

Evaluation of adherence and persistence with oral versus long-acting injectable antipsychotics in patients with early psychosis

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Abstract

Introduction: Despite the theory that long-acting injectable (LAI) antipsychotics should be more likely to improve adherence, reduce gaps in therapy, and prevent relapse compared with oral antipsychotics, there is little published evidence on this issue, specifically in patients with early psychosis.

Methods: Patients with a new diagnosis for a psychotic disorder between July 1, 2013, and August 31, 2014, were retrospectively evaluated during a 12-month duration. The primary outcomes were adherence and persistence. Adherence was determined by proportion of days with medication, and persistence was defined as zero gaps in medication therapy. The secondary outcome was the number of times a psychiatric acute care service was used. Patients were divided into 3 groups based on their antipsychotic prescription history: oral only, LAI only, or both formulations at separate times throughout the study period.

Results: Forty-seven patients met inclusion criteria. The average proportions of days with medication were 32%, 76%, and 75% for the oral, LAI, and both formulations groups, respectively ($P < .001$). For medication persistence, there were 32 patients (91%), 3 patients (75%), and 5 patients (63%) with at least 1 gap in therapy for the oral, LAI, and both formulations groups, respectively ($P = .098$). For acute care services, there was a median number of zero acute care visits for each of the 3 groups ($P = .179$). A post hoc subgroup analysis found medication adherence to be statistically different between the oral and LAI groups.

Discussion: Long-acting injectable antipsychotics were associated with better adherence compared with oral antipsychotics in patients with early psychosis.

Keywords: antipsychotic, adherence, persistence, acute care services, early psychosis, long-acting injectable antipsychotic

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Introduction

Patients with psychotic illness cycle between periods of recovery and acute psychotic episodes.¹ Effective early treatment with antipsychotic medication decreases relapse risk. Relapse prevention after early psychosis leads to better patient outcomes.² Nonadherence to oral antipsychotic medications may inhibit achieving a significant time period without relapse.³ Long-acting injectable (LAI) antipsychotic development has provided a treatment that omits daily dosing in order to potentially improve treatment adherence and efficacy. Despite the theory that LAI antipsychotics should be more likely to prevent relapse compared with oral antipsychotics, there is little

published evidence on this issue, specifically in patients with early episode psychosis.

Studies⁴⁻⁹ involving both early and chronic psychosis have focused on hospitalization rates and adverse effects associated with LAI antipsychotics. Clinical trials¹⁰⁻¹³ for patients with early psychosis have evaluated adherence to LAI antipsychotics without comparison to oral agents. In studies^{14,15} comparing the 2 formulations with respect to adherence, many include all patients with schizophrenia regardless of time since diagnosis. Studies^{13,16-21} including patients with early psychosis, comparing the 2 formulations, included only 1 antipsychotic or referred to all-cause discontinuation without specific parameters denoted. Previous literature³⁻⁹ suggests nonadherence or inconsistent administration with antipsychotics puts individuals at higher risk for needing acute care. This study aims to retrospectively compare adherence, persistence, and frequency of psychiatric acute care services in patients treated at an early psychosis outpatient clinic.

Methods

Study Design

This retrospective, single-center study involved patients receiving a new diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, or psychosis not otherwise specified who were receiving outpatient treatment at Eskenazi Health's Prevention and Recovery Center for Early Psychosis (PARC) between July 1, 2013, and August 31, 2014. Clinic enrollment requires an age between 16 and 30 years and psychosis onset within 2 years prior. Each patient included was monitored for 1 year following his or her clinic enrollment date. Although the study took place during the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition release, documentation for psychosis not otherwise specified remained consistent throughout the study period. Specifiers defined by *Diagnostic and Statistical Manual of Mental Disorders* (5th edition) were not used for diagnosis. Electronic health records and prescription fill histories provided fill dates and quantities dispensed for oral antipsychotics, administration dates of LAI antipsychotics, and documentation of visits to Eskenazi Health acute care settings (crisis intervention unit, inpatient mental health unit, or the emergency department with a psychiatric-related emergency). All LAI injections given at PARC were documented by nursing staff in the electronic health record after each administration. Outside pharmacies were contacted to determine prescription fill histories. The only antipsychotic prescriptions not captured were those possibly administered at outside facilities, because information from outside hospitals was not gathered. Comorbidities and other psychiatric medications were not accounted for.

Each patient was placed in 1 of 3 groups dependent on the formulation of antipsychotic prescribed during the follow-up period: oral only, LAI only, or both formulations at separate times. All commercially available oral and LAI antipsychotics were eligible for study inclusion, with the exception of asenapine and iloperidone, which were nonformulary during the study. The Indiana University Institutional Review Board approved the protocol.

Study Population

For inclusion, at least 1 administered LAI or 1 filled oral antipsychotic prescription was necessary during the study period. Patients could have used antipsychotics prior to the study. Those with a wrong diagnosis, those with insufficient information available, or those requiring long-term simultaneous oral and LAI antipsychotics were excluded. Long-term simultaneous therapy involved a duration longer than manufacturer-recommended oral overlap when switching from oral to LAI therapy. Separate analyses were conducted, including and excluding patients on civil commitment at any point during the study. No PARC patients are involved in assertive community treatment teams.

Study Outcomes

The primary outcomes were adherence and persistence to medication therapy for 1 year following PARC enrollment. Adherence was defined as the proportion of days with medication based on total day supply of all prescribed antipsychotics during the study period. Patient-specific LAI dosing frequencies were used to calculate the proportion of days covered. Persistence was evaluated by gaps in medication therapy. If more time had elapsed than the quantity available from the previous oral antipsychotic prescription, or if there was no documented administration date within the patient's prescribed LAI dosing frequency (including manufacturer-recommended grace periods), then a gap in therapy was present.

The secondary outcome was frequency of psychiatric acute care services used. Patients presenting to Eskenazi Health psychiatric acute care settings as described in "Study Design" were considered to have required acute care.

Statistical Analysis

Data analysis was completed using SPSS 24.0 (SPSS Inc, Chicago, IL). A power calculation was not used. One-way analysis of variance was used for normally distributed data, whereas Kruskal-Wallis analysis of variance was used for nonparametric data. Nominal data were analyzed using the Fisher exact test. A multiple regression analysis was conducted to predict adherence from the other

variables collected. A post hoc subgroup analysis was conducted evaluating the oral and LAI-only groups, excluding patients in the both formulations group. The *t* test was used for continuous data, whereas Mann-Whitney *U* test was employed for nonparametric data.

Results

A total of 100 patients received a diagnosis in PARC during the study period. A total of 44 patients were excluded, including 15 with a wrong diagnosis (major depressive disorder with psychotic features, substance-induced psychosis), 21 who did not follow up in PARC after their intake appointment and were never prescribed antipsychotics from a PARC provider, 6 with insufficient information available in the electronic health record, and 2 who required long-term concomitant oral and LAI therapy. For the statistical analysis excluding patients on civil commitment at any point during the study period, an additional 9 patients were excluded, leaving 47 patients eligible for inclusion, including patients prescribed oral ($n=35$), LAI ($n=4$), and both formulations ($n=8$). All 4 patients in the LAI group were prescribed paliperidone. There were no significant differences in baseline characteristics (Table 1). A separate statistical analysis for the 3 study outcomes was conducted including patients on civil commitment, increasing the inclusion population to 56 ($n=37$, $n=9$, and $n=10$ for oral, LAI, and both formulations groups, respectively).

Table 1 shows antipsychotics prescribed in each treatment group. For the primary end point of adherence, the average proportion of days with medication was 32% (interquartile range [IQR], 41.7), 76% (IQR, 63.9), and 75% (IQR, 41.7) for the oral, LAI, and both formulations groups, respectively (Figure). This was found to be statistically significant ($P < .001$). Statistical analysis including patients on civil commitment determined statistically significant differences between groups, with an average proportion of days with medication of 17% (IQR, 41.7), 97% (IQR, 16.7), and 79% (IQR, 41.7) for the oral, LAI, and both formulations groups, respectively ($P < .001$). Multiple regression analysis showed that formulation group and having a gap in therapy statistically significantly predicted adherence. Use of LAI antipsychotics was associated with a positive trend in days with medication available, and having at least 1 gap in therapy was associated with a negative trend, as identified by the coefficient values (Table 2).

For the second primary outcome of medication persistence, there were 32 patients (91%), 3 patients (75%), and 5 patients (63%) with at least 1 gap in therapy for the oral, LAI, and both formulations groups, respectively (Figure). This primary outcome was not statistically significant

between treatment groups ($P=.098$). Statistical analysis including patients on civil commitment showed statistically significant differences between groups for persistence including 34 patients (92%), 5 patients (56%), and 7 patients (70%) for the oral, LAI, and both formulations groups, respectively ($P=.021$).

The secondary outcome of acute care services use resulted in a median number of zero visits for each of the 3 groups (IQRs, 0, 0.75, and 2.5 for the oral, LAI, and both formulations groups, respectively). The group prescribed both formulations had 3.5-fold more acute care visits, on average, because of 2 outliers seeking acute care 3 times during the study period; however, there was no statistically significant difference between groups ($P=.179$). All of these patients were prescribed oral antipsychotics during the times of the acute care visits.

The post hoc statistical comparison of oral and LAI treatment groups, which excluded patients on civil commitment, found statistical significance for the adherence primary outcome ($P=.008$) favoring LAI therapy. Statistically significant differences in persistence and use of acute care services between treatment groups were not found ($P=.363$ and $P=.918$, respectively). The post hoc statistical comparison including patients on civil commitment found statistical significance between groups for both primary outcomes, including average proportion of days with medication ($P < .001$) and a gap in therapy present ($P=.02$), favoring LAI therapy. The secondary outcome of acute care services was not statistically significant between treatment groups ($P=.935$).

Discussion

This study evaluated adherence, persistence, and rate of use of acute care services in patients with early episode psychosis prescribed oral and LAI antipsychotics. The results point to LAI antipsychotics being associated with better adherence. When patients on civil commitment were excluded, there was statistical significance for the primary outcome of adherence; however, there was no difference between groups for both the primary outcome of persistence or the secondary outcome involving rate of use of acute care services. The results of this study differ from other previous research including patients with early episode psychosis because the end points and definitions of adherence often differ among studies.

Limitations of this study include the sample size and its retrospective nature. The sample size had an impact on persistence of use and use of acute care services, with few patients able to be included in the LAI group. Additionally, in the statistical analysis including patients on civil commitment, all 4 patients in the LAI group were

TABLE 1: Baseline characteristics and antipsychotics prescribed to study patients

Antipsychotic Formulation Group	Oral	Long-Acting Injectable	Both Therapies	P Value
Not including patients on civil commitment				
No. of patients	35	4	8	
Mean age, y	21	21	21	.816
Sex, No. (%)				.236
Male	33/35 (94)	3/4 (75)	8/8 (100)	
Female	2/35 (6)	1/4 (25)	0/8 (0)	
Race, No. (%)				.267
White	11/35 (31)	1/4 (25)	1/8 (13)	
Black	17/35 (49)	3/4 (75)	7/8 (87)	
Other/unknown	7/35 (20)	0/4 (0)	0/8 (0)	
Diagnosis, No. (%)				.638
Schizophrenia	8/35 (23)	1/4 (25)	1/8 (13)	
Schizophreniform	8/35 (23)	1/4 (25)	1/8 (13)	
Schizoaffective	2/35 (5)	1/4 (25)	2/8 (25)	
Psychosis NOS	17/35 (49)	1/4 (25)	4/8 (50)	
Antipsychotic prescribed	<ul style="list-style-type: none"> • Aripiprazole (n = 3) • Risperidone (n = 19) • Olanzapine (n = 6) • Haloperidol (n = 1) • Fluphenazine (n = 6) 	<ul style="list-style-type: none"> • Paliperidone (n = 4) 	<ul style="list-style-type: none"> • Olanzapine (n = 1)^a • >1 Agent as monotherapy (n = 7), listed in prescribed order^b: <ul style="list-style-type: none"> ○ Oral ziprasidone, oral risperidone, LAI haloperidol ○ Oral risperidone, LAI paliperidone ○ LAI risperidone, oral olanzapine ○ Oral aripiprazole, oral olanzapine, LAI olanzapine ○ Oral risperidone, oral olanzapine, oral aripiprazole, LAI aripiprazole ○ Oral risperidone, LAI paliperidone ○ Oral risperidone, LAI paliperidone 	<.001
Including patients on civil commitment				
No. of patients	37	9	10	
Mean age, y	21	22	21	.586
Sex, No. (%)				.346
Male	35/37 (95)	8/9 (89)	8/10 (80)	
Female	2/37 (5)	1/9 (11)	2/10 (20)	
Race, No. (%)				.077
White	11/37 (30)	1/9 (11)	1/10 (10)	
Black	19/37 (51)	8/9 (89)	9/10 (90)	
Other/unknown	7/37 (19)			
Diagnosis, No. (%)				.669
Schizophrenia	9/37 (24)	2/9 (22)	1/10 (10)	
Schizophreniform	8/37 (22)	2/9 (22)	2/10 (20)	
Schizoaffective	2/37 (5)	2/9 (22)	2/10 (20)	
Psychosis NOS	18/37 (49)	3/9 (34)	5/10 (50)	

prescribed paliperidone, which does not allow for comparison to other LAI antipsychotics. The retrospective nature made complete data collection difficult for patients prescribed oral antipsychotics; the only information available regarding medication adherence and persistence was prescription fill history, which does not guarantee medica-

tion ingestion. It is difficult to determine the clinical significance of a short gap in LAI treatment (greater than the manufacturer-recommended grace period following a missed dose) because of scheduling issues or lack of transportation; having only retrospective data available limits investigators to gauge quality of life based on use of

TABLE 1: Baseline characteristics and antipsychotics prescribed to study patients (continued)

Antipsychotic Formulation Group	Oral	Long-Acting Injectable	Both Therapies	P Value
Civil commitment status at any time during study period, No. (%)				.004
No commitment	35/37 (94)	4/9 (44)	8/10 (80)	
Temporary commitment ^c	1/37 (3)	1/9 (12)	1/10 (10) ^d	
Regular commitment ^e	1/37 (3)	4/9 (44)	1/10 (10) ^f	
Antipsychotic prescribed	<ul style="list-style-type: none"> • Paliperidone (n = 1) • Aripiprazole (n = 3) • Risperidone (n = 20) • Olanzapine (n = 6) • Haloperidol (n = 1) • Fluphenazine (n = 6) 	<ul style="list-style-type: none"> • Paliperidone (n = 6) • > 1 LAI as monotherapy (n = 3)^b <ul style="list-style-type: none"> ○ Olanzapine and paliperidone ○ Haloperidol and paliperidone ○ Aripiprazole and haloperidol 	<ul style="list-style-type: none"> • Olanzapine (n = 1)^a • >1 Agent as monotherapy (n = 9), listed in prescribed order^b: <ul style="list-style-type: none"> ○ Oral ziprasidone, oral risperidone, LAI haloperidol ○ Oral risperidone, LAI paliperidone ○ LAI risperidone, oral olanzapine ○ LAI paliperidone, oral aripiprazole ○ Oral aripiprazole, oral olanzapine, LAI olanzapine ○ Oral risperidone, oral olanzapine, oral aripiprazole, LAI aripiprazole ○ Oral risperidone, LAI paliperidone ○ Oral olanzapine, oral ziprasidone, LAI paliperidone, oral lurasidone ○ Oral risperidone, LAI paliperidone 	<.001

LAI = long-acting injectable; NOS = not otherwise specified.

^aOne patient was on oral and LAI olanzapine at different times during the study period.

^bEach agent was used at different times as monotherapy. No patient received antipsychotic polytherapy.

^cTemporary civil commitment in Indiana is up to 90 days.

^dPatient was on LAI during the course of temporary commitment.

^eRegular civil commitment in Indiana can be in place for an indefinite amount of time.

^fPatient was on both oral and LAI therapies during the course of regular commitment.

acute care visits, but it does not identify hardships due to lack of medication adherence or persistence. In addition, only the acute care services within Eskenazi Health were captured. One factor to consider is that patients who are

more severely ill tend to be the patients considered for LAI antipsychotics. Investigators question whether this factor may have impacted the statistical significance for gaps in therapy and use of acute care services for those patients in the LAI and both formulations groups. Unfortunately, retrospective data do not provide much supporting evidence of this theory.

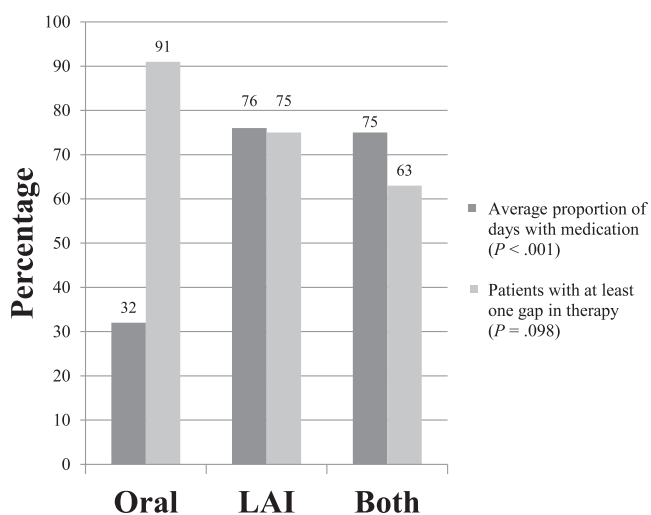


FIGURE: Primary outcome results: medication adherence and persistence; only the patients not on civil commitment were included in this analysis (LAI = long-acting injectable)

A strength of the present study is the inclusion of patients with early episode psychosis. Patients who have had a psychotic disorder for many years may not respond as well to treatment because of multiple relapses without full recovery to baseline.² Inclusion of only patients with early episode psychosis allows us to gain a better picture of adherence and persistence in patients with fewer confounding factors. Another strength is inclusion of all commercially available antipsychotics except asenapine and iloperidone, which is more reflective of clinical practice; thus, it provides higher external validity compared with studies evaluating only 1 antipsychotic. An additional strength is the multiple regression analysis, which points to medication formulation as a specific predictor of adherence in this population. This study also includes statistical analysis including and excluding

TABLE 2: Logistic regression analysis for adherence^a

Predictor	Coefficient	SE Coefficient	t Value	P Value
Age	-1.57	1.29	-1.22	.232
Sex	-21.04	14.07	-1.51	.144
Race	2.39	3.87	0.62	.540
Diagnosis	-1.47	3.01	-0.49	.627
Antipsychotic	-0.62	1.25	-0.49	.625
Formulation group (oral, LAI, or both)	17.11	5.14	3.33	.002
No. of gaps	12.17	7.15	1.71	.098
Gaps in therapy (Y/N)	-70.67	13.34	-5.31	<.001
No. of acute care service	-2.41	8.52	-0.28	.780
Acute care service (Y/N)	1.61	15.81	0.11	.920

LAI = long-acting injectable.

^aMultiple regression analysis was used to predict proportion of days with medication from the variables listed within the table ($n = 47$). Only the patients not on civil commitment were included in this analysis. Two variables (LAI formulation group and having a gap in therapy) statistically significantly predicted the average proportion of days with medication, $F_{30,36} = 7.904$; $P < .001$; $R^2 = 0.687$. Use of LAI antipsychotics was associated with a positive trend in days with medication available, and having at least one gap in therapy was associated with a negative trend in days with medication, as identified by the reported coefficient values. Both variables added statistically significantly to the prediction ($P = .002$ for formulation group and $P < .001$ for the having a gap in therapy).

patients on a civil commitment at some point during the study period, which allows for a better understanding of adherence patterns between those with and without a civil commitment; as often observed in clinical practice, civil commitment does not translate to better adherence in all patients. Although this study does not show statistical significance for 2 study end points excluding patients on civil commitment, it does point to an important observation that patients with early psychosis have significant trouble with medication adherence while taking oral antipsychotics.

Conclusions

This study found that LAI antipsychotics were associated with better adherence compared with oral antipsychotics in patients with early psychosis but did not significantly decrease gaps in therapy or use of psychiatric acute care services. Large prospective studies may be beneficial for this unique population.

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