the inclusion criteria. There were 316 patients in the traditional group and 47 patients in the nontraditional group. The most common reason for exclusion in both groups was previous history of PP within 12 months of index PP initiation. Baseline characteristics are presented in Table 1. The median ages for the traditional and nontraditional groups were 31 and 32 years, respectively, and most patients were men. Urine drug screening upon admission revealed methamphetamine and/or THC (cannabinoid) in 28% and 40% of patients in the traditional

TABLE 1: Baseline characteristics

Characteristic	Traditional (N = 316)	Nontraditional (N = 47)	*P* Value
Age, y, Median (IQR)	31 (25, 43)	32 (25.5, 47.5)	0.23
Male, n (%)	204 (65)	26 (55)	
Female, n (%)	112 (35)	21 (45)	0.29
Ethnicity, n (%)			
Caucasian	106 (34)	17 (36)	
African American	62 (20)	9 (20)	
Hispanic	132 (42)	17 (36)	
Asian	8 (2)	2 (4)	
Other	8 (2)	2 (4)	0.86
Urine Drug Screen, n (%)			
Negative	145 (46)	18 (38)	
Methamphetamine	21 (7)	7 (15)	
THC	45 (14)	9 (19)	
Methamphetamine + THC	22 (7)	3 (6)	0.42
Diagnosis, n (%)			
Schizophrenia	165 (52)	21 (45)	
Schizoaffective disorder	65 (21)	9 (19)	
Bipolar disorder	23 (7)	5 (11)	
Psychosis, unspecified	47 (15)	12 (26)	
Other	16 (5)	0 (0)	0.18
DC Placement, n (%)			
Home	194 (62)	33 (70)	
Homeless shelter	14 (4)	5 (11)	
Room and board	20 (6)	1 (2)	
Board and care	12 (4)	0 (0)	
IMD	20 (6)	2 (4)	
Nursing home	1 (1)	0 (0)	
Parole/jail	6 (2)	0 (0)	
Crisis residential	35 (11)	5 (11)	
Rehabilitation facility	14 (4)	1 (2)	0.54
Prior Oral Risp/Pali ≥5 Days, n (%)	209 (66)	34 (72)	0.49
Previous AP Trials, n, Median (IQR)	1 (1, 2)	1 (1, 2)	0.38
DC with Oral Risp/Pali, n (%)	102 (32)	14 (30)	0.86
DC with Other Oral AP, n (%)	59 (19)	8 (17)	0.94

THC = cannabinoid; IMD = institution of mental disease; DC = discharge; Risp = risperidone; Pali = paliperidone; AP = antipsychotic.

and nontraditional groups, respectively, without significant differences.

There were no significant differences between groups at baseline for discharge diagnosis, although the most common discharge diagnosis for both groups was schizophrenia (52.2% in traditional vs 44.7% in nontraditional). A greater number of patients were diagnosed with an unspecified psychosis in the nontraditional than in the traditional group.

The median number of previous antipsychotic trials prior to index PP initiation in both groups was 1. Approximately 66% of patients in the traditional group and 72% of patients in the nontraditional group had at least 5 days of therapy with oral risperidone or paliperidone prior to PP initiation. An average of 31% of patients were discharged with oral risperidone or paliperidone, while 18% of patients were discharged with an oral antipsychotic other than risperidone or paliperidone. Notably, of the 116 total patients who received oral risperidone or paliperidone upon discharge, 10% were treated with an EPS medication (11 patients in the traditional group and 1 patient in the nontraditional group).

Most patients from each group received both injections via the deltoid muscle (Table 2). The median numbers of days after the first injection in the traditional and nontraditional groups were 4 and 2, respectively. In the nontraditional group, 9 patients (19%) received the second injection 1 day later. No patients received both injections on the same day. In a subgroup analysis comparing 30-day readmission and injection administration site in each group, no statistically significant differences were found (Table 2).

A total of 29 patients (9.2%) in the traditional group and 6 patients (12.8%) in the nontraditional group were readmitted within 30 days of the index hospitalization ($P = 0.604$) (Table 3). The median index hospitalization LOS was significantly shorter in the nontraditional group (7 days) than in the traditional group (11 days) ($P < 0.001$). Although not significant, the median times until the next psychiatric admission were 47 days in the traditional group and 25 days in the nontraditional group ($P = 0.50$).

No secondary outcomes reached statistical significance (Table 3). Readmission rates within 6 months were nearly identical between groups, 21.2% (68 patients) in the traditional group and 21.3% (10 patients) in the nontraditional group ($P = 1.0$). The Cox proportional hazard analysis (HR, 1.026; $P = 0.938$) and Kaplan-Meier survival curve ($P = 0.94$) (Figure) revealed no statistically significant difference in time to rehospitalization by 6 months. In terms of safety, PP was relatively well tolerated, as there were minimal to no reported adverse drug reactions in most patients in both groups (Table 3). Thirty-four patients (11%) in the traditional group and 1 patient (2%) in the nontraditional group were prescribed a medication for the treatment of EPSs after the 2-dose regimen was completed.

Discussion

In this study, the early administration of the second PP initiation dose was not significantly associated with a higher 30-day or 6-month readmission rate or median time until the next psychiatric hospitalization. The hospital LOS was significantly shorter in the nontraditional than in the

TABLE 2: Injection information and subgroup analysis

Characteristic	Traditional (N = 316)	Nontraditional (N = 47)	*P* Value
Injection Location 1, n (%)			
Deltoid	190 (60)	30 (64)	0.75
Gluteal	126 (40)	17 (36)	
Injection Location 2, n (%)			
Deltoid	176 (56)	30 (64)	0.37
Gluteal	140 (44)	17 (36)	
Time After Initial Injection, Days, Median (IQR)	4 (3, 5)	2 (2, 2)	<0.001
Injection Order (1st injection/2nd injection), n (%)			
Deltoid/deltoid	134 (42)	23 (49)	. . .
Gluteal/gluteal	84 (27)	10 (21)	. . .
Deltoid/gluteal	56 (18)	7 (15)	. . .
Gluteal/deltoid	42 (13)	7 (15)	. . .
	Subgroup Analysis		
	Traditional	Nontraditional	*P* Value
30-Day Readmission, n (%)			
Deltoid/deltoid	11 (8)	3 (13)	T: 0.791
Gluteal/gluteal	9 (11)	2 (20)	NT: 0.804
Deltoid/gluteal	4 (7)	0 (0)	
Gluteal/deltoid	5 (12)	1 (14)	

T = traditional group; NT = nontraditional group.

traditional group, as anticipated given the rapid dosing schedule used. Initiation regimens were relatively well tolerated in both groups, with no significant differences in adverse drug reactions or treatment with an EPS medication after regimen completion.

Although there were no significant differences across most outcomes or baseline characteristics, a trend toward a higher 30-day readmission rate and a shorter time until the next psychiatric hospitalization was observed in those administered the second PP dose less than 3 days after the first. The causes of these trends cannot be determined, but they are likely attributable to multiple factors. One explanation theorizes that when both doses are given in the deltoid muscle, the early administration of the second dose results in more rapid therapeutic serum concentrations accompanied by a shorter duration within the therapeutic plasma range. Consequently, this may lead to

TABLE 3: Primary and secondary outcomes

Outcome	Traditional (N = 316)	Nontraditional (N = 47)	*P* Value
Primary Outcomes			
30-Day Readmission, n (%)	29 (9)	6 (13)	0.60
Hospital Length of Stay, Days, Median (IQR)	11 (7, 16)	7 (6, 10.5)	<0.001
Time Until Next Psychiatric Hospitalization, Days, Median (IQR)	47 (18, 86)	25 (16, 78)	0.50
Secondary Outcomes			
6-Month Readmission, n (%)	68 (21)	10 (21)	1
Safety/Tolerability			
Reported Adverse Drug Events After Regimen Completion, n (%)			
None	311 (98)	45 (96)	0.091
Injection site pain	0 (0)	1 (2)	
Akathisia	2 (1)	0 (0)	
Dystonic reaction	2 (1)	0 (0)	
Tardive dyskinesia	0 (0)	1 (2)	
Pseudoparkinsonism	1 (1)	0 (0)	
Prescribed Extrapyramidal Symptom Medications, n (%)			
Propranolol	5 (2)	0 (0)	0.70
Benztropine	26 (8)	1 (2)	
Trihexyphenidyl	1 (0.3)	0 (0)	
Amantadine	1 (0.3)	0 (0)	
Propranolol + benztropine	1 (0.3)	0 (0)	

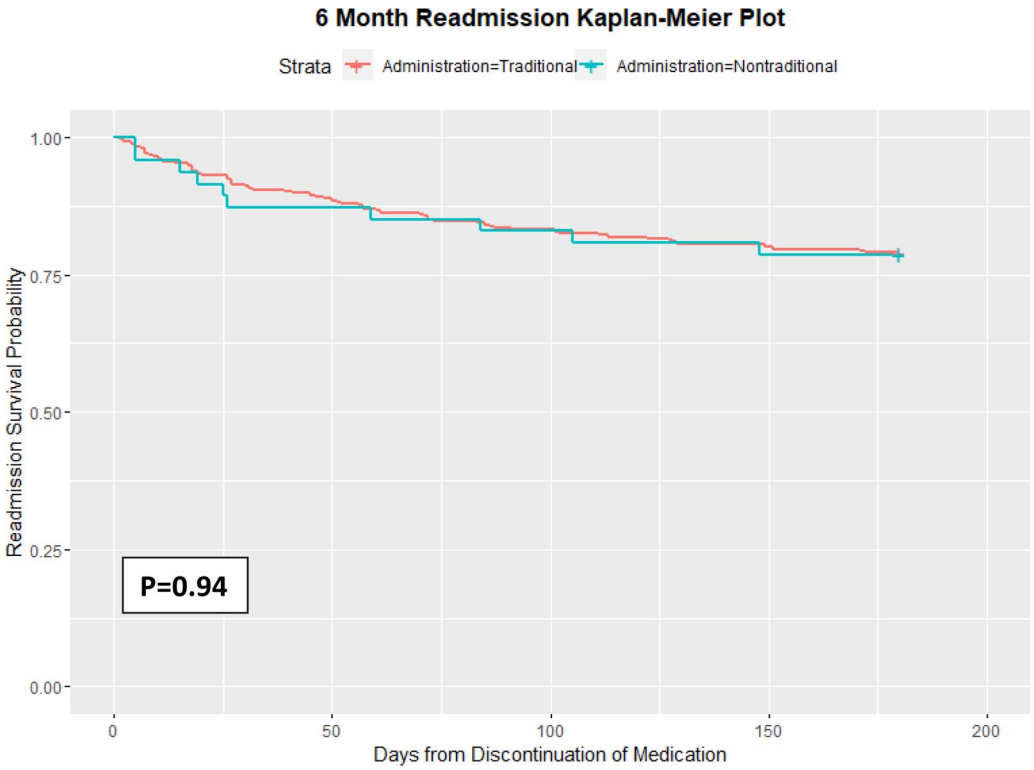

FIGURE: **Kaplan-Meier survival curve**

an insufficient amount of the drug by the end of the 1-month dosing period before the maintenance dose is due, thus possibly precipitating decompensation and the need for psychiatric hospitalization. Furthermore, while most patients received both injections via the deltoid muscle as indicated per labeled use, a relatively large percentage received them in the gluteal muscle. As 28% higher initial paliperidone concentrations have been observed with treatment initiation in the deltoid muscle than in the gluteal muscle, it would be interesting to further investigate the clinical effects of gluteal administration.[5,6] In a subgroup analysis, our study revealed a numerically higher readmission percentage in those who received the first injection in the gluteal muscle regardless of treatment group, although this did not reach statistical significance. As such, one may theorize that prolonged drug release from gluteal administration, particularly the first injection, may prevent the acquisition of peak serum concentrations required for psychiatric stabilization, resulting in readmission. This finding may further reinforce the manufacturer-recommended route of administration.

Several possible confounders and risk factors may be associated with readmission and time until the next psychiatric hospitalization, including potential differences in disease severity, the presence of close follow-up after discharge, and co-occurring substance use disorders. While providers may argue that utilizing a nontraditional loading dose may shorten the patient's LOS, a shorter LOS was previously observed to be a predictor of a shorter time to readmission.[7] The results of our study further support this finding.

It is also worth highlighting the potential discharge placement patterns between the groups. While individuals in the traditional group were more frequently discharged to settings that offer prompt access to support, such as institutions for mental disease and crisis residential facilities, the nontraditional group exhibited a higher tendency toward discharges to homeless shelters and room-and-board accommodations. Although statistical significance was not attained, it would be interesting to explore the influence of discharge placement on psychiatric readmission rates considering our study's observation of a lower readmission rate in the former group.

Furthermore, although approximately 70% of patients received at least 5 days of oral risperidone or paliperidone prior to PP initiation, it is unknown whether this was an adequate duration of therapy to determine efficacy given the possible delay in the full therapeutic benefit for weeks.[8,9] It is also unknown if individuals were prescribed an adequate dose required for stabilization. It should be noted that, depending on the dose required for stabilization, PP may not offer an equivalent conversion for patients who require higher doses of risperidone or paliperidone, thus leading to early decompensation. Moreover, given that 31% of our patients were discharged with oral risperidone or paliperidone, it is possible that patients who continued with oral medication after discharge experienced greater stabilization

than those who did not. Similarly, oral overlap may also serve as a possible confounder for EPS risk and treatment.

As a final point, although nonsignificant, a greater number of patients in the nontraditional group tested positive for methamphetamine in the urine upon admission, thus further complicating the diagnosis and management of substance use disorders and drug-induced psychosis versus organic psychosis in the study population. Given the lack of evidence that antipsychotics prevent methamphetamine-induced psychosis, this raises the question of whether individuals in the nontraditional group returned to methamphetamine use after discharge, thus presenting an additional possible cause of increased readmissions.

Further limitations compel caution when interpreting the results of this study, including its retrospective, observational design. As such, the results depend solely on the accuracy and completion of provider and nursing documentation, and the noncontrolled study nature heightens the risk of evaluator bias as well as subjective interpretation of the collected data. In addition, being a single-center study, the results may not represent the general population or prescribing practices of other institutions. Moreover, those with renal impairment were excluded from the study, thus possibly reducing real-world data. Investigators were also unable to account for whether patients were rehospitalized and/or treated elsewhere for psychiatric reasons other than at the study institution. The study's evaluation of EPS treatment was also limited considering that only 4 oral medications were examined and the use of diphenhydramine and benzodiazepines was excluded. Finally, given that patients in the nontraditional group obtained a shorter LOS, it is possible that there was not an adequate amount of time between postregimen completion and the onset of side effects before discharge to assess safety from these regimens.

Despite these limitations, the current study contains valuable information that observes real-world prescribing practices of an academic inpatient county, safety-net psychiatric hospital with limited exclusion criteria to allow for generalization to a diverse patient population. Based on our results, we were unable to find differences in readmission rates or adverse events between the traditional and nontraditional timings of the second PP dose; however, further larger, prospective, randomized controlled trials are needed to contribute to these results and provide additional data regarding clinical differences in efficacy and safety.

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