

Evaluation of adherence in patients prescribed long-acting injectable antipsychotics: A comparison of biweekly versus monthly administered neuroleptics

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Abstract

Background: Long-acting injectable antipsychotics (LAIAs) have been developed to decrease medication nonadherence. LAIAs are usually given biweekly or monthly, with the exception of new 3-month and 6-week formulations. There has been no known evaluation regarding whether the frequency of LAIA formulation affects adherence. The purpose of this study is to evaluate whether there is a difference in adherence between LAIAs administered biweekly or monthly.

Methods: Eligible participants were identified from the Louis Stokes Cleveland VA electronic medical record as having an active prescription for a LAIA between September 1, 2009, and September 1, 2014. Participants were then evaluated using inclusion and exclusion criteria to determine study entrance. Medication possession ratios (MPRs) were calculated for each participant to determine adherence for comparison of objectives. Descriptive statistics and *t* tests were used to identify significant differences between groups.

Results: There were 128 participants enrolled based on eligibility criteria. There were no differences in MPRs for biweekly versus monthly administered LAIAs (0.98 versus 0.97, respectively; $P=.691$). No differences in adherence were observed between first- and second-generation LAIAs (0.98 versus 0.98, respectively; $P=.975$), or for risperidone LAI versus paliperidone palmitate (0.97 versus 0.99, respectively; $P=.269$). Hospitalizations were observed to decrease by 61% after LAIA initiation ($P=.021$).

Discussion: Based on the findings of this retrospective cohort review, there was no difference in adherence in patients prescribed biweekly versus monthly injected LAIAs. Patient preference and response, safety, tolerability, cost, and availability of follow-up appointments should be other factors to take into consideration for agent selection.

Keywords: long-acting injectable antipsychotic, LAIA, LAIAs, long-acting injectable, adherence, monthly, biweekly

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Introduction

Chronic treatment of psychiatric disorders with antipsychotics is often a necessary approach to prevent relapse and subsequent hospital readmissions. Antipsychotics, both first- and second-generation, are the mainstay of treatment for patients with schizophrenia and other thought disorders. Although continuous treatment with antipsychotics is required to prevent relapse, adherence to these medications is often dismal. It has been reported that nearly half of the patients prescribed antipsychotics for schizophrenia or schizoaffective disorder take less than 70% of their medication.¹ Medication nonadherence is complex and multifactorial. Intolerable adverse effects, negative stigma associated with the indication for therapy, and feeling as though symptoms have resolved are just a few of the reasons for patients to discontinue therapy.¹ With a large portion of patients nonadherent to their antipsychotic regimens, one option that is becoming more common is to initiate a long-acting injectable antipsychotic (LAIA).²

Currently, there are 2 first-generation (typical) LAIAs available: fluphenazine decanoate and haloperidol decanoate. Fluphenazine decanoate can be administered every 2 to 4 weeks depending on the facility and prescriber, whereas haloperidol decanoate is typically administered every 4 weeks. Haloperidol decanoate may require oral overlap if the prescriber does not load the medication for the first injection, and fluphenazine decanoate requires oral overlap, albeit for a shorter duration.³ Conversely, there are 4 second-generation (atypical) antipsychotics that are manufactured in a LAI formulation: risperidone, olanzapine pamoate, aripiprazole, and paliperidone palmitate. Risperidone and olanzapine pamoate are typically administered every 2 weeks, whereas aripiprazole (Maintena®) and paliperidone palmitate (Invega Sustenna®) are administered every 4 weeks. Additionally, depending on the dose, olanzapine pamoate can be administered every 4 weeks.⁴ Risperidone and aripiprazole LAIs require initial concurrent oral antipsychotic administration; however, paliperidone palmitate and olanzapine pamoate can be administered without oral overlap. Additionally, new formulations of paliperidone palmitate and aripiprazole LAI have been introduced. Paliperidone palmitate now has an every 3-month LAI (Invega Trinza®),⁵ and aripiprazole lauroxil (Aristada™) can now be prescribed up to every 6 weeks.⁶ Choosing between the available LAIAs requires careful consideration of potential advantages and disadvantages of the individual agents. Frequency of administration is just one of the factors that may have an impact on this decision in order to increase the likelihood of continued adherence.

Since the development of the first LAIA, there have been a number of clinical trials evaluating the benefits of

switching from oral antipsychotics to LAIAs in patients who have difficulty with adherence. A randomized, open-label study conducted by Rosenheck and colleagues⁷ evaluated adherence to risperidone LAI versus a physician-chosen oral antipsychotic. Adherence was not found to be statistically superior in the LAIA group, but more participants (12%) in the oral group switched to the LAIA within 24 months of follow-up.⁷ Conversely, a prospective, observational trial conducted by Olivares and colleagues⁸ evaluated adherence to risperidone LAI versus oral formulations of risperidone or olanzapine. Adherence was observed to be 81.8% in the LAIA group, whereas adherence in the oral antipsychotic group was 63.4% ($P < .0001$).⁸ This study identified a potential benefit in LAIAs compared with oral antipsychotics. Zhu and colleagues⁹ evaluated time to discontinuation in participants prescribed oral or LAI fluphenazine, as well as oral or LAI haloperidol. Time to discontinuation was significantly longer in both of the LAIA groups compared with participants given the oral formulation ($P < .01$).⁹ With regard to relapse rates, a randomized trial conducted by Gaebel and colleagues¹⁰ aimed to identify a difference between risperidone LAI versus oral quetiapine. The authors concluded that time to relapse was significantly longer in the LAIA group ($P < .0001$) compared with the quetiapine group. Although this trial did not compare time to relapse of risperidone in both oral and long-acting formulations, the findings suggest improved adherence when switching from oral antipsychotics in general to LAIAs.¹⁰

Although a number of studies have alluded to improved adherence with the use of LAIAs, to date there is no known available literature directly comparing adherence rates between the various agents. Thus, it is unknown whether LAIA formulations have greater adherence if given more or less frequently. The purpose of this study was to assess whether there is a difference in adherence when comparing LAIAs administered biweekly versus monthly.

Methods

Eligible participants were identified via the Veterans Affairs electronic medical record system and were sorted based on LAIA received between September 1, 2009, and September 1, 2014, at the Louis Stokes Cleveland VA Medical Center (LSCVAMC). Participants were subsequently enrolled in the review if they were age 18 years or older and received at least 3 doses of paliperidone palmitate, because of the loading of paliperidone palmitate requiring 2 injections within 1 week, or 2 or more doses of all other LAIAs. Olanzapine pamoate was not included in the study as a researchable LAIA because of the absence of its use at the LSCVAMC. Additionally,

paliperidone palmitate 3-month LAI and aripiprazole lauroxil were not included, because these products were not on the market at the time of the review. Participants prescribed fluphenazine decanoate and risperidone LAI were only included if dosed biweekly. Similarly, haloperidol decanoate, paliperidone palmitate, and aripiprazole LAI prescriptions were only included if dosed monthly, to aid in consistency of data collection and comparisons. Participants were excluded only if they did not meet the criteria determined above. The primary objective of this study was to determine any difference in adherence of LAIAs administered biweekly versus monthly. Subsequent secondary objectives included differences in adherence between first-generation and second-generation antipsychotics, and risperidone LAI versus paliperidone palmitate, as well as differences in adherence in participants taking concurrent oral antipsychotics versus participants on only a LAIA. The number of psychiatric hospitalizations after the initiation of a LAIA and reasons for nonadherence were also evaluated.

Adherence was measured by calculating the medication possession ratio (MPR), defined as the sum of days covered by all prescription fills in the study period divided by the total number of days the participant was intended to be on the prescription. The VA Computerized Patient Record System provided refill history, as well as injection clinic progress notes to determine adherence to the study medication(s). Participants were considered nonadherent if they received their injection more than 7 days after their scheduled injection date or were lost to follow-up. The missed injection days were then calculated by subtracting the 7-day grace period from total missing days and were used to calculate the numerator of the MPR. If a participant was lost to follow-up, his or her missed injection days continued until the end of the study period, after subtracting the 7-day grace period. For any participant who received 2 or more different LAIAs at different points during the study period, each individual LAIA was determined to be “unique” and was then evaluated as a separate subject. For evaluation of concurrent oral antipsychotic use, participants were deemed eligible for this arm if they received an oral antipsychotic for a minimum of 1 month during the time they were receiving a LAIA. This included participants who were on oral antipsychotics for overlap after initiation of a LAIA that extended the prespecified duration of overlap in the package insert. VA psychiatric hospitalizations were evaluated for 1 year prior to LAIA initiation and compared to the number of admissions 1 year after LAIA initiation. Hospitalizations were recorded between September 1, 2010, and September 1, 2013, in order to ensure participants had 1 year of data both before and after initiation of the LAIA. If a participant was not on a LAIA for a minimum of 1 year after LAIA initiation, hospital-

izations were not compared for analysis, in order to annualize the data.

All study data were recorded in a Microsoft Excel® spreadsheet (Redmond, WA) and analyzed using SPSS® software (SPSS Inc, Chicago, IL). A power analysis for an independent *t* test was conducted, and it was determined that a sample size of 128 participants—64 participants in each group—would be necessary to meet a power of 80%, with an alpha set at .05 and an effect size of 0.5 SDs. Comparisons of mean values were examined using dependent paired *t* tests for pretest and posttest data, and independent *t* tests for group data. Descriptive statistics, including means, SDs, and ranges for continuous data, and frequencies and percentages for categorical data, were used to examine baseline variables and reasons for nonadherence.

Results

A total of 128 participants were included for analysis (Figure 1). There were 34 total participants on oral antipsychotics concurrently with their prescribed LAIA. Demographic data are reported in Table 1. There were minimal differences in participant demographics between arms with respect to age, sex, and diagnosis. Overall, most participants were male (94%) and younger than 65 years. Schizophrenia and schizoaffective disorder accounted for 95% of diagnoses. The number of prescriptions for first-generation (56%) and second-generation (44%) LAIAs were similar, although more participants were prescribed first-generation LAIAs. The most commonly used LAIA was haloperidol decanoate ($n=39$), whereas aripiprazole LAI was used the least, with only 1 participant prescribed this medication. There were 15 participants who received 2 separate LAIAs, and 1 participant who had received 4 LAIAs within the study period. Each LAIA was considered “unique” and evaluated as an individual subject.

For the primary end point, the mean MPR was 0.98 (98% adherent; 0.65-1.00) for biweekly administered LAIAs, and 0.97 (0.66-1.00) for monthly administered LAIAs ($P=.691$). No differences in adherence were observed between first-generation and second-generation LAIAs, risperidone LAI versus paliperidone palmitate, or participants prescribed a concurrent oral antipsychotic with their LAIA (Table 2). Coincidentally, adherence to oral antipsychotics within study participants on concurrent LAIAs was 75% (MPR, 0.75), which is higher than other averages reported in the literature.¹ Overall, reasons for nonadherence were not well documented in charts. A total of 40 participants were nonadherent, and 70% ($n=28$) of nonadherent participants missed injection appointments for unknown reasons. One participant was lost to follow-up. Per electronic records, a total of 17% ($n=7$) of

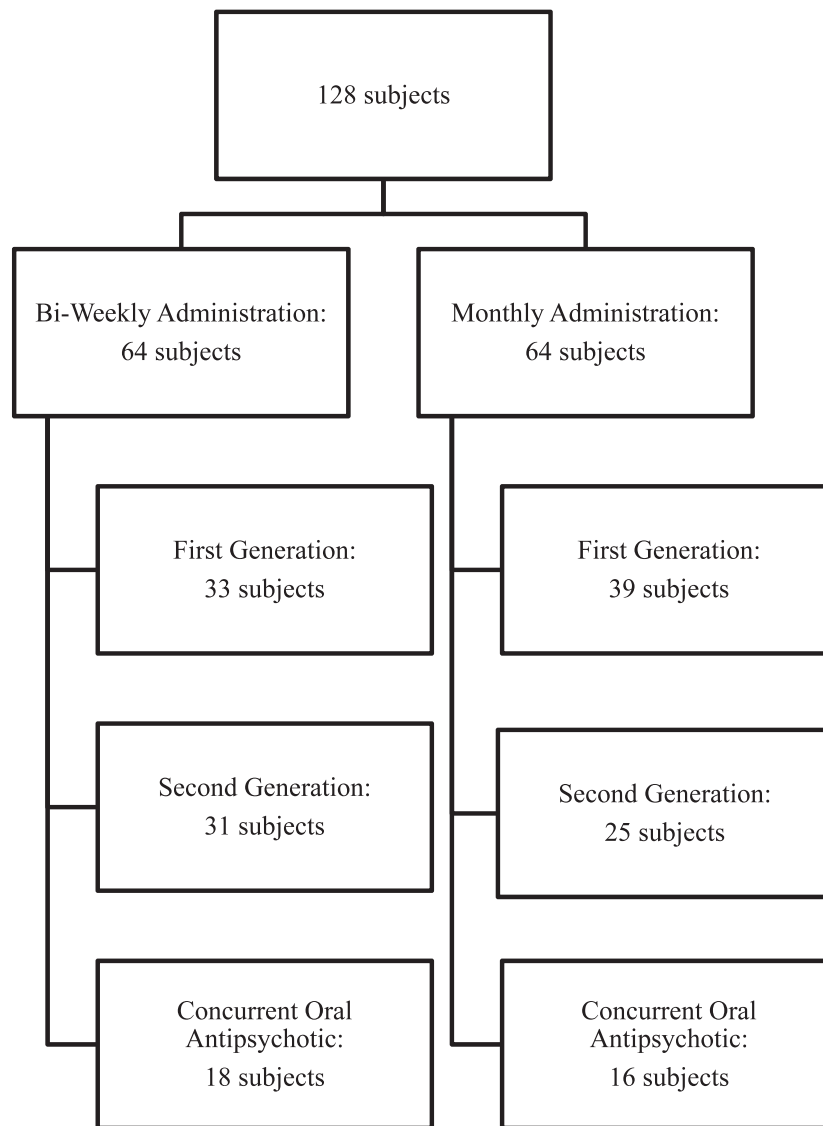


FIGURE 1: Categorization of participants

nonadherent participants were unable to make it in for their appointment because of hospitalizations, incarcerations, vacations, etc, and the remaining 13% (n = 5) of nonadherent participants were documented for refusal to come to their appointment. There were also significantly fewer VA psychiatric hospitalizations after starting a LAIA (Figure 2). Hospitalizations were reduced by 61% (27 fewer admissions) after initiation of a LAIA ($P = .021$).

Discussion

The results of this study indicated that adherence was not affected by frequency of administration of LAIAs. Ultimately, adherence was not observed to improve with regard to generational differences, the use of paliperidone palmitate versus risperidone LAI, or concurrent use of oral antipsychotics. Although the reasoning behind these

results is currently unknown, the findings may have been influenced by patient preference when choosing initial drug therapy, as well as through positive collaborative relationships between patients and providers. Current practice at the LSCVAMC is that many psychiatrists will align medication management appointments on the same day as monthly injection clinic appointments, providing veterans with more convenient appointment times, as well as more reasons to come into the medical center. Patients prescribed biweekly LAIAs may have consistent adherence due to the increased frequency of contact with their providers, and more frequent recall of the medication. Given the main reason for using LAIAs, an interesting finding was the lack of difference in adherence when patients were placed on LAIAs with an oral antipsychotic. Furthermore, adherence to oral antipsychotics was higher when compared to the adherence rates reported in the literature.¹ Although some VA institutions assist patients

TABLE 1: Baseline demographics

Characteristic	Participants (n = 128)
Sex, male, No. (%)	120 (94)
Age, y, mean	59
Participants on a LAIA and oral antipsychotic, No. (%)	34 (27)
Diagnosis, No. (%)	
Schizophrenia	92 (72)
Schizoaffective disorder	30 (23)
Bipolar disorder	3 (2)
Unspecified psychotic disorder	2 (2)
Major Depressive Disorder with psychotic features	1 (1)
LAIA, No. (%)	
First-generation	72 (56)
Haloperidol decanoate	39 (30)
Fluphenazine decanoate	33 (26)
Second-generation	56 (44)
Risperidone	31 (24)
Paliperidone palmitate	24 (19)
Aripiprazole	1 (1)

LAIA = long-acting injectable antipsychotic.

with automatic refills, the LSCVAMC requires veterans to request refills via phone, My HealtheVet, during appointments at outpatient clinics, as well as visiting the outpatient pharmacy. Because veterans are primarily accountable for their refills, the improvement in adherence may be explained by increased insight and judgment that may facilitate consistent stabilization while on the LAIA, leading to better recollection of taking the oral antipsychotic regularly.

As expected, hospitalizations decreased significantly with the initiation of LAIAs, which similarly aligns with the results of other studies.¹¹⁻¹³ Evidence has inconsistently demonstrated improved adherence with the use of LAIAs, given factors such as nonnaturalistic study designs and inappropriate patient selection; however, it can be hypothesized that hospitalizations decrease because of improved adherence and thus provide more continuous stability. While not surprising, it was unknown why patients who were nonadherent missed their injection clinics despite documentation of phone calls. One patient was unfortunately lost to follow-up, although frequent attempts to contact the patient were evident.

There are several noteworthy limitations of this study. First, secondary objectives were not powered to find significant differences. This may lead to premature conclusions with regard to generational factors, individual

TABLE 2: Adherence outcomes for secondary objectives

	Average MPR (Range)	P Value
Generation		
First (n = 72)	0.98 (0.66-1.00)	.975 (ns)
Second (n = 56)	0.98 (0.65-1.00)	
Paliperidone versus risperidone		
Paliperidone (n = 24)	0.99 (0.79-1.00)	.269 (ns)
Risperidone (n = 31)	0.97 (0.65-1.00)	
LAIA and oral antipsychotics		
LAIA alone (n = 94)	0.98 (0.65-1.00)	.822 (ns)
Concurrent oral antipsychotic (n = 34)	0.98 (0.69-1.00)	

LAIA = long-acting injectable antipsychotic; MPR = medication possession ratio; ns = not significant.

agents, or concurrent oral antipsychotic differences. Second, adherence to oral antipsychotics may be exaggerated given calculations based on refills. Fortunately, the electronic medical record documents all refills of oral medications, but knowledge of whether the patient takes the medication consistently is not information that can be provided through a chart review. Similarly, to account for variances in duration of LAIA use, hospitalizations were calculated using annualized data, and therefore may alter results. Another limitation observed includes the issue that the data were collected solely from VA records, and any additional medications, changes, or hospitalizations encompassed through the private sector may not have been accounted for. This may also alter the external validity, because other populations outside of the VA may not observe the same findings. Next, this facility does not use olanzapine pamoate because of risks of postinjection delirium and sedation syndrome, and use of aripiprazole LAI was limited at the time this study was conducted, with only 1 patient included in the review of LAIAs. This factor contributes to incompleteness in testing all available LAIAs for adherence differences and an inability to draw adequate conclusions about those agents. Finally, this is a retrospective cohort study. Although it is the first of its kind to directly evaluate adherence related to administration frequency, the results may confer correlation without regard to causation and must be interpreted appropriately. Future prospective studies are warranted to duplicate data and demonstrate these positive results, as well as include new extended-duration LAIAs for evaluation.

Conclusion

This study demonstrated similar adherence rates between subjects prescribed biweekly LAIAs compared with those

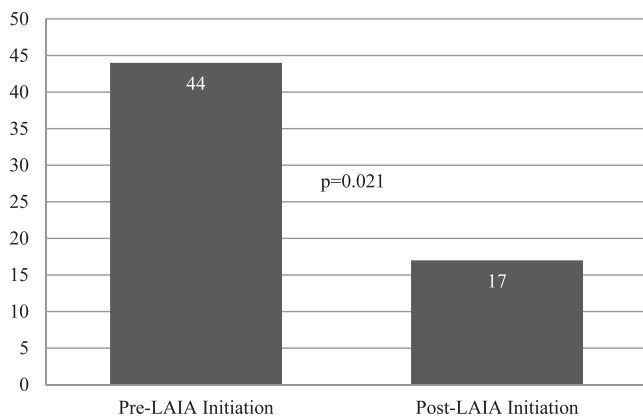


FIGURE 2: Hospitalizations are calculated as unique occurrences because some participants were hospitalized more than once in the time period described; LAIA = long-acting injectable antipsychotic

prescribed monthly LAIAs. Comparably, adherence was not observed to be different with respect to generation of antipsychotic, selection of paliperidone palmitate versus risperidone LAI, or use of concurrent oral antipsychotics. Appreciably, hospitalizations were observed to decrease after initiation of a LAIA. Given these findings, it is reasonable for providers to work with the patients on selection of the most appropriate agent based on patient preference and response, cost of the agent, safety concerns, tolerability issues, and availability of follow-up appointments, in order to ensure adherence and continued stabilization.

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