Do Long-Acting Injectable Antipsychotics Prevent or Delay Hospital Readmission?
By Thomas J. Maestri, Lisa M. Mican, Heather Rozea, Jamie C. Barner

ABSTRACT ~ Introduction: Long-acting injectable (LAI) antipsychotics were developed as a way to decrease pill burden and simplify medication regimens by allowing less frequent administration to assist with medication adherence. Methods: The purpose of this study was to determine whether LAI antipsychotics prevent or delay hospital readmission in patients with a known history of medication non-adherence. The study is a retrospective evaluation of 240 men and women 18–65 years of age diagnosed with bipolar disorder, schizophrenia, or schizoaffective disorder discharged from an inpatient state hospital over a 2 year period of time on a LAI antipsychotic (fluphenazine LAI, haloperidol LAI, risperidone LAI or paliperidone LAI) or oral antipsychotic. Patients on LAIs were matched to patients on an equivalent oral dose, psychiatric diagnosis, number of prior hospital admissions, and length of stay. Results: Those who received a LAI (N = 120) had a significantly longer survival time (mean 278.0 days) without readmission compared to those who did not (N = 120; mean 243.6 days). There was no statistically significant difference in the frequency of one-year readmission between those who did receive a LAI (43.1%) and those who did not (56.9%). Those who received a LAI with administration frequency of a month or longer had a significantly longer survival time without readmission (mean 307.9 days) when compared to those with a shorter administration frequency (mean 245.0 days). Conclusion: This study revealed the use of LAI antipsychotics in those with a history of medication non-adherence, particularly those with longer administration frequency, have potentially promising outcomes. Psychopharmacology Bulletin. 2018;48(3):8–15.

INTRODUCTION

The National Alliance on Mental Illness reports that approximately 44 million adults are diagnosed with mental illness every year.1 Nearly 60% of people diagnosed...
with mental illness have not received any mental health services in the prior year, and of the remaining 40%, two-thirds do not remain adherent to medication in the year following diagnosis. In other words, roughly 12 million adults who are in need of mental health treatment are not receiving the assistance necessary to manage their illness due to non-adherence.

There are many barriers that can prohibit those with mental illness from utilizing resources and taking medication effectively, which include cognitive decline, medication costs, inability to receive follow-up care, medication beliefs and difficulty remembering to either take or refill medications. Multiple strategies are available to improve psychiatric medication non-adherence, such as text message medication reminder systems and pillboxes. Providers can also play a role in medication adherence by offering long-acting injectable (LAI) medications when appropriate. This strategy can eliminate the need to remember to take a daily medication for symptom management.

LAI antipsychotics were developed as a means to improve medication adherence in psychiatric populations. However, previous randomized controlled trials (RCTs) comparing the use of LAIs to oral antipsychotic medications have not consistently found a benefit on readmission rates or length of stay on readmission. The type of study design used to evaluate LAI medication may impact the efficacy results. Although RCTs are normally considered the gold standard of study designs, they are not ideal in studying real world medication adherence. A distinct advantage for LAI antipsychotics was shown in prospective observational, retrospective observational and mirror-image study designs. For evaluating the use of LAI compared to oral antipsychotic medications, it is recommended that if efficacy and safety is being evaluated in the natural clinical practice, the design should be pragmatic in order to demonstrate a more real world situation with treatment schedules seen in clinical practice, which avoid blinding and use customary adherence interventions. This study employs a retrospective observational study design with a protocol that matches the oral antipsychotic to the LAI group. The aim of this study is to explore the potential benefit of LAIs compared to oral medication in a population that has a history of non-adherence with antipsychotic therapy.

METHODS

The primary aims of this study are to determine whether LAI antipsychotic use is associated with a longer time to readmission when used in patients with a history of medication non-adherence and to determine whether LAI antipsychotic initiation decreases one-year readmission rates. Other outcomes evaluated include whether the injection
frequency or antipsychotic atypicality are associated with a longer time to readmission and if LAI antipsychotic use is associated with a shorter length of stay on readmission.

This study is a retrospective, matched evaluation of patients 18–65 years of age diagnosed with schizophrenia, schizoaffective disorder or bipolar disorder discharged from an inpatient state hospital from November 30, 2011 to November 30, 2013 with documented medication non-adherence that received a LAI (haloperidol, fluphenazine, risperidone or paliperidone) or a corresponding equivalent scheduled dose of oral antipsychotic. Patients were matched based on the number of prior admissions, psychiatric diagnosis, length of stay, and equivalent antipsychotic dose. Those with a length of stay less than 2 days or greater than 1 year were excluded. Oral equivalent doses were defined as follows: paliperidone LAI dose divided by 20, haloperidol LAI dose divided by 10, risperidone LAI dose divided by 10, and fluphenazine LAI dose divided by 1.25. All calculated equivalent oral antipsychotic doses were rounded to the closest available oral dose.

Kaplan Meier and Cox Proportional Hazards were used to analyze time to readmission and Chi-square and Logistic Regression were used to analyze one-year readmission rates. Secondary outcomes were evaluated using Kaplan Meier, Cox Proportional Hazards, T-test, and Multivariate Linear Regression. Alpha levels were set at 0.05, with a 95% confidence interval for all outcomes. This study was approved with a waiver for informed consent by the Texas Department of State Health Services IRB and the University of Texas at Austin IRB.

Results

Data from 240 patients were included in this retrospective study. Baseline clinical characteristics including primary psychiatric diagnosis, prior number admissions and length of stay were similar for the oral antipsychotics and their LAI counterparts due to the matching process. Baseline demographics such as age, gender and race/ethnicity were also similar between the oral antipsychotic and LAI groups (Table 1). Similar rates of antipsychotic polypharmacy at the time of discharge were found between the oral (18.3%) and LAI (20.0%) groups.

Compared to those who received an oral agent (N = 120), those who received a LAI (N = 120) had a significantly (mean ± SE: 278.0 ± 11.5 days vs. mean ± SE: 243.6 ± 12.8 days, p = 0.0481) longer survival time without readmission. Regarding specific antipsychotic agents, there was a longer time to readmission for all LAIs compared to their oral counterparts except for risperidone LAI (Table 2). There was no statistically significant difference in the frequency of
1-year readmission between those discharged on an oral agent (56.9%) and those discharged on a LAI (43.1%) (Chi-square = 3.3419, df = 1, p = 0.0675). The 1-year readmission frequency was 13.8% lower in the LAI group, which is considered clinically significant and the difference is statistically significant at the p < 0.10 level. All of the LAIs had a lower frequency of 1-year readmission compared to their oral counterparts except for risperidone LAI (risperidone LAI n = 19, 50.0%; risperidone oral n = 15, 39.5%) as shown in Table 2.

Patients that received a LAI with an administration frequency of a month or longer, primarily consisting of patients treated with haloperidol or paliperidone LAI, had a significantly longer survival time without readmission (mean ± SE: 307.9 ± 13.1 days) than those who received a LAI with an administration frequency of less than a month (mean ± SE: 245.0 ± 18.5 days) primarily consisting of patients treated with fluphenazine or risperidone LAI (Chi-square = 6.5180, df = 1, p = 0.0107). There was not a statistically significant difference in mean length of stay on subsequent readmission between patients on oral antipsychotic therapy (mean ± SE: 50.1 ± 75.6 days) compared to those on a LAI (mean ± SE: 44.3 ± 47.3 days) (t-value = 0.47, df = 1, p = 0.6384). Examining specific antipsychotics, those on paliperidone LAI and haloperidol LAI had a shorter length of stay on readmission compared to their oral counterparts which was not found for risperidone LAI or fluphenazine LAI (Table 2). Those prescribed LAIs had the same or lower rate of medication non-adherence reported on readmission than their oral counterparts except for the risperidone LAI group.
TABLE 2

Results

<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>RISP LAI (N = 38)</th>
<th>RISP PO (N = 38)</th>
<th>PALI LAI (N = 23)</th>
<th>PALI PO (N = 23)</th>
<th>HLD LAI (N = 42)</th>
<th>HLD PO (N = 42)</th>
<th>FLU LAI (N = 17)</th>
<th>FLU PO (N = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of therapy, days</td>
<td>29.3 (27.4)</td>
<td>47.9 (39.9)</td>
<td>33.1 (38.4)</td>
<td>29.0 (24.8)</td>
<td>32.2 (29.0)</td>
<td>24.4 (23.4)</td>
<td>16.8 (15.9)</td>
<td>29.6 (21.2)</td>
</tr>
<tr>
<td>Discharge dose, mg</td>
<td>35.5 (11.1)</td>
<td>5.0 (2.1)</td>
<td>186.5 (43.9)</td>
<td>9.1 (2.3)</td>
<td>146.4 (38.9)</td>
<td>16.1 (6.1)</td>
<td>27.2 (7.9)</td>
<td>17.9 (5.9)</td>
</tr>
<tr>
<td>1 year readmission, n (%)</td>
<td>19 (50.0)</td>
<td>15 (39.5)</td>
<td>9 (39.1)</td>
<td>10 (43.5)</td>
<td>10 (23.8)</td>
<td>24 (57.1)</td>
<td>6 (35.3)</td>
<td>9 (52.9)</td>
</tr>
<tr>
<td>Time to readmission, days</td>
<td>251.5 (136.0)</td>
<td>264.8 (140.6)</td>
<td>304.2 (98.6)</td>
<td>263.6 (133.3)</td>
<td>302.8 (121.6)</td>
<td>231.6 (145.6)</td>
<td>263.1 (147.2)</td>
<td>231.2 (159.7)</td>
</tr>
<tr>
<td>Readmission LOS, days</td>
<td>52.2 (57.8)</td>
<td>36.9 (39.3)</td>
<td>47.7 (46.7)</td>
<td>77.3 (128.1)</td>
<td>23.1 (22.0)</td>
<td>58.0 (76.5)</td>
<td>49.8 (40.3)</td>
<td>20.8 (19.0)</td>
</tr>
<tr>
<td>Readmission nonadherence, n (%)</td>
<td>15 (39.5)</td>
<td>11 (28.9)</td>
<td>3 (13.0)</td>
<td>4 (17.4)</td>
<td>4 (9.5)</td>
<td>13 (31.0)</td>
<td>4 (23.5)</td>
<td>4 (23.5)</td>
</tr>
</tbody>
</table>

Note: Data expressed as mean (SD) unless otherwise indicated.

Abbreviations: RISP, risperidone; PALI, paliperidone; HLD, haloperidol; FLU, fluphenazine; LAI, long-acting injection; PO, oral.
There were no significant differences in time to readmission (Chi-square = 2.3543, df = 1, p = 0.1249) between patients who received an atypical LAI, risperidone or paliperidone, (mean ± SE: 268.6 ± 15.9 days) compared to those who received a typical LAI, haloperidol or fluphenazine, (mean ± SE: 199 ± 10.5 days). The Kaplan-Meier curve showed that in the first 90 days, more patients on an atypical LAI survived longer without hospital readmission; however, after that time, more patients on a typical LAI survived longer without being readmitted. Because the outcomes changed at day 90, the time to readmission was not statistically significant. A post-hoc Chi-square analysis was conducted in order to further explore potential differences in the 1 year readmission rate between atypical versus typical antipsychotic LAIs. The results indicate that significantly more patients on an atypical LAI (45.9%) had a readmission compared to patients on a typical LAI (27.1%) by the 1 year follow-up time period (Chi-Square = 4.5564, df = 1, p = 0.0328).

**DISCUSSION**

LAIs are often prescribed for those with a history of medication non-adherence. Some RCTs have not found benefit with LAI use compared to their oral counterparts, though study design could play a role in these findings due to the pre-requisite of adherence in many randomized controlled trials. Several recent observational studies have utilized various techniques to eliminate this confound and have shown improved relapse prevention and hospitalization rates. This is the first study to our knowledge that assesses the benefit of LAIs versus their oral counterparts using a specific matched comparison design in a population with nonadherence. The benefit of this design is the ability to assess equivalent doses of antipsychotics in patients with a similar diagnosis and markers for symptom severity (number of prior hospital admissions and length of stay).

In this study, the primary objective of time to hospital readmission was significantly delayed by more than a month (34.4 days) through the use of a LAI compared to oral medication at discharge in those with a history of medication non-adherence. When looking into the 1-year readmission frequency, there were 56.9% (n = 58/120) of patients in the oral group that were readmitted within a year, and only 43.1% (n = 44/120) of patients readmitted within a year in the LAI group (difference of 13.8%). This endpoint did not reach statistical significance (p = 0.0675), and may be attributable to the small sample size. This finding does, however, appear to be clinically significant since it led to 14 less readmissions in a year through use of a LAI formulation.
When broken down by drug, the frequency of 1-year readmission was reduced in all LAI groups compared to their oral counterparts except risperidone, which had a higher frequency of 1-year readmission in the LAI group (po 39.5% vs. LAI 50%). The most impressive finding regarding LAI performance was for haloperidol decanoate with a 1-year readmission frequency of only 23.8% compared to 57.1% for oral haloperidol. The use of haloperidol LAI compared to oral haloperidol at discharge in those with a history of nonadherence reduced 1-year readmission by more than half (58%).

Of the secondary endpoints, an interesting finding was that compared to LAIs with an injection frequency of a month or longer, those that had a shorter injection frequency had a much shorter time to readmission (245.0 days vs 307.9 days). This finding may suggest that in patients with a history of nonadherence, use of LAIs with a longer administration frequency may be more advantageous. Further studies are needed to fully elucidate this hypothesis.

Although this study was limited by being an observational study, confounding factors were reduced through the matching process. Covariates such as antipsychotic polypharmacy, age, prior number of admissions and length of stay were evaluated and only prior number of admissions was significantly related in the analysis. Prior number of admissions was one of the items the LAI and oral groups were matched for, which would decrease the influence of this variable on observed outcomes.

Though this study attempted to address possible confounders and equilibrate groups through a matched design, possible confounders could still exist including the potential for remission of symptoms from other forms of treatment such as mood stabilizer use and other factors outside the hospital after discharge that cannot be controlled for such as substance use. Other limitations include difficulties locating some data from the record such as medication adherence on readmission and the small sample size for some of the antipsychotic groups due to low utilization. Also, despite the use of an LAI at discharge, documented non-adherence on readmission was still reported in some cases.

CONCLUSION

This study utilized a matched-comparator design and found potentially promising outcomes for LAI use in non-adherent patients. This was particularly true for the LAIs with a longer administration frequency. Though alone this study does not fully elucidate the effectiveness of LAIs in non-adherent populations, it does add to the body of literature through use of a unique study design. Preventing or
Delivering readmission is an important clinical endpoint and continued studies in this area are needed to further evaluate this outcome.

**ACKNOWLEDGMENT**

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**CONFLICTS OF INTEREST**

Authors have no conflicts of interest or funding to report.

**REFERENCES**


