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Dosing strategies for switching from oral risperidone to paliperidone palmitate: Effects on clinical outcomes

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Abstract

Introduction: There are currently no guidelines for switching patients from oral risperidone to paliperidone palmitate (Invega Sustenna®). Furthermore, the paliperidone long-acting injectable (LAI) package insert does not recommend bridging with oral antipsychotics, which may result in inadequate serum concentrations in patients on ≥4 mg/d risperidone.

Methods: This study evaluated the effects of suboptimal dosing and bridging in patients switched from oral risperidone to paliperidone LAI on hospitalization days, emergency department (ED)/mental health urgent care visits, and no-shows/cancellations to mental health appointments. Patients were categorized into *optimal* or *suboptimal* dosing based on their loading and maintenance paliperidone doses. Patients on risperidone ≥4 mg/d were categorized as *bridged* if they received risperidone for ≥7 days after the first paliperidone injection.

Results: There were no significant differences in outcomes between optimally and suboptimally dosed patients. There were statistically significant reductions in hospitalization days in patients who were bridged compared with patients who were not bridged. There were statistically significant reductions in hospitalization days and ED/mental health urgent care visits after switching to paliperidone LAI.

Discussion: The results of this study indicate that bridging patients who are on ≥4 mg/d risperidone, when converting to paliperidone LAI, is associated with reductions in hospitalization days. However, more research is required to determine the optimal dose and duration of the bridge. The results also indicate that switching patients from oral risperidone to paliperidone LAI, even if the dose is suboptimal, is associated with reductions in hospitalization days and ED/mental health urgent care visits.

Keywords: paliperidone palmitate, Invega Sustenna, risperidone, schizophrenia, schizoaffective, hospitalizations, dosing, bridging, dose, bridge, long-acting injectable, injectable, antipsychotics, outcome

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Introduction

Studies have demonstrated that patients with schizophrenia started on the long-acting injectable (LAI) paliperidone palmitate (Invega Sustenna®, Janssen Pharmaceutical Titusville, NJ) have improved adherence, reduction in

rehospitalizations, and prolonged time to relapse compared with patients on typical and atypical oral antipsychotics.[1-3] These studies also note that dose adjustments in paliperidone LAI maintenance doses are often required because of incomplete efficacy.[4-6] There are limited guidelines for switching patients from oral antipsychotics to paliperidone LAI. The primary guidance comes from the paliperidone LAI package insert, which provides equivalencies for paliperidone extended-release (ER) tablets and paliperidone LAI.[7] At the Veterans Affairs San Diego Healthcare System (VASDHS) and other institutions, risperidone is the most commonly prescribed oral antipsychotic before patients are switched to paliperidone LAI, because it is inexpensive.[8] Additionally, paliperidone LAI is preferred over risperidone LAI because it is dosed monthly (risperidone LAI is every 2 weeks) and does not require refrigeration.[7] Although patients are often switched from oral risperidone to paliperidone LAI, there are no published studies recommending or evaluating a conversion between the two.[4,7,8]

The paliperidone LAI package insert recommends loading doses that result in plasma concentrations approximately equivalent to those of 6 to 12 mg of oral paliperidone ER.[7] The package insert also states bridging with oral antipsychotics is not necessary. However, because 4 mg/d oral risperidone is approximately equivalent to 8 mg/d paliperidone ER, recommended loading doses of paliperidone LAI would yield concentrations approximately equivalent to 3 to 6 mg of oral risperidone.[9] Especially if the plasma concentrations are closer to 6 mg of paliperidone ER (3 mg of oral risperidone), this may lead to subtherapeutic concentrations in patients who require doses of oral risperidone $\geq$4 mg/d.

The objectives of this study were to evaluate the effects of optimal dosing and bridging on clinical outcomes in patients with schizophrenia and schizoaffective disorder who were switched from oral risperidone to paliperidone LAI at VASDHS. The purpose of this study was to develop dosing guidance for switching patients from oral risperidone to paliperidone LAI.

Methods

Study Design

This study was an Institutional Review Board–approved, retrospective chart review involving patients at the VASDHS. Patients were included if they were 18 years or older, had a diagnosis of schizophrenia or schizoaffective disorder, were switched from oral risperidone to paliperidone LAI at VASDHS between January 1, 2009, and December 31, 2014, and received their paliperidone injections at a VA facility. Patients were excluded if they failed to meet inclusion criteria, had a creatinine clearance $\leq$50 mL/min, or were on a scheduled antipsychotic other than paliperidone or risperidone (ie, antipsychotic polypharmacy). Creatinine clearance was calculated using the Cockcroft-Gault equation and adjusted body weight. Baseline characteristics (demographic variables, medication history), psychiatric hospitalizations, emergency department (ED) visits for a psychiatric complaint, mental health (MH) urgent care visits, and number of scheduled and attended MH appointments were collected via chart review for 6 months prior to and after initiation of paliperidone LAI. Only hospitalizations, ED/MH urgent care visits, and MH appointments within the VA system were included in the data.

Data Categorization: Optimal and Suboptimal Dosing

Patients were categorized as optimal if they received optimal loading doses and an optimal maintenance dose. Optimal loading doses were based on recommendations from the paliperidone LAI package insert.[7] Optimal maintenance dose was based on the patient's last daily risperidone dose before the first paliperidone injection and approximate equivalencies between oral risperidone, paliperidone ER, and paliperidone LAI found in the literature and package insert.[7-9] For patients with creatinine clearance $\geq$80 mL/min, optimal loading doses were defined as paliperidone LAI 234 mg intramuscularly (IM) on day 1, followed by paliperidone LAI 156 mg IM between days 3 and 11. Maintenance dose was classified as optimal if it was given between 2 and 6 weeks after the second loading dose and was dosed based on oral risperidone dose: for patients on $\leq$3 mg/d, a maintenance dose of $\geq$117 mg; for patients on 4 to 5 mg/d, a maintenance dose of $\geq$156 mg; for patients on $\geq$6 mg/d, a maintenance dose of 234 mg. For patients with creatinine clearance $<$80 mL/min, optimal loading doses were defined as paliperidone LAI 156 mg IM on day 1, followed by 1 dose of 117 mg IM between days 3 and 11. Optimal maintenance dose was defined as $\geq$78 mg of paliperidone LAI between 2 and 6 weeks after the second loading dose. All patients who did not meet criteria for optimal dosing were categorized as suboptimally dosed.

Data Categorization: Bridging

Only patients who were on risperidone doses $\geq$4 mg/d prior to switching to paliperidone LAI were included in the bridging arm, because these were patients at risk of subtherapeutic levels from the recommended loading doses.[7-9] Patients were categorized as bridged if they were continued on oral risperidone for $\geq$7 days past the first dose of paliperidone LAI.

TABLE 1: Baseline demographics

	All	Suboptimal	Optimal	Not Bridged	Bridged
No. (%) of patients	75	48 (64)	27 (36)	. . .	. . .
Risperidone ≥4 mg/d, No. (%)	55 (73.3)	. . .	. . .	29 (52.7)	26 (47.3)
Age, y, mean	48.5	50.5	44.9	47.3	50.9
Sex, No. (%)					
Male	68 (90.7)	44 (91.7)	24 (88.9)	26 (89.7)	25 (96.2)
Female	7 (9.3)	4 (8.3)	3 (11.1)	3 (10.3)	1 (3.8)
Ethnicity, No. (%)					
White	36 (48.0)	22 (45.8)	14 (51.9)	15 (51.7)	10 (38.4)
African American	26 (34.7)	18 (37.5)	8 (29.6)	11 (37.9)	11 (42.3)
Asian	5 (6.7)	3 (6.3)	2 (7.4)	0 (0)	2 (7.7)
Not specified	8 (10.7)	5 (10.4)	3 (11.1)	3 (10.3)	3 (11.5)
Diagnosis					
Schizoaffective, No. (%)	26 (34.7)	13 (27.1)	13 (48.1)	13 (44.8)	6 (23.1)
Schizophrenia, No. (%)	49 (65.3)	35 (72.9)	14 (51.9)	16 (55.2)	20 (76.9)
CrCl, mL/min, mean	106	104	110	108	104
CrCl <80 mL/min, No. (%)	10 (13.3)	8 (80)	2 (20)	3 (33.3)	6 (66.7)
CrCl ≥80 mL/min, No. (%)	65 (86.7)	40 (61.5)	25 (38.4)	26 (56.6)	20 (43.5)
Alcohol/drug dependence, No. (%)					
Yes	36 (48.0)	21 (43.8)	15 (55.6)	14 (48.3)	10 (38.5)
No	39 (52.0)	27 (56.3)	12 (44.4)	15 (51.7)	16 (61.5)
Other psychiatric medications, No. (%)[a]					
Yes	44 (58.7)	31 (64.6)	13 (48.1)	13 (44.8)	7 (26.9)
No	31 (41.3)	17 (35.4)	14 (51.9)	16 (61.5)	19 (73.1)
Oral risperidone dose, mean	4.8	5	4.5	5	6.4
Paliperidone LAI maintenance dose, mg, mean	114	77	181	93	147

CrCl = creatinine clearance; LAI = long-acting injectable.

[a]Other psychiatric medications include antidepressants and mood stabilizers.

Outcomes

The primary outcome was difference in reduction of hospitalization days 6 months prior to and after initiation of paliperidone LAI. Secondary outcomes were differences in reduction of ED/MH urgent care visits and in percentage of no-shows/cancellations to MH appointments. The primary and secondary outcomes were compared for the following groups: suboptimal and optimal (between groups), bridged and not bridged (between groups), and prepaliperidone and postpaliperidone (within group).

Statistical Analysis

An intent-to-treat analysis was conducted. Change in hospitalization days, ED/MH urgent care visits, and percentage of no-show/canceled MH appointments were calculated using Microsoft Excel (Redmond, WA). Mann-Whitney *U* tests for independent samples were used to compare outcomes between the optimal and suboptimal, and the bridged and not bridged groups. The Wilcoxon signed rank test for paired samples was used to compare outcomes 6 months prior to 6 months after the switch to paliperidone LAI. Fisher exact *t* tests were used to detect significant differences in baseline characteristics. All statistical analyses were conducted using SPSS software (Chicago, IL).

Results

Baseline Demographics

A total of 162 patients were identified who were initiated on paliperidone LAI at the VASDHS between January 1, 2009, and December 31, 2014. Of the 162, a total of 75 met inclusion criteria. The most common reasons for being excluded were having a diagnosis other than schizophrenia/schizoaffective disorder (33) and being switched from an antipsychotic other than risperidone (31). Of the 75 included, 48 (64%) were classified as suboptimal and 27 (36%) as optimal, and 55 were on ≥4 mg/d oral risperidone before switching to paliperidone LAI. Of the 55 patients, 26 (47%) were bridged with ≥7

TABLE 2: Outcomes between suboptimal versus optimal and bridged versus not bridged groups

	Suboptimal	Optimal	*P* Value	Not Bridged	Bridged	*P* Value
Change in hospitalization days[a]						
First quartile	−20.25	−18		−14	−31.5	
Median	−11	−8	.787	−8	−17.5	.027*
Third quartile	−0.75	0		8	−1.5	
Change in emergency department/mental health urgent care visits[a]						
First quartile	−1	−1.5		−2	−1	
Median	−1	−1	.397	−1	−1	.743
Third quartile	0	0		0	0	
Change in percentage of no-showed/canceled mental health visits[a]						
First quartile	−6.79	−19.0		−6.78	−22.2	
Median	0	0	.311	0	0	.083
Third quartile	33.3	25		25	20	

CrCl = creatinine clearance.

[a]Postpaliperidone value – prepaliperidone value.

*$P < .05$.

days of oral risperidone and 29 (53%) were not. Table 1 summarizes the baseline characteristics of the comparator groups. There were no statistically significant differences in baseline characteristics between the suboptimal and optimal, and the bridged and not bridged groups. The most common reasons for suboptimal dosing were failure to receive a maintenance dose (35%), followed by receiving a suboptimal maintenance dose (25%), and failure to receive a second loading dose (17%).

Optimal Versus Suboptimal Dosing

Table 2 summarizes the primary and secondary outcomes for the optimal versus suboptimal and bridged versus not bridged groups. There was no significant difference in median reduction of days of hospitalization between the optimal and suboptimal groups. The first and third quartiles for reduction in hospitalization days were numerically, but not statistically, greater in the suboptimal group compared with the optimal group. The median, first quartile, and third quartile for change in ED/MH urgent care visits were approximately the same for suboptimal and optimal groups. The first and third quartiles for change in percentage of no-shows/cancellations to MH appointments were numerically, but not statistically, lower/more negative in the optimal group than in the suboptimal group. The median change in percentage of no-show/canceled MH visits was the same in the optimal and suboptimal groups.

Bridged Versus Not Bridged

The dose of the risperidone bridge ranged from 2 to 12 mg/d and from 33% to 100% of the patient's oral risperidone dose, with a mode and median bridge dose of 4 mg/d. The length of the risperidone bridge ranged from 7 to 470 days, with a mode of 7 days and median of 29 days. The trimmed mean duration of bridging was 30 days. The median, first-quartile, and third-quartile reductions in hospitalization days were significantly greater in patients who were bridged compared with those who were not bridged. There were no significant differences in the median, first quartile, and third quartile for reduction of ED/MH urgent care visits between bridged and not bridged groups. The first- and third-quartile reductions in percentage of no-shows/cancellations to MH appointments were numerically, but not statistically, greater in the bridged group compared with the not bridged group. There was no difference in the median reduction of percentage of no-showed/canceled MH appointments between the bridged and not bridged groups.

Prepaliperidone LAI Versus Postpaliperidone LAI

Table 3 summarizes the primary and secondary outcomes 6 months prior to and following the initiation of paliperidone LAI. There were statistically significant reductions in median, first-quartile, and third-quartile hospitalization days and ED/MH urgent care visits in the 6 months after initiation of paliperidone LAI compared with the 6 months prior to initiation. There was a numerically, albeit not statistically significant, reduction in median, first-quartile, and third-quartile percentage of no-shows/cancellations to MH visits.

Discussion

Although there were some numeric trends favoring patients who were optimally dosed, none of these reached

TABLE 3: Outcomes between prepaliperidone long-acting injectable (LAI) versus postpaliperidone LAI

	Prepaliperidone	Postpaliperidone	*P* Value
Hospitalization days			
First quartile	8	0	
Median	15	0	<.001*
Third quartile	23	10.5	
Emergency department/mental health urgent care visits			
First quartile	1	0	
Median	1	0	<.01*
Third quartile	2	1	
Percentage of no-show/canceled mental health appointments			
First quartile	0	0	
Median	33	25	.059
Third quartile	66.7	50	

*$P < .05$.

statistical significance. This may in part be due to the small sample size and the broad distribution of data. A post hoc power analysis determined that, given the small sample size, there was insufficient power to determine statistical significance between the optimal and suboptimal groups. Additionally, the conversion from oral risperidone to paliperidone LAI was based on reported equivalencies in the literature and may require revision. It is notable that the most prevalent reason (35%) for patients receiving suboptimal dosing was a failure to receive a maintenance dose injection. This indicates that although LAI antipsychotics have been associated with improved adherence compared with oral antipsychotics, nonadherence to these medications can still occur and should be addressed.

The results of this study suggest that bridging patients who are on ≥4 mg/d risperidone with oral risperidone for at least 7 days may be associated with a greater reduction in hospitalization days. Since the recommended loading doses result in levels approximately equivalent to 3 to 6 mg/d risperidone, bridging patients with oral risperidone may help maintain therapeutic levels until the paliperidone LAI reaches steady state. There was a wide range of bridging doses and durations. The most commonly used bridging strategy was continuation of risperidone 4 mg/d for 7 days after the first loading dose. However, further research is required before a specific recommendation for bridging can be made.

Switching from oral risperidone to paliperidone LAI was associated with statistically significant decreases in hospitalization days and ED/MH urgent care visits, even though 64% of included patients were dosed suboptimally. This suggests that, even if the paliperidone LAI is dosed suboptimally, switching patients from oral risperidone to paliperidone LAI may be associated with decreased hospitalization days and ED/MH urgent care visits. There was large variability in the dosing strategies for loading, maintenance doses, and bridging, which further illustrates the importance of a standardized dosing protocol for transitioning patients from oral risperidone to paliperidone LAI.

The primary limitations of this study were its retrospective nature, small sample size, specific population (predominantly male and white), and restriction to VA data. Additionally, outcomes were only assessed for 6 months prior to and following initiation of paliperidone LAI. In future studies, it may be beneficial to follow clinical outcomes across a longer time period (eg, 1 year) and across multiple health systems if possible.

Conclusion

This study suggested that bridging patients on risperidone ≥4 mg/d with at least 7 days of oral risperidone upon initiation of paliperidone LAI is associated with greater reduction in hospitalization days. Although there were no significant differences between optimally and suboptimally dosed patients, this study was also underpowered to detect such a difference, given the small sample size. This study also indicated that switching patients from oral risperidone to paliperidone LAI is associated with significant reductions in hospitalization days and visits to the ED/MH urgent care clinics, regardless of whether patients were dosed optimally or suboptimally. Given the retrospective nature of the study and the large variability of dosing and bridging strategies, further studies are warranted to determine the appropriate dose conversion and bridging dose when switching from oral risperidone to paliperidone LAI. As has been demonstrated in previous studies, paliperidone LAI is associated with improved clinical outcomes and remains a viable option for patients who are nonadherent to oral medications. Given the increasing utility of LAI antipsychotics, it is crucial to determine optimal dosing of these medications. By doing so, we can use these medications effectively to improve quality of life and clinical outcomes for our psychiatric patients.

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