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The effects of concurrent oral paliperidone or risperidone use with paliperidone long-acting injection

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Abstract

Introduction: Dosing recommendations for paliperidone long-acting injectable antipsychotic (LAIA) do not include oral antipsychotic (OAP) overlap; however, OAPs are often given concurrently despite limited evidence describing both the risks and benefits of this practice.

Methods: A retrospective chart review was conducted in patients initiated on paliperidone palmitate (PP) during a psychiatric hospitalization to compare patients who received OAP overlap versus those who did not. The primary outcome is the proportion of patients who receive prescription claims for benztropine, a medication commonly prescribed for extrapyramidal symptoms, at the time of LAIA discontinuation and 6 months postdischarge. Secondary outcomes include prescription claims for beta blockers and diphenhydramine, number of psychiatric emergency visits and hospitalizations, length of stay of the index hospitalization, frequency of LAIA discontinuation and the time to LAIA discontinuation.

Results: There is a significant difference in the proportion of benztropine prescription claims in the OAP overlap group versus the no-overlap group at the time of LAIA discontinuation (30% vs 0%, $P = .046$) but not at 6 months postdischarge. There are also significant differences in the number of psychiatric emergency visits (0.7 vs 0.1, $P = .02$) and psychiatric hospitalizations (0.6 vs 0.1, $P = .029$) at the time of LAIA discontinuation. No other differences are observed in defined secondary outcomes.

Discussion: Patients who receive OAP overlap while receiving PP receive more benztropine and have more psychiatric emergency visits and hospitalizations than those treated without OAP. Larger studies with better control for confounding variables are needed to confirm these results.

Keywords: paliperidone palmitate, long-acting injectable antipsychotic, oral antipsychotic overlap, benztropine, adverse events, decompensation

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Introduction

Long-acting injectable antipsychotics (LAIAs) were developed with the goal of improving adherence and preventing relapse in patients with psychotic disorders.[1-3] LAIAs have been shown to prevent psychiatric hospitalizations in patients previously treated with oral antipsychotics (OAPs), promote medication adherence, and prevent relapse in patients with early phase or first-episode psychosis.[1,4-8] LAIAs are designed to slowly release medication, providing extended antipsychotic coverage. As a result of this slow release and delayed onset, product labeling for different LAIAs recommend strategies such as OAP overlap or specific initiation doses to achieve therapeutic concentrations. Despite these recommendations, OAPs are commonly continued concomitantly with LAIAs contrary to recommendations in the product labeling with studies reporting concurrent prescribing frequencies of 21%-76%.[9-14]

Paliperidone palmitate (PP) is a second-generation antipsychotic available in 2 LAIA formulations.[15,16] The product labeling for the monthly PP recommends a 2-dose regimen when initiating PP.[15] In model-based pharmacokinetic simulations, this initiation regimen reaches therapeutic plasma concentrations within the first week for 84% of patients and maintains these concentrations on days 8 and 36 for 90% of patients.[17-19] The product labeling recommends caution when administering PP with oral paliperidone or risperidone, which is metabolized to paliperidone, due to the limited safety data available for this combination.[15,16]

Although most studies focused on LAIA and OAP prescribing patterns, only 3 studies[11,20,21] reported any tolerability or efficacy outcomes as a result of using LAIA and OAP concomitantly. One study[11] describing the prevalence of concomitant LAIA and OAP prescribing in a veteran population incidentally found no difference in prescriptions for the treatment of EPS in patients receiving both LAIAs and OAPs versus those receiving LAIAs alone. A second study[20] assessing differences between patients treated with long-acting olanzapine with or without oral olanzapine supplementation found that participants who received oral supplementation were more likely to drop out of the study for any cause. Finally a retrospective chart review[21] assessed the effects of OAP overlap with risperidone on patients initiated on PP. The study calculated a reduction in hospitalization days based on total hospitalization days in the 6 months before and after PP initiation. Patients who received at least 7 days of oral risperidone following PP initiation had a significantly larger decrease in hospitalization days.[21]

Contrary to recommendations in the product labeling, oral paliperidone and risperidone are commonly continued concurrently with PP, and little is known about the consequences or benefits of this concurrent use. Because the initiation regimen of PP is designed to achieve therapeutic plasma concentrations independent of OAP overlap,[15,17-19] little is known about the impact of this practice on the efficacy of PP, and patients may be at risk for adverse effects with concurrent oral use. The objective of this study is to assess the effects of concurrent OAP overlap with paliperidone or risperidone and PP.

Methods

This study was a single-site retrospective chart review of PP use and concurrent OAP overlap at an acute care psychiatric facility. IRB and facility approval was obtained prior to data collection. Patients were included if they were 18 years or older, had active Medicaid coverage at discharge, and received the 2-dose initiation regimen of PP while admitted to the facility between January 1, 2017, and June 30, 2018. Patients were excluded if they were discharged to correctional, residential treatment, or skilled nursing facilities. Patients discharged to such facilities may not have reliable prescription claims data. Additionally, the monitoring of medication adherence would likely be a confounding variable for some of our secondary outcomes, such as the proportion of patients who discontinued their LAIA and the number of days to LAIA discontinuation.

Baseline demographics and data from the index hospitalization were collected using Cerner electronic health record. Subsequent LAIA administration, psychiatric emergency visits, and psychiatric hospitalizations for the 6 months following discharge were collected through Missouri HealthNet's CyberAccess electronic health record, which provided access to prescription, procedural, and other Medicaid claims data. Following screening for inclusion, patients were divided into 2 groups based on concurrent OAP use. Patients who received at least 1 dose of oral paliperidone or risperidone after their first PP LAI injection were assigned to the oral overlap group.

The primary outcome of this study was the proportion of patients with prescription claims for benztropine, a medication commonly prescribed to treat EPS. This outcome was chosen as a surrogate marker for adverse effects. Secondary outcomes included the proportion of patients who received prescription claims for beta

TABLE 1: Baseline demographics and concurrent medication use

	All Patients (n = 33)	Overlap (n = 13)	No Overlap (n = 20)	*P* Value
Age, y, mean ± SD	35.3 ± 11.8	40 ± 12.9	32.2 ± 10.1	.061
Male, n (%)	17 (51.5)	7 (53.8)	10 (50.0)	.829
Race, n (%)				
White	17 (51.5)	8 (61.5)	9 (45.0)	.353
African American	14 (42.4)	4 (30.8)	10 (50.0)	.275
Other	2 (6.1)	1 (7.7)	1 (5.0)	1.000
Primary diagnosis, n (%)				
Schizophrenia	15 (45.5)	6 (46.2)	9 (45.0)	.948
Schizoaffective	5 (15.2)	2 (15.4)	3 (15.0)	1.000
Bipolar disorder	4 (12.1)	1 (7.7)	3 (15.0)	1.000
Psychosis NOS	7 (21.2)	4 (30.8)	3 (15.0)	.393
Other	2 (6.1)	0 (0)	2 (10.0)	.508
BMI, kg/m^2, mean ± SD	27.9 ± 8.4	28 ± 10	27.8 ± 7.5	.928
History of PP, n (%)	14 (42.4)	7 (53.8)	7 (35.0)	.284
PP maintenance dose, mg, n (%)				
234	3 (9.1)	1 (7.7)	2 (10.0)	1.000
156	27 (81.8)	12 (92.3)	15 (75.0)	.364
117	3 (9.1)	0 (0)	3 (15.0)	.261
Medication use during admission, n (%)				
Antipsychotic[a,b]	27 (81.8)	10 (76.9)	17 (85.0)	.659
Antidepressant	8 (24.2)	3 (23.1)	5 (25.0)	1.000
Mood stabilizer	2 (6.1)	2 (15.4)	0 (0)	.148
Medication at PP discontinuation, n (%)				
Antipsychotic[a,b]	8 (30.1)[c]	5 (50)[d]	3 (18.8)[e]	.189
Antidepressant	3 (11.5)[c]	2 (20)[d]	1 (6.3)[e]	.538
Mood stabilizer	5 (19.2)[c]	4 (40)[d]	1 (6.3)[e]	.055

NOS = not otherwise specified; PP = paliperidone palmitate.

[a]Includes as-needed medications.

[b]Antipsychotics excluding oral paliperidone or risperidone.

[c]Only includes patients who discontinued long-acting injectable antipsychotic (n = 26).

[d]Only includes patients who discontinued long-acting injectable antipsychotic (n = 10).

[e]Only includes patients who discontinued long-acting injectable antipsychotic (n = 16).

blockers or diphenhydramine, the number of psychiatric emergency visits, the number of psychiatric hospitalizations, the average length of stay of the index hospitalization, the proportion of patients who discontinued their LAIA, and the number of days to LAIA discontinuation. All outcomes for the study were assessed at 2 time points: at the time of LAIA discontinuation and at 6 months after discharge. LAIA discontinuation was defined as 45 days after the last documented administration of PP to account for late doses.

Pearson correlations were utilized to identify variables that correlated with OAP overlap use. These results were then confirmed with chi-square or Fisher exact tests for categorical variables, and *t*-tests for continuous variables.

Results

An initial 142 patients were screened for study eligibility. Of these patients, 33 met inclusion criteria, and 13 received oral overlap. Most patients were excluded for lack of Medicaid coverage for the entire 6-month follow-up period. Demographic information is included in Table 1. Overall, the sample was balanced by gender (51.5% male) and race (51.5% White, 42.4% African American). Most patients had a primary diagnosis of schizophrenia (45.5%) followed by schizoaffective disorder (15.2%) or bipolar disorder (12.1%). Fourteen patients (42.4%) had a documented history of receiving PP prior to this study and, thus, were reinitiated on PP during their index hospitalization. Of the patients included, a high proportion (78.8%) discontinued their LAIA during the 6 months following discharge.

TABLE 2: Pearson correlations for primary and secondary outcomes

	Overlap (n = 13)	No Overlap (n = 20)	*r* Value	*P* Value
Primary outcome				
Benztropine use, n (%)				
At PP discontinuation	3 (30)[a]	0 (0)[b]	.457	.019[c]
At 6 mo	4 (30.77)	3 (15)	.188	.294
Secondary outcomes				
Beta blocker use, n (%)				
At PP discontinuation	1 (10)[a]	1 (6.3)[b]	.068	.740
At 6 mo	1 (7.69)	1 (5)	.055	.761
Diphenhydramine use, n (%)				
At PP discontinuation	0 (0)[a]	0 (0)[b]	. . .[d]	. . .[d]
At 6 mo	0 (0)	0 (0)	. . .[d]	. . .[d]
Time to PP discontinuation, mean ± SD	106.5 ± 56.65	82.5 ± 52.2	.219	.220
PP discontinued, n (%)	10 (76.92)	16 (80)	−.037	.839
Length of stay, mean ± SD	14.9 ± 16.23	19.4 ± 14	−.151	.402
Psychiatric emergency visits, mean ± SD				
At PP discontinuation	0.7 ± 0.8[a]	0.1 ± 0.3[b]	.454	.020[c]
At 6 mo	1.2 ± 1.1	0.65 ± 1.1	.218	.224
Psychiatric hospitalizations, mean ± SD				
At PP discontinuation	0.6 ± 0.7[a]	0.1 ± 0.3[b]	.429	.029[c]
At 7 mo	0.8 ± 0.8	0.4 ± 0.6	.292	.099

PP = paliperidone palmitate.

[a]This outcome only includes patients who discontinued paliperidone palmitate (n = 10).

[b]This outcome only includes patients who discontinued paliperidone palmitate (n = 16).

[c]Results statistically significant with a 2-tailed alpha of .05.

[d]Correlation is unable to be calculated given constant (0) diphenhydramine prescription claims in both groups.

In the OAP overlap group, most patients received paliperidone (69.2%). Daily doses ranged from 3 to 9 mg with an average of 6 mg. The remainder of the patients received OAP overlap with risperidone with an average daily dose of 4 mg and doses ranging from 1 to 6 mg. The median duration of overlap was 7 days (interquartile range 5 to 42); however, most patients only received OAP overlap while admitted. Four patients (30.7%) were discharged with prescriptions for OAP overlap of 42 to 126 days.

Results for both primary and secondary outcomes are displayed in Table 2. For the primary outcome, benztropine prescription claims, 30% of patients had a documented claim at the time of LAIA discontinuation in the OAP overlap group versus no patients in the no-overlap group. This showed a significant correlation at the time of LAIA discontinuation ($r = .457$, $P = .019$), which was confirmed with a Fisher exact test ($P = .046$). This correlation did not persist at the 6-month time point, at which most patients had discontinued PP (78.8%). There were no prescription claims for diphenhydramine, trihexyphenidyl, or other medications used commonly for EPS at either time point.

For secondary outcomes, a significant correlation was found for both psychiatric emergency visits ($r = .454$, $P = .02$) and hospitalizations ($r = .429$, $P = .029$) at the time of LAIA discontinuation, which were confirmed with *t*-tests ($P = .02$ and $P = .029$, respectively). Once again, these correlations did not persist at the 6-month time point. Despite the smaller number of patients in the OAP group, 53.6% of all psychiatric emergency visits (15/28) and 58.8% of all psychiatric hospitalizations (10/17) occurred in the OAP group. Patients who received OAP overlap were also more likely to have prescription claims for an OAP other than paliperidone or risperidone at the time of LAIA discontinuation (50%, n = 10 vs 19%, n = 16). There were no significant correlations found in other secondary outcomes as described in Table 2.

Discussion

In this study, concurrent oral paliperidone or risperidone use with PP was associated with more frequent prescription claims for benztropine, psychiatric emergency visits, and psychiatric hospitalizations. Because benztropine is commonly used to treat EPS, this finding could indicate that patients who received OAP overlap were more likely

to experience EPS. EPS can be uncomfortable and functionally impairing to patients and represent a leading cause of treatment nonadherence.[22-26] The addition of anticholinergic medications, such as benztropine, can magnify anticholinergic burden, which worsens anticholinergic adverse effects and has been associated with impairments in cognitive and physical function and increased risk of hospitalization and mortality in the elderly.[27-37]

A higher frequency of psychiatric hospitalizations and emergency visits and no difference in length of stay of the index hospitalization was seen with OAP overlap. Although the cause of this increase in hospitalizations and emergency visits cannot be determined, it is likely multifactorial. One possible explanation is that patients who received OAPs had a more severe presentation at baseline, which may have been part of the initial rationale for utilizing OAP overlap. However, in contrast to findings by Hsia et al,[21] we found an increase rather than a reduction in hospitalization with the use of OAP overlap. Our study used a different definition of oral overlap than the $\geq$7 days of oral risperidone used by Hsia et al.[21] Patients in our study received higher mean PP maintenance doses (OAP 162 mg vs no-OAP 140.4 mg) compared to patients in the study by Hsia et al[21] (OAP 147 mg vs no-OAP 93 mg). In addition to the differences in maintenance regimens, other confounding variables likely contributed to the differences in our results.

To our knowledge, our study is the first to specifically examine both aspects of safety and outcomes related to psychiatric emergency visits and hospitalizations associated with OAP overlap use with PP. In addition, the study was not limited to the index hospitalization, but followed patients for 6 months after hospital discharge. During this 6-month time point, most patients in both the overlap (76.9%) and no-overlap groups (80%) discontinued their LAIA. Because most patients had discontinued their LAIA, it is unlikely that there would have been additional efficacy or safety changes that resulted after the 6 months.

These results are not without limitations. First, a small sample size from a single institution may have impacted the ability to detect statistically significant differences. Additionally, no baseline assessments of illness severity were collected as these are not routinely collected or systematically documented at the study institution. Thus, baseline illness severity is an important confounding variable that may have influenced our results. Although we did collect some information on concurrent medications, this information was limited, and due to our small sample size, analysis based on concurrent medication use would not have yielded meaningful results. Finally, the study utilizes Medicaid claims data for many of its outcomes. Although this allowed for patients to be followed for 6 months after discharge regardless of the location of outpatient follow-up, claims data is not without its limitations. Adherence to prescribed oral medications was unable to be assessed. Additionally, inpatient administration of PP given outside of our facility would not have been captured in data collection; some oral medications, such as over-the-counter diphenhydramine, a medication commonly used for EPS, may not be captured by prescription claims data; and information on prescribed frequency, including as needed frequencies, was limited. In addition, this claims data was used as a surrogate marker for adverse effects; however, some providers may have elected to prescribe anticholinergic medications prophylactically or for other indications.

In this study, concurrent oral paliperidone or risperidone use with PP was associated with more frequent prescription claims for benztropine, psychiatric emergency visits, and hospitalizations. Although this could suggest a higher frequency of adverse effects and decompensation in patients with concurrent OAP and LAIA, larger prospective studies with better control for confounding variables would be needed to confirm these results. In addition, although the definition of OAP overlap used in this study was justified by the product labeling, duration of OAP overlap likely impacts both efficacy and safety outcomes, and future studies should evaluate a relationship between duration of OAP overlap and these outcomes.

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