OPEN SUBMISSIONS

mhc MENTAL HEALTH CLINICIAN

ORIGINAL RESEARCH Open Access

Impact on length of stay and readmission rates when converting oral to long-acting injectable antipsychotics in schizophrenia or schizoaffective disorder

Fabienne Chou, PharmD[1]
Earle Reome, PharmD, BCPS[2]
Patricia Davis, PharmD[3]

How to cite: Chou F, Reome E, Davis P. Impact on length of stay and readmission rates when converting oral to long-acting injectable antipsychotics in schizophrenia or schizoaffective disorder. Ment Health Clin [Internet]. 2016;6(5):254-9. DOI: 10.9740/mhc.2016.09.254.

Abstract

Introduction: Nonadherence with oral antipsychotics in patients with schizophrenia has been associated with symptom relapse and rehospitalizations, resulting in increased morbidity and health care costs. Long-acting injectable antipsychotics (LAIAs) are an alternative to enhance adherence and decrease relapse requiring hospitalization. The objectives of this study are to determine the impact of LAIAs on reducing length of stay, the rate of annual readmissions, and the number of failed annual discharges (defined as a readmission in less than 30 days) in patients with schizophrenia or schizoaffective disorder admitted to an acute inpatient psychiatric unit.

Methods: Using the hospital database, 52 patients receiving a diagnosis of schizophrenia or schizoaffective disorders treated with oral antipsychotics and later transitioned to LAIAs were evaluated retrospectively.

Results: Patients treated with LAIAs did not show a statistically significant reduction in length of stay compared with their length of stay on oral antipsychotics. Patients treated with LAIAs experienced a statistically significant reduction in the rate of annual readmissions and a reduction in the number of failed annual discharges, although the latter was not statistically significant ($P = .076$ when compared to treatment with oral antipsychotics).

Discussion: These findings suggest a potential role for maintaining patients with a diagnosis of schizophrenia or schizoaffective disorder on LAIAs to prevent relapse and rehospitalizations. The reduction in the number of failed annual discharges between the oral versus LAIA group, although not statistically significant, warrants further investigation to determine the impact of LAIAs on readmission within 30 days.

Keywords: schizophrenia, schizoaffective, long-acting injectable antipsychotics (LAIAs), oral antipsychotics, compliance, relapse, rehospitalizations, length of stay, rate of annual readmissions, number of failed annual discharges

[1] (Corresponding author) PGY2 Psychiatric Pharmacy Resident, Department of Pharmacy, VA Western New York Healthcare System, Buffalo, New York, nasa27@uw.edu; [2] Behavioral Health Pharmacist, United Health Services, Binghamton, New York; [3] Pharmacist, United Health Services, Binghamton, New York

Disclosures: There was no external funding for this manuscript. The authors have no financial relationships to disclose. The authors have no conflicts of interest to disclose.

Introduction

Schizophrenia and schizoaffective disorders are chronic debilitating psychiatric disorders in which relapses can occur despite the implementation of pharmacologic interventions, such as oral atypical antipsychotic agents.[1] Relapse prevention is essential because shortened duration of disease remission can lead to impairment of social function, worsened prognosis, and repeat hospital admis-

sions. Poor patient adherence is the most common cause of relapse.[2] According to Glazer,[3] rates of nonadherence to oral antipsychotics in patients with schizophrenia are as high as 50%. Research carried out by Kaplan et al[2] suggests discontinuation rates ranging from 26% to 44%.

A retrospective analysis by Lafeuille et al[1] identified potential consequences of patient nonadherence with oral antipsychotics to include increased relapse and rehospitalization rates, longer duration of inpatient stay, and higher health care costs.

The use of long-acting injectable antipsychotics (LAIAs) offers an alternative to oral antipsychotic medication therapy to enhance adherence and decrease relapse and rehospitalization rates. Other advantages of LAIAs include consistent plasma drug concentrations, reduction in the risk of accidental or intentional overdose, and improved patient outcomes.[4-6] Integrating these agents into routine clinical practice has limitations. Literature suggests that factors associated with reluctance to use LAIAs include patient perceptions of coercion, negative stigma, lack of insight, fear of injection and related injection site effects, drug-related side effects, and cost.[2,7-10] The first LAIA dates back to the 1960s with the introduction of fluphenazine decanoate.[11] Currently, there are 2 first-generation LAIA agents (fluphenazine decanoate and haloperidol decanoate) and 4 second-generation LAIA agents (risperidone microspheres, paliperidone palmitate, aripiprazole monohydrate, and olanzapine pamoate monohydrate).

A literature search of randomized controlled trials failed to conclusively identify the superiority of LAIAs over oral antipsychotics. Kishimoto et al[11] conducted a meta-analysis of 21 randomized controlled trials that were of at least 6 months in duration. These studies looked at relapse prevention rates when comparing LAIAs to oral antipsychotic use. The authors[11] concluded there was no difference in relapse reduction with the use of LAIAs compared with oral therapy, with the exception of a few studies using fluphenazine decanoate. A retrospective cohort review by Lafeuille et al[1] of the largest hospital database in the United States concluded that second-generation LAIAs were superior to oral antipsychotics in the reduction of rehospitalizations and emergency room visits. Large randomized controlled trials comparing LAIAs to oral antipsychotic therapy in the inpatient setting are needed to determine the role of LAIAs in the treatment of schizophrenia and schizoaffective disorders.

Methods

We conducted a retrospective review of patients with schizophrenia or schizoaffective disorders to determine the impact on length of stay and rate of readmissions LAIAs have on our inpatient psychiatric practice site. Only patients who had medical records showing oral antipsychotic medication usage between January 1, 2010, and December 31, 2012, and who were treated with a LAIA at least once between January 1, 2013, and December 1, 2014, were selected for the study. This selection of 52 patients allows each patient to serve as his or her own control, minimizing the effects of between-patient variability. Covariates for age and sex were also assessed. Patient distribution characteristics are summarized in Table 1. The three primary end points for the study were length of stay, rates of annual readmission, and number of failed annual discharges. We averaged all lengths of stay for each patient to calculate the length of stay used in each arm of the study. The paired Wilcoxon signed-rank test was used to evaluate differences in the mean length of stay between treatment arms and the stratified subgroups based on age ($\geq$40 years versus $<$40 years) and sex. In the absence of clearly defined age criteria used a priori in this subject, we have chosen to use the median to divide the participants in the study into 2 groups (40 years or younger versus older than 40 years). Although we could have retained the numeric values of age in the model, we believe using a binary categorization of age is more appropriate in this case because using the numeric age value would imply a constant and linear relationship between age and each of our explored outcomes.

To compare differences in the rate of annual readmissions, we first determined the observed rate of annual readmissions for each patient. The rate of annual readmissions (λ) was calculated as $\lambda = Y / t$, where Y was the total number of readmissions observed and t was the length of "at-risk time." More specifically, the length of "at-risk time" (t) was determined from the first recorded hospital admission to the end of each phase of study (December 31, 2012, for oral antipsychotics and December 1, 2014, for LAIAs). Correspondingly, the total number of readmissions (Y) was determined based on the total number of observed readmissions during each phase of study. The number of annual readmissions was modeled using a Poisson regression[12] with "at-risk time" as part of the model. Under this model, the varying number of patient readmissions is accounted for and adjusted to provide a common basis of comparison. The treatment choice of LAIAs or oral antipsychotics was included as a covariate to determine whether there were significant differences in the rate of annual readmissions between the two options. Failed annual discharge is a metric reviewed by Medicaid defined as a readmission within 30 days of a prior discharge. The number of failed annual discharges was also modeled using a Poisson regression with treatment choice as a covariate.

All statistical analyses were done using R statistical software version 3.2.0.[13]

TABLE 1: Patient distribution characteristics stratified by age and sex

	No. of Admissions[a]						No. of Antipsychotics[b]					
	Oral (n = 52)			LAIA (n = 52)			Oral (n = 52)			LAIA (n = 52)		
	1	2-3	≥4	1	2-3	≥4	1	2-3	≥4	1	2-3	≥4
Male (n = 31)												
Age <40 years	4	8	6	14	4	0	7	10	1	17	1	0
Age ≥40 years	4	3	6	6	7	0	4	9	0	11	2	0
Female (n = 21)												
Age <40 years	2	3	2	4	1	2	4	3	0	6	1	0
Age ≥40 years	5	8	1	10	4	0	7	7	0	13	1	0

LAIA = long-acting injectable antipsychotic.

[a]Number of admissions for each patient in each arm.

[b]Number of different antipsychotics patients had received in each arm.

Results

Differences in the length of stay between patients on oral antipsychotics versus LAIAs were not statistically significant ($P = .97$). Analysis of the age and sex subgroups did not show a difference in length of stay between oral antipsychotics and LAIAs. A summary of observed differences when comparing patients on oral antipsychotics versus LAIAs is shown in Figure 1.

The study showed patients treated with LAIAs have fewer annual readmissions than those treated with oral agents. The LAIA patients experienced 50.7% (95% confidence interval, 33.6%-76.5%; $P = .001$) the rate of annual readmissions relative to the oral patient group. A summary of the number of annual readmissions when comparing patients treated with LAIAs and oral agents is shown in Figure 2.

The number of failed annual discharges was examined for patients using oral antipsychotics versus LAIAs. Patients treated with LAIAs experienced 47.1% of failed annual discharges annually compared with patients treated with oral agents (95% confidence interval, 20.5%-108.2%; $P = .076$). A summary of failed discharges is shown in Figure 3. Although not statistically significant, the observed decrease from the data is consistent with our previous findings that there is also a decrease in the number of annual readmissions. The combination of these 2 separate observations leads us to believe that patients are showing fewer annual readmissions because they are being successfully discharged when treated with LAIAs.

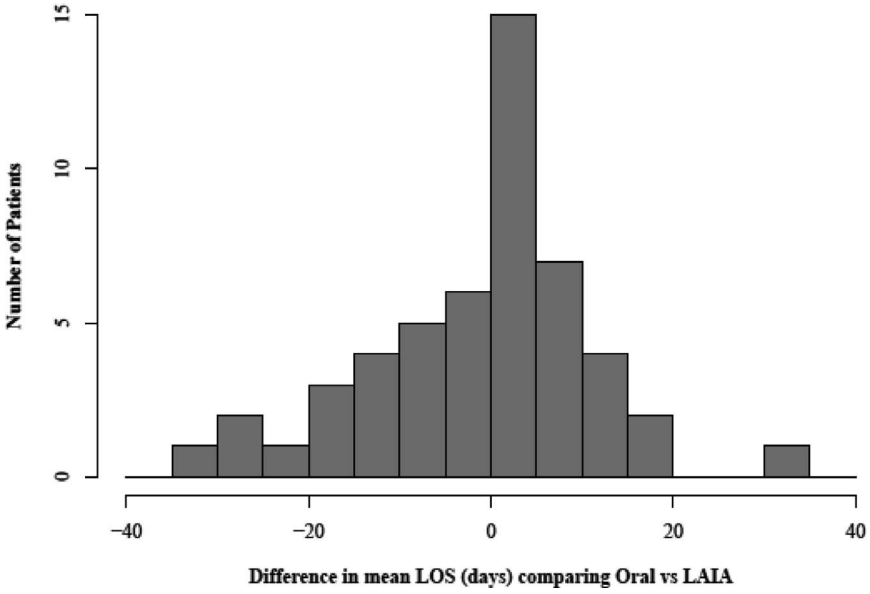

FIGURE 1: Differences in mean length of stay (LOS) between oral versus long-acting injectable antipsychotics (LAIAs) for each patient

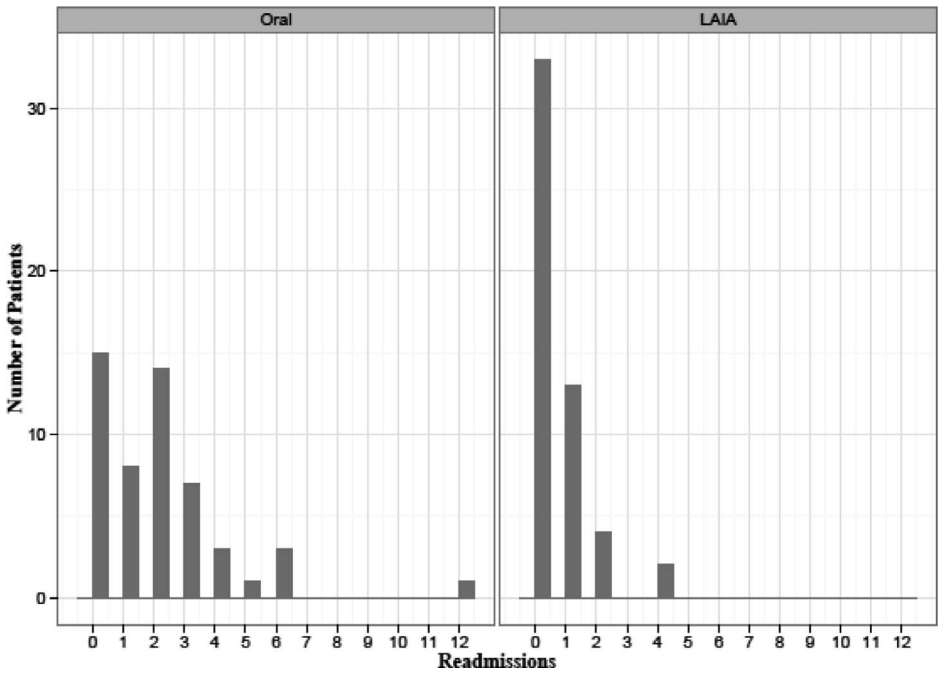

FIGURE 2: **Total hospital readmissions for each patient comparing oral and long-acting injectable antipsychotics (LAIAs)**

Discussion

The study determined that the use of LAIAs had a significant impact in decreasing the number of total annual readmissions. Although not statistically significant, LAIA use reduced the number of failed annual discharges compared with oral antipsychotic use. We were not able to demonstrate a reduction in the average hospital length of stay.

There were limitations in the selection of patients and the design of the study that may have affected our results. Only patients who received both LAIAs and oral agents and had at least one hospital admission during both arms of the study were included. Poor medication adherence is associated with a higher risk of rehospitalization, whereas patients with fewer hospital readmissions are generally more adherent.[14]

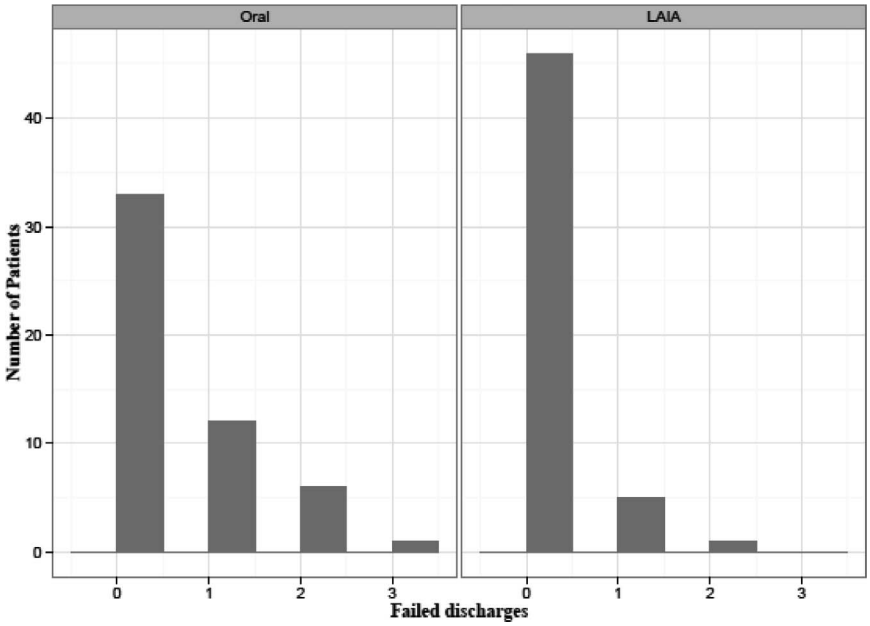

FIGURE 3: **Comparison of the number of failed hospital discharges between oral and long-acting injectable antipsychotics (LAIAs)**

TABLE 2: Oral and long-acting injectable antipsychotic (LAIA) prescribing distribution

Drug	Males		Females	
	Age <40 years	Age ≥40 years	Age <40 years	Age ≥40 years
Oral				
Chlorpromazine	0	1	0	0
Fluphenazine	5	6	2	3
Haloperidol	8	6	3	4
Perphenazine	0	0	0	1
Thiothixene	1	0	1	1
Aripiprazole	1	1	0	0
Clozapine	0	0	0	1
Olanzapine	8	5	3	7
Quetiapine	2	1	1	1
Risperidone	8	3	0	4
Ziprasidone	1	1	0	2
LAIA				
Fluphenazine	5	5	2	5
Haloperidol	9	5	3	5
Paliperidone	5	4	3	2
Risperidone	0	1	0	3

The study also did not take into consideration whether difference in administration techniques of LAIAs would have an impact on adherence, and thus the three main objectives of this study. It is possible that agents that require less frequent administration or do not require oral overlap can enhance adherence.

Trends in the choice of oral antipsychotic prescribing were observed, with greater use of fluphenazine, haloperidol, olanzapine, and risperidone, and less use of clozapine, quetiapine, thiothixene, aripiprazole, ziprasidone, perphenazine, and chlorpromazine (Table 2). In the LAIA arm, risperidone microspheres use was low because the study population primarily received first-generation antipsychotics and paliperidone palmitate. The hospital participates in a manufacturer-sponsored program for paliperidone palmitate. This program may have affected prescriber choice of second-generation LAIA. The prescribing patterns we observed may be different in other institutions. In the oral arm of the study, switching antipsychotic medications occurred more frequently than in the LAIA arm of the study (Table 1).

The diagnoses of patients in the study were not well defined, with several patients having mixed presentation of schizophrenia and schizoaffective disorder. It is difficult to determine the true impact of antipsychotic treatment in patients without a defined diagnosis. The study population only included patients with diagnoses of schizophrenia, schizoaffective disorder, and mixed/rule out diagnosis.

The Poisson model assumes that there is a constant risk of hospital readmission and a constant risk of failed discharges, respectively. This may not be reflective of situations where it is expected that patients would have a lower risk of immediate hospital readmission. However, the observed differences are large between LAIAs and oral treatment in this study and should not have a significant impact on the results.

The findings from this study are notable in that they indicate switching from oral antipsychotics to LAIAs can lead to fewer hospital readmissions and possibly also a decrease in the number of failed annual discharges. The fact that there is no difference in lengths of stay between the LAIAs versus oral antipsychotics is also a finding that deserves further attention. Current evidence regarding length of hospital stay in this population when patients were on LAIAs is scarce. Ren et al[15] and Fuller et al[16] demonstrated that LAIA use significantly reduced the duration of hospitalization, but their results are confounded by weaknesses, such as having a predominantly male study population, a study design that is observational in nature, and an exclusion criterion for patients who received fewer number of injections.

Further research with significant power could determine whether use of LAIAs conclusively results in fewer failed hospital discharges. In addition, future research could incorporate cost analysis to determine whether the reduction in the number of hospital readmissions does indeed lead to cost savings, because the higher expense of LAIAs can potentially be offset by the reduced readmissions over a long-term basis. Finally, a well-designed prospective study incorporating balanced patient covariates can also address some of the limitations in dealing with a retrospective observational study.

References

1. Lafeuille MH, Laliberté-Auger F, Lefebvre P, Frois C, Fastenau J, Duh MS. Impact of atypical long-acting injectable versus oral antipsychotics on rehospitalization rates and emergency room visits among relapsed schizophrenia patients: a retrospective database analysis. BMC Psychiatry. 2013;13:221. DOI: 10.1186/1471-244X-13-221. PubMed PMID: 24016390; PubMed Central PMCID: PMC3847215.
2. Kaplan G, Casoy J, Zummo J. Impact of long-acting injectable antipsychotics on medication adherence and clinical, functional, and economic outcomes of schizophrenia. Patient Prefer Adherence. 2013;7:1171-80. DOI: 10.2147/PPA.S53795. PubMed PMID: 24265549.
3. Glazer WM. Who receives long-acting antipsychotic medications? Psychiatr Serv. 2007;58(4):437. DOI: 10.1176/ps.2007.58.4.437. PubMed PMID: 17412839.

4. Gerlach J. Depot neuroleptics in relapse prevention: advantages and disadvantages. Int Clin Psychopharmacol. 1995;9 Suppl 5:17-20. PubMed PMID: 7622829.
5. Olfson M, Mechanic D, Hansell S, Boyer CA, Walkup J. Prediction of homelessness within three months of discharge among inpatients with schizophrenia. Psychiatr Serv. 1999;50(5):667-73. DOI: 10.1176/ps.50.5.667. PubMed PMID: 10332904.
6. Waddell L, Taylor M. Attitudes of patients and mental health staff to antipsychotic long-acting injections: systematic review. Br J Psychiatry Suppl. 2009;52:S43-50. DOI: 10.1192/bjp.195.52.s43. PubMed PMID: 19880916.
7. Jaeger M, Rossler W. Attitudes towards long-acting depot antipsychotics: a survey of patients, relatives and psychiatrists. Psychiatry Res. 2010;175(1-2):58-62. DOI: 10.1016/j.psychres.2008.11.003. PubMed PMID: 20004980.
8. Patel MX, Haddad PM, Chaudhry IB, McLoughlin S, Husain N, David AS. Psychiatrists' use, knowledge and attitudes to first- and second-generation antipsychotic long-acting injections: comparisons over 5 years. J Psychopharmacol. 2010;24(10):1473-82. DOI: 10.1177/0269881109104882. PubMed PMID: 19477883.
9. Agid O, Foussias G, Remington G. Long-acting injectable antipsychotics in the treatment of schizophrenia: their role in relapse prevention. Expert Opin Pharmacother. 2010;11(14):2301-17. DOI: 10.1517/14656566.2010.499125. PubMed PMID: 20586707.
10. Bera RB. Patient outcomes within schizophrenia treatment: a look at the role of long-acting injectable antipsychotics. J Clin Psychiatry. 2014;75 Suppl 2:30-3. DOI: 10.4088/JCP.13065su1c.07. PubMed PMID: 24919169.
11. Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. Schizophr Bull. 2014;40(1):192-213. DOI: 10.1093/schbul/sbs150. PubMed PMID: 23256986.
12. Frome EL, Checkoway H. Epidemiologic programs for computers and calculators. Use of Poisson regression models in estimating incidence rates and ratios. Am J Epidemiol. 1985;121(2):309-23. PubMed PMID: 3839345.
13. The R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing; 1999-2012; 1-3604.
14. Valenstein M, Copeland LA, Blow FC, McCarthy JF, Zeber JE, Gillon L, et al. Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. Med Care. 2002;40(8):630-9. DOI: 10.1097/01.MLR.0000021003.43524.64. PubMed PMID: 12187177.
15. Ren XS, Crivera C, Sikirica M, Dirani R, Qian S, Kazis LE. Evaluation of health services use following the initiation of risperidone long-acting therapy among schizophrenia patients in the veterans health administration. J Clin Pharm Ther. 2011;36(3):383-9. DOI: 10.1111/j.1365-2710.2010.01211.x. PubMed PMID: 21062329.
16. Fuller M, Shermock K, Russo P, Secic M, Dirani R, Vallow S, et al. Hospitalisation and resource utilisation in patients with schizophrenia following initiation of risperidone long-acting therapy in the Veterans Affairs Healthcare System. J Med Econ. 2009;12(4):317-24. DOI: 10.3111/13696990903303902. PubMed PMID: 19817665.