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Switching patients with schizophrenia from paliperidone palmitate to aripiprazole lauroxil: A 6-month, prospective, open-label study☆

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ABSTRACT

We assessed the effectiveness of switching from paliperidone palmitate (PP) or risperidone long-acting injection (RLAI) to aripiprazole lauroxil (AL). Prospective, 6-month study in patients with schizophrenia with residual symptoms or intolerance with PP/RLAI. Effectiveness assessed via all-cause and medication-related discontinuation; CGI-S/BPRS and adverse event monitoring assessed efficacy/tolerability, respectively. Fifty-one patients ($n = 50$ PP; $n = 1$ RLAI) enrolled; 35 completed the study. All-cause and medication-related discontinuation was 30% and 9% over 6 months, respectively. CGI-S/BPRS improved significantly in those continuing treatment. Adverse events were generally mild to moderate. Patients with efficacy or tolerability concerns with PP/RLAI can be switched to AL.

1. Introduction

As the number of long-acting injectable antipsychotic medication options increases, the need has grown for commensurate data pertaining to safety and outcomes when switching between different LAIs (Correll et al., 2016). In particular, clinicians may hesitate to recommend a medication change because they are unsure about the relative safety of switching a patient from one long-acting injectable antipsychotic medication based on suboptimal response to another long-acting injectable with a different pharmacodynamic profile.

Paliperidone palmitate (PP) and risperidone LAI (RLAI) are widely used atypical long-acting injectable antipsychotics. Although PP and RLAI are effective, as with any first-line antipsychotics, PP and RLAI will not be fully effective or tolerable for all patients, and clinicians may consider switching to another LAI with a different pharmacodynamic profile. Aripiprazole lauroxil (AL), a prodrug of the atypical antipsychotic aripiprazole, is an long-acting injectable for the treatment of adults with schizophrenia (Citrome, 2016; Cruz, 2016). The objective of this study was to assess the clinical outcomes and safety of switching patients who continue to experience persistent symptoms or tolerability problems from PP/RLAI to AL.

2. Experimental methods

2.1. Study design

This was a prospective, 6-month, open-label study in patients with schizophrenia who were clinically stable on PP/RLAI but who continued to experience persistent symptoms or tolerability problems that may be addressed by a change in antipsychotic medication (ClinicalTrials.gov, NCT02634320; Fig. 1). The primary objective was to explore the treatment effectiveness, safety, and tolerability of AL in patients who had switched from PP/RLAI.

The first AL dose and subsequent dose adjustments were according to the investigator's clinical judgment. Stepwise dose decreases were allowed for tolerability, while increases were allowed for efficacy or up-titration. Most dose changes were performed after the second injection in accordance with protocol recommendations. Oral antipsychotics prescribed and administered at therapeutic levels before the start of the study could be continued at the investigator's discretion.

☆ Previous presentation: Study results have been presented as a poster at the 30th US Psychiatric and Mental Health Congress 2017 (New Orleans, LA, September 16–19).

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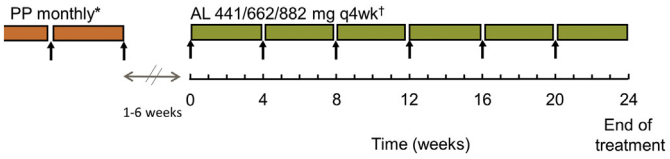


Fig. 1. Study design. Vertical arrows indicate PP monthly or AL q4wk administration. * Previous PP doses were in the range of 117–234 mg monthly; one patient previously received RLAI. † Flexibly dosed with q4wk injections occurring in weeks 4, 8, 12, 16, and 20. After the first injection, patients returned to the study site q4wk (441, 662, or 882 mg) or q6wk (882 mg only) for IM AL administration and outpatient assessments. Most patients (50 of 51) were on a q4wk AL regimen. ‡ Eligible patients must have demonstrated tolerability to oral aripiprazole (see text). Patients received their first dose of AL within 1 to 6 weeks after the last injection of the previous LAI. Administration of oral aripiprazole supplementation for 21 days with the initial dose of AL was at the discretion of the investigator. AL = aripiprazole lauroxil; IM = intramuscular; PP = paliperidone palmitate; RLAI = risperidone long-acting injection; qXwk = every 4 or 6 weeks.

2.2. Patients

Eligible participants were from 18 to 65 years of age with a diagnosis of schizophrenia as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (American Psychiatric Association, 2013). Patients had to have been clinically stable for ≥2 months (no hospitalizations and Brief Psychiatric Rating Scale [BPRS] score ≥30 and ≤45), and had to have been treated with ≥3 doses of PP/RLAI before screening, with no antipsychotic medication regimen change for 4 weeks before day 1.

2.3. Outcome measures and assessments

A composite measure of treatment effectiveness was "all-cause discontinuation" (defined as discontinuation for any reason) (Lieberman et al., 2005) and "medication-related discontinuation" (defined as discontinuations specifically attributed to limitations of AL [i.e., due to lack of efficacy or an adverse event (AE)]).

Clinical symptoms were assessed using the Clinical Global Impressions–Severity (CGI-S; 7-point scale ranging from 1 [normal] to 7 [among the most extremely ill patients] (Guy, 1976)) and BPRS scores (18 items on which clinicians rate patients' symptoms on a 7-point scale (Overall and Gorham, 1962)) at baseline and monthly thereafter. Safety and tolerability was assessed by monitoring AEs.

2.4. Statistical analysis

The initial planned enrollment was 90 patients but the final enrollment included 51 patients because of enrollment challenges. Summary statistics (number, mean, and SD for continuous variables; number and percentage of patients in each category for categorical variables) are provided for variables evaluated.

Patient disposition and baseline demographics were summarized. Patients were categorized into three groups—persistent positive symptoms, persistent negative symptoms, and tolerability concerns—based on the primary reasons for switching at the time of study enrollment. Differences in baseline demographics and characteristics among the three groups were compared using analysis of variance for continuous outcomes and chi-square test for categorical outcomes.

Kaplan-Meier survival curves were used to estimate the time to discontinuation of treatment (all-cause and medication-related) in all enrolled patients. CGI-S and BPRS scores and change from baseline at each visit were summarized by switch group and overall using descriptive statistics. A one-sample *t*-test at each visit and at the end of the treatment period for all patients was conducted to determine whether changes from baseline were statistically significant. Changes in CGI-S and BPRS scores were also analyzed using a mixed-effects model for repeated measures (MMRM) for patients previously administered PP ($n = 50$) (excluding one patient previously treated with RLAI). These analyses included visits as factors and baseline values as covariates. The unstructured variance and covariance matrix was used to model within-subject variability. Least squares mean change from baseline and SE at each visit were reported and were compared for statistical significance on a 2-sided alpha level of 0.05.

3. Results

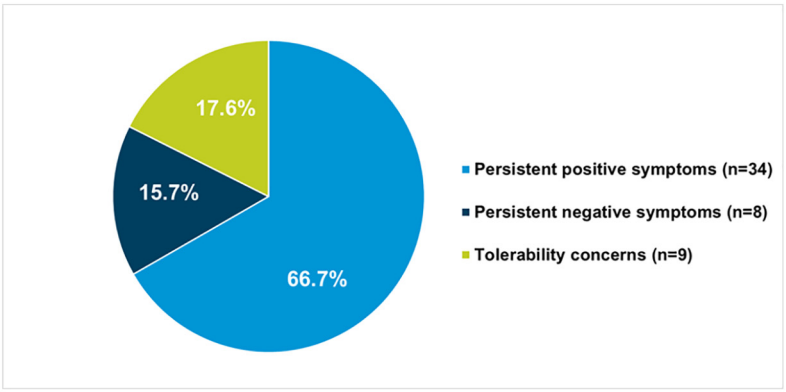
3.1. Patient disposition and baseline demographics

Fifty-one patients enrolled in the study and switched to AL from PP ($n = 50$) and RLAI ($n = 1$). Mean age was 40.6 years and most (72.5%) were men (Table 1). Primary reasons for switching patients from previous LAI to AL included persistent positive symptoms ($n = 34$; 66.7%), ongoing tolerability concerns ($n = 9$; 17.6%), and persistent negative symptoms ($n = 8$; 15.7%) (Fig. 2). Baseline characteristics were comparable between subgroups (Table 1), except for lower baseline CGI-S scores in the group who switched for tolerability reasons.

Table 1
Baseline demographics and characteristics.

Characteristic[a,b]	Reason for medication switch			All patients $N = 51$
	Persistent positive symptoms $n = 34$	Persistent negative symptoms $n = 8$	Tolerability concerns $n = 9$	
Age, years	40.6 (11.9)	40.5 (10.3)	41.1 (13.7)	40.6 (11.7)
Male, *n* (%)	24 (70.6)	7 (87.5)	6 (66.7)	37 (72.5)
Primary race, *n* (%)				
Black or African American	15 (44.1)	3 (37.5)	7 (77.8)	25 (49.0)
White	16 (47.1)	4 (50.0)	2 (22.2)	22 (43.1)
Asian	3 (8.8)	0	0	3 (5.9)
Other	0	1 (12.5)	0	1 (2.0)
BMI, kg/m^2	31.8 (6.2)	31.9 (10.6)	30.6 (3.6)	31.6 (6.6)
Duration of previous long-acting injectable antipsychotic use, months	15.1 (19.3)	20.9 (20.7)	8.6 (11.3)	14.9 (18.4)
Concomitant oral antipsychotic use, *n* (%)	13 (38.2)	2 (25.0)	1 (11.1)	16 (31.4)
BPRS total score	38.7 (6.37)	34.6 (2.97)	36.1 (3.82)	37.6 (5.74)
CGI-S score	4.1 (0.60)	3.9 (0.35)	3.3 (0.50)	3.9 (0.61)

BMI = body mass index; BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Improvement-Severity Scale.
[a] All values presented as mean (SD) unless otherwise indicated.
[b] No statistically significant differences in baseline demographics and characteristics among the three groups except for CGI-S score ($p = 0.004$).



Persistent Positive Symptoms (*n*=34)		Persistent Negative Symptoms (*n*=8)		Tolerability Concerns (*n*=9)	
Symptom	***n* (%)**	**Symptom**	***n* (%)**	**Tolerability Concern**	***n* (%)**
Hallucinations not improved	21 (61.8)	Suboptimal efficacy in negative symptoms	3 (37.5)	Movement disorder	3 (33.3)
Thought disorder not improved	7 (20.6)	Cognitive dulling/slowing	2 (25.0)	Sexual dysfunction	3 (33.3)
Suboptimal efficacy in positive symptoms	6 (17.6)	Social withdrawal	2 (25.0)	Other AE/ill effect	2 (22.2)
—	—	Blunting of affect	1 (12.5)	Excessive weight gain	1 (11.1)

Fig. 2. Primary reason for switch. During screening, reasons for changing antipsychotic medication were recorded by the investigator using a checkbox questionnaire.

3.2. Patient retention and time to treatment discontinuation

Of 51 patients, 68.6% ($n = 35$) completed all study follow-up visits over 6 months, and 16 (31.4%) discontinued before the final assessment. Of the 16 early discontinuations, the mean time between the last AL injection and end of study assessment was 39.9 days (SD 21.7; median, 36). The discontinuation rate attributed to lack of efficacy was 3.9% ($n = 2$) and to any AE was 3.9% ($n = 2$). Other reasons for discontinuation not attributed to either efficacy or tolerability included patient decision (9.8%; $n = 5$), loss to follow-up (5.9%; $n = 3$), other (5.9%; $n = 3$), and protocol deviation (2.0%; $n = 1$). The completion rate by initial reason for switching to AL was 88.9% (8/9) when switching for tolerability, 65% (22/34) for switching related to positive symptoms, and 62% (5/8) when switching for negative symptoms.

Kaplan-Meier plots of time to all-cause and medication-related discontinuations are shown in Fig. 3. The estimated probability of all-cause discontinuation at 6 months was 30.4% and of medication-related discontinuation was 9.2%.

3.3. Clinical symptoms and outcomes

3.3.1. CGI-S

Statistically significant improvements in CGI-S score were observed at month 3 and through the end of the treatment period using both one-sample *t*-test (mean change [SD] −0.4 [0.7], $p < 0.001$; Table 2) and MMRM (mean change [SE] −0.3 [0.12], $p = 0.01$) (Fig. 4a).

3.3.2. BPRS

The mean (SD) BPRS score decreased from 37.6 (5.7) to 32.7 (6.7) after 6 months of AL treatment (mean change [SD] −4.9 [8.5]; $p = 0.002$) (Table 2). Statistically significant improvements in BPRS scores were also observed at month 6 using MMRM (mean change [SE] −4.0 [1.3]; $p < 0.01$) (Fig. 4b).

3.4. Safety and tolerability

AEs were reported in 41.2% ($n = 21$) of patients; the most common were psychotic disorder (7.8%; $n = 4$), anxiety (5.9%; $n = 3$), and suicidal ideation (5.9%; $n = 3$) (Table 3). Nine patients (17.6%) had AEs

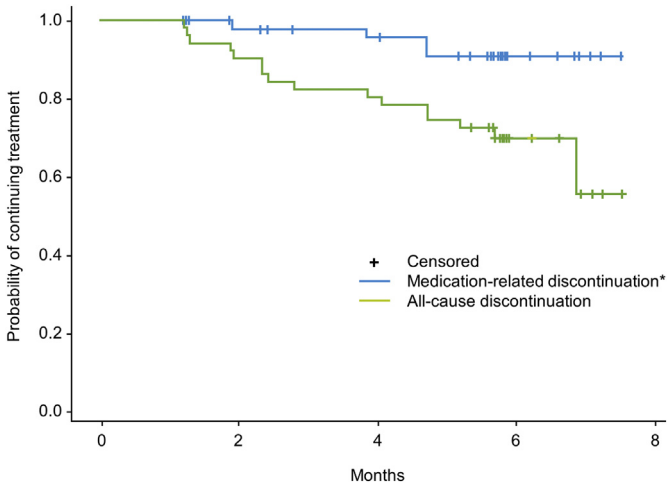


Fig. 3. Kaplan-Meier plot of time to medication-related and all-cause discontinuation. Discontinuation was defined as last study assessment, with a median of 36 days between the final AL injection and the discontinuation date. *Medication-related discontinuation was defined as any occurrence of discontinuation because of lack of efficacy or an adverse event.

Table 2
Clinical outcomes by reasons for switching to AL.

	Reasons for switch (switch group)			All patients $N = 51$
	Persistent positive symptoms $n = 34$	Persistent negative symptoms $n = 8$	Tolerability concerns $n = 9$	
CGI-S				
Baseline				
n	34	8	9	51
Mean (SD)	4.1 (0.6)	3.9 (0.4)	3.3 (0.5)	3.9 (0.6)
Day 169				
n	21	5	8	34
Change from baseline, mean (SD)	−0.4 (0.8)	−0.6 (0.6)	−0.4 (0.5)	−0.4 (0.7)
p-Value				<0.001
Last on-treatment visit				
n	33	7	9	49
Change from baseline, mean (SD)	−0.2 (0.9)	−0.6 (1.0)	−0.2 (0.7)	−0.2 (0.9)
p-Value				0.078
BPRS				
Baseline				
n	34	8	9	51
Mean (SD)	38.7 (6.4)	34.6 (3.0)	36.1 (3.8)	37.6 (5.7)
Day 169				
n	21	5	8	34
Change from baseline, mean (SD)	−4.3 (9.6)	−6.2 (5.0)	−5.9 (7.8)	−4.9 (8.5)
p-Value				0.002
Last on-treatment visit				
n	33	7	9	49
Change from baseline, mean (SD)	−1.6 (10.0)	−5.1 (6.2)	−4.8 (8.0)	−2.7 (9.2)
p-Value				0.045

Baseline is defined as the last non-missing value on or before the first dose of study drug. The *p*-value is for comparison of the mean change with 0 at each visit using a one-sample *t*-test. The *p*-value is provided for the "all patients" group only because of the small number in each group.
AL = aripiprazole lauroxil; BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impressions–Severity.

considered to be study drug-related. Most AEs (76.2%; $n = 16$) were mild or moderate. Two patients discontinued the study because of AEs (one due to psychotic disorder, one due to gynecomastia). Serious AEs were reported in five (9.8%) patients, none of which were related to the study drug, and no deaths were reported during the study. One patient experienced two episodes of akathisia, one mild and one moderate, which resolved spontaneously; no other extrapyramidal symptom–related AEs were reported.

4. Discussion

To our knowledge, this is the first prospective study of the safety of switching from other long-acting injectable antipsychotics to AL. More than two-thirds of patients completed the full 6-month course of AL and <10% discontinued treatment for medication-related reasons (lack of efficacy or an AE). The 6-month flexible AL regimen was associated with statistically significant improvements in clinical symptoms, as measured by the CGI-S and BPRS. As is the case with open-label switch studies, symptom improvement cannot be used to assess the relative efficacy of antipsychotics before and after switching because of selection of patients who, by definition, had efficacy or tolerability problems with the pre-switch medication.

In general, the switch from PP or RLAI to AL was well tolerated, with an AE profile consistent with the known safety profile of AL (Meltzer et al., 2015).

The strengths of this study are that it approximated clinical practice by using minimal inclusion/exclusion criteria, permitted the use of concomitant medications (including valproate and oral antipsychotics), and allowed flexible dosing based on the needs of patients. This is one of the few switching studies not limited by unknown adherence to

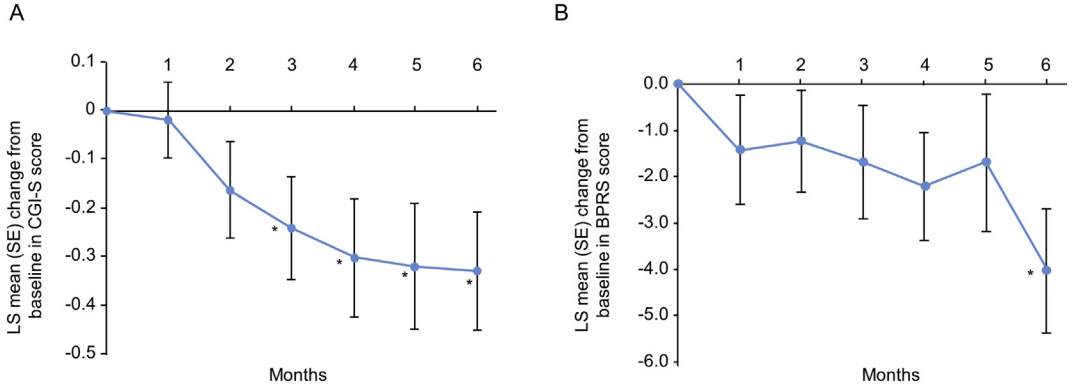


Fig. 4. Clinical outcomes. (A) Change in CGI-scores from baseline to 6 months of AL treatment (MMRM). Mean (SD) CGI-S score at baseline: 3.9 (0.6). *$p < 0.05$. (B) Change in BPRS total score from baseline to 6 months of AL treatment (MMRM). Mean (SD) BPRS score at baseline: 37.6 (5.7). *$p < 0.01$. AL = aripiprazole lauroxil; BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Index of Severity scale; LS = least squares; MMRM = mixed-effects model for repeated measurement.

Table 3
Overview of AEs.

AE category	All patients $N = 51$ n (%)
Any AE	21 (41.2)
Mild	6 (11.8)
Moderate	10 (19.6)
Severe	5 (9.8)
Any drug-related AE	9 (17.6)
Any AE leading to treatment discontinuation	2 (3.9)
Any SAE[a]	5 (9.8)
Any drug-related SAE	0
AEs in ≥3% of patients	
Psychotic disorder	4 (7.8)
Anxiety	3 (5.9)
Suicidal ideation	3 (5.9)
Diarrhea	2 (3.9)
Hypertension	2 (3.9)
Insomnia	2 (3.9)
Pyrexia	2 (3.9)
Weight decreased	2 (3.9)
Weight increased	2 (3.9)

AE = adverse event; SAE = serious adverse event.
[a] SAEs were as follows: psychotic disorder ($n = 2$), suicidal ideation ($n = 2$), chronic obstructive pulmonary disease ($n = 1$).

a patient's previous antipsychotic regimen. Limitations of this study are its open-label, single-arm study design and the small study population.

In summary, this study demonstrates the feasibility of switching patients with persistent symptoms or tolerability issues from PP or RLAI to AL. The clinical benefit observed in the study occurred irrespective of the investigator-determined AL dosing regimen, suggesting that clinicians have the flexibility to select the regimen that is most compatible with the individual needs of their patients.

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Conflict of interest

Dr. Miller has received grants or research support from Alkermes, National Institute of Mental Health, NARSAD, the Stanley Medical Research Institute, and Augusta University, and honoraria from Psychiatric Times.

Dr. Potkin has been a consultant or participated in advisory boards for Otsuka, Sunovion, Roche, Lundbeck, FORUM, Allergan, and Alkermes; has received grants or research support from Eli Lilly, Toyama, Otsuka, FORUM, Alkermes, Eisai, and Lundbeck; and has been a member of the speakers bureau or received speaker honoraria for Otsuka, Sunovion, Novartis, Teva, Acadia, and Allergan.

Dr. Claxton, Dr. Du, and Dr. Weiden are employees of and hold stock in Alkermes, Inc.

Contributors

AC designed the study and protocol. YD undertook the statistical analysis. BJM, SGP, and PJW were study investigators. All authors contributed to the interpretation of the data and approved the final manuscript for publication.

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