

Switching from risperidone long-acting injectable to paliperidone long-acting injectable or oral antipsychotics: analysis of a Medicaid claims database

Erica A. Voss^a, Patrick B. Ryan^a, Paul E. Stang^a, David Hough^a and Larry Alphas^b

This report examines relapse risk following a switch from risperidone long-acting injectable (RLAI) to another long-acting injectable antipsychotic [paliperidone palmitate (PP)] versus a switch to oral antipsychotics (APs). Truven Health's MarketScan Multistate Medicaid Database compared relapses following switches from RLAI. New user cohorts for these two groups were created on the basis of first incidence of exposure to the 'switched to' drug. Groups were balanced using 1:1 propensity score matching. Time-to-event analysis assessed schizophrenia-related hospital/emergency department visits. A total of 188 patients switched from RLAI to PP, and 131 patients switched from RLAI to oral AP. Propensity score-matched cohort included 109 patients who switched to PP and 109 patients who switched to an oral AP. Patients who switched from RLAI to PP had fewer events (26 vs. 32), longer time to an event (mean 70 vs. 47 days), and lower risk of relapse (hazard ratio, 0.54; 95% confidence interval, 0.32–0.92; $P = 0.024$)

compared with those who switched from RLAI to oral AP. Switching from RLAI to PP may be associated with a lower risk for relapse and longer duration of therapy compared with switching to oral AP. Given the limitations of observational studies, these results should be confirmed by other prospective evaluations. *Int Clin Psychopharmacol* 30:151–157 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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^aJanssen Research & Development, LLC and ^bJanssen Scientific Affairs, LLC, Titusville, New Jersey, USA

Correspondence to Erica A. Voss, Janssen Research & Development, LLC, 1125 Trenton-Harbourton Road, Titusville, NJ 08560, USA
Tel: +1 908 927 7537; e-mail: EVoss3@its.jnj.com

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Introduction

The primary goals of antipsychotic (AP) pharmacotherapy in schizophrenia patients are to reduce symptoms, prevent relapse, and improve outcomes (American Psychiatric Association, 1997). One of the greatest challenges in treating patients with severe and persistent schizophrenia is maintaining continuity of effective, well-tolerated AP therapy that provides adequate symptom control and maintains clinical stability. Despite the need for stable treatment, research has found that as many as 50% of patients will switch AP medications in a given year because of inadequate effectiveness, poor tolerance of side effects, inconsistent adherence, or comorbid psychiatric conditions (Weiden, 2006; Faries *et al.*, 2009; Nyhuis *et al.*, 2010).

The time during which medications are switched often represents a time of potential clinical instability. Patients may already be in an unstable state because of prior inadequate adherence or worsening of their underlying disease. In addition, dosing of the new drug must be optimized on an individual basis. This is not formulaic,

and side effects of the new drug, efficacy optimization, and drug–drug interactions must be addressed. Failures during switching of treatment may result in increased healthcare resource use, particularly hospitalizations, which account for up to two-thirds of the total direct healthcare costs of schizophrenia patients (Weiden and Olfson, 1995; Wu *et al.*, 2005; Nicholl *et al.*, 2010).

Appropriate dose finding following initiation or termination of long-acting injectable (LAI) AP medications poses particular challenges. Unique individual-based genetic, pharmacological, and psychological factors prevent determination of absolute dosing conversion equivalencies across AP products. The use of LAIs is further complicated by one of their key benefits: long half-life. Steady state is not achieved for four to five half-lives of the new medication, which is months following initiation of LAI treatment, whereas time to new steady state is much shorter when a switch is made to oral medications. These challenges may mean that switching from LAI treatments to other LAI treatments could pose increased risks compared with switching to oral treatments.

This epidemiological study examined whether there was a difference in clinical instability as reflected by time to hospitalization after switching between APs

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in a real-world setting. In particular, the time to schizophrenia-related hospitalization following a switch from risperidone long-acting injectable (RLAI) to another LAI AP [paliperidone palmitate (PP)] versus a switch to alternative oral AP medications was examined.

Materials and methods

Study design and data source

This observational database study represents a retrospective cohort analysis of hospitalizations following switching from RLAI to PP or oral AP medication. Only individuals with a clinical diagnosis of schizophrenia were evaluated. A cohort design was chosen for the evaluation, as it allows direct comparison of the rate of outcomes that occur following exposure and allows for control of between-person confounding factors observed before exposure.

A multistate Medicaid database [Truven Health's MarketScan Multistate Medicaid Database (MMMD)], reflecting care provided from 2006 to 2011 across a population of more than 11 million Medicaid beneficiaries, was used for the analysis. MMMD contains deidentified administrative claims data from inpatient and outpatient medical services, including all associated procedure and diagnosis codes that have been submitted to the state for reimbursement. It also includes pharmacy dispensing claims records for Medicaid beneficiaries during their enrollment in the program. The analysis performed using this database was reviewed by the New England Institutional Review Board and was determined to be exempt from broad institutional review board approval, as this research project involved no risk to the participants. We obtained the de-identified patient-level data set through a license agreement with each data holder.

Study cohort

The study cohort consisted of patients with a prior diagnosis of schizophrenia (International Classification of Diseases, Ninth Revision, Clinical Modification 295) who had been exposed to an AP medication [defined by National Drug Codes and Healthcare Common

Procedure Coding System (HCPCS) codes]. The Observational Medical Outcomes Partnership (OMOP) Vocabulary, Version 4 (Observational Medical Outcomes Partnership (OMOP), 2014), was used to find relevant National Drug Codes and HCPCS codes (Overhage *et al.*, 2012; Reich *et al.*, 2012; Defalco *et al.*, 2013) for AP treatments. The condition codes and drug ingredients used to identify patients within the MMMD are given in Table 1.

A switch between medications was defined as a gap or overlap between treatments that was shorter than or equal to 30 days. The 30-day interval was selected on the basis of prior research (Ryan, 2010), with the goal of reflecting a consistently meaningful therapeutic window for 30-day prescriptions for oral medications. This interval also reflects a reasonable period of time following treatment with a 2- or 4-week injectable medication. The date on which the second AP drug was dispensed or administered was considered the index date. This study used a new-user switch cohort design: The first switch of each switch type was used for analysis; the patient could not have had prior exposure to the 'switched to' drug. We required at least 2 years of observation in the database before the date of the switch to increase our confidence that the patient was recently naive to the initial drug and to record a baseline period that is sufficient to define covariates that required medical history, such as numbers of prior AP treatments and prior hospitalizations. Figure 1 illustrates aspects of a switch.

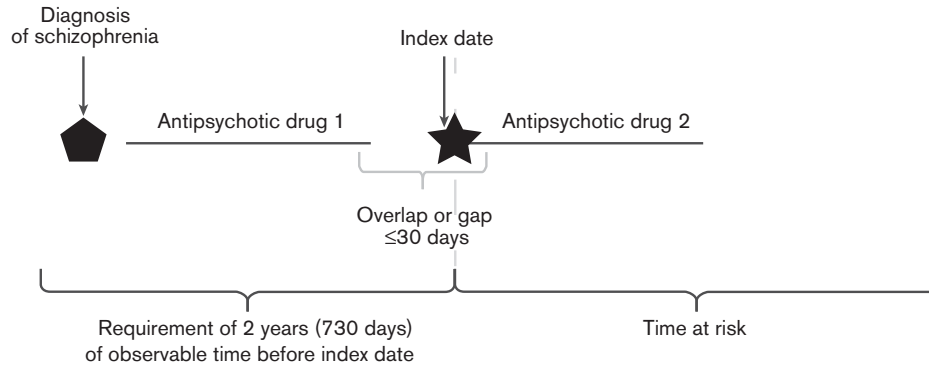
Assessments

The main focus of this study was to compare the switching individuals who switched from RLAI to PP versus individuals who switched from RLAI to an oral AP. The outcome of interest was schizophrenia-related hospitalization after the index date, defined as an inpatient admission or an emergency department (ED) visit that included any mention of a schizophrenia diagnosis in any position within a medical service claim (this is the definition of relapse used in this paper unless otherwise stated). A retrospective sensitivity analysis was performed to assess the robustness of the outcome

Table 1 Condition codes and drugs used to identify patients within the database

Schizophrenia	ICD-9 diagnosis codes: 295, 295.0, 295.00, 295.01, 295.02, 295.03, 295.04, 295.05, 295.1, 295.10, 295.11, 295.12, 295.13, 295.14, 295.15, 295.2, 295.20, 295.21, 295.22, 295.23, 295.24, 295.25, 295.3, 295.30, 295.31, 295.32, 295.33, 295.34, 295.35, 295.4, 295.40, 295.5, 295.50, 295.51, 295.52, 295.55, 295.6, 295.60, 295.61, 295.83, 295.84, 295.85, 295.9, 295.90, 295.91, 295.93, 295.94, 295.95, 295.41, 295.42, 295.43, 295.44, 295.45, 295.53, 295.54, 295.71, 295.72, 295.73, 295.74, 295.75, 295.8, 295.80, 295.81, 295.82, 295.63, 295.64, 295.65, 295.7, 295.70, 295.92
Antipsychotic – injectable risperidone	Injectable ingredients: Risperidone
Antipsychotic – injectable paliperidone	Injectable ingredients: Paliperidone
Oral antipsychotic	Oral ingredients: Asenapine, chlorpromazine, clozapine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, risperidone, thioridazine, thiothixene, trifluoperazine, aripiprazole, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, ziprasidone

Fig. 1



Schematic of switching definition used.

definition. For this analysis, a broader definition of all-cause hospitalization was used that identified all inpatient admissions or ED visits regardless of the presence of a schizophrenia diagnosis. An additional sensitivity analysis applied a narrower definition that used only inpatient admissions and ED visits that had schizophrenia listed as the primary diagnosis on the medical service claim.

Time at risk, which was defined by the period of observation after the index date, varied across individuals. The end of an individual's time at risk was censored by the earliest of the following: (a) 60 days after the end of successive dispensing of the 'switched to' drug that are no more than 30 days apart, (b) 365 days after the index date, (c) the date on which the patient's follow-up time in the database ends (disenrolls from Medicaid), or (d) the date on which a different AP medication is dispensed.

Propensity score modeling

Disease severity and treatment use among patients with schizophrenia are likely to be associated with the risk of schizophrenia-related hospitalization (i.e. between-person confounding). For the two cohorts to be similar outside their switch type, a propensity score adjustment strategy was used to adjust for potential confounders (Rosenbaum and Rubin, 1983). The propensity score derived reflects the conditional probability of a patient receiving PP versus an oral AP following switching from injectable risperidone. To calculate the propensity score, a regularized regression was fit, using 5853 candidate covariates found for each patient during the 2 years before the index date. These included 11 demographic covariates for age, age deciles, and sex, and eight continuous covariates for number of visits (outpatient, inpatient, ED), days on AP treatment, number of switches, and numbers of conditions, drugs, and procedures in the patient's medical history, with 4982 covariates representing each condition or procedure as a binary indicator

of the presence or absence of the condition or procedure administered and 851 covariates representing each of the possible generic ingredients and drug classes observed. The propensity score was estimated using Bayesian logistic regression software (Genkin *et al.*, 2007).

The propensity score was used to produce a 1-to-1 match between the two cohorts. Matching individuals were selected randomly from among candidates falling within a caliper of 0.2 times the SE of the propensity score distribution (Austin, 2011). Covariate balance was assessed with standardized differences before and after matching to determine the degree to which observed confounders were brought into alignment after adjustment and to identify potential sources of residual confounding that persist after matching. After matching was performed, we classified the outcome status of all patients within the matched groups by determining whether they experienced a subsequent schizophrenia-related hospitalization after the index date (the outcome of interest).

Statistical analysis

A conditional Cox proportional hazards model was used to compare the matched comparison groups on time to schizophrenia-related hospitalization and to produce a hazard ratio (HR) and corresponding 95% confidence interval (CI) that allowed for variation in time at risk (time-dependent explanatory variables). An absolute variance estimate convergence criterion of 0.001 was used. Kaplan–Meier curves were produced to depict differences in time-to-event distribution between groups. A proportionality test was used to test whether an interaction occurred between time and outcome at an α level of 0.05. All analyses were performed in SAS Enterprise Guide 5.1 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patients and disposition

We identified 188 patients who had switched from RLAI to PP and 131 patients who had switched from RLAI to

an oral AP. Table 2 summarizes patient demographics before and after matching. The matched population comprised 109 patients in each cohort. In the matched population, patients who were switched to PP were more likely to be male than those switched to an oral treatment (56.9 vs. 50.5%). The age distribution appeared similar in both cohorts, with an average age of 40 years (SD 13) for those who switched to PP and 42 years (SD 13) for those

Table 2 Patient characteristics of unmatched and propensity score-matched cohorts for the analysis of switching from injectable risperidone to injectable paliperidone versus switching from injectable risperidone to oral antipsychotic

Characteristics	Unmatched		Matched	
	Injectable risperidone to injectable paliperidone (n = 188)	Injectable risperidone to oral antipsychotic (n = 131)	Injectable risperidone to injectable paliperidone (n = 109)	Injectable risperidone to oral antipsychotic (n = 109)
Sex [n (%)]				
Female	88 (46.8)	64 (48.9)	47 (43.1)	54 (49.5)
Male	100 (53.2)	67 (51.1)	62 (56.9)	55 (50.5)
Age at index [mean (SD)] (years)	42.0 (13)	41.7 (14)	40.4 (13)	42.2 (13)
Age group [n (%)] (years)				
00–09	–	–	–	–
10–19	6 (3.2)	1 (0.8)	4 (3.7)	1 (0.9)
20–29	36 (19.1)	28 (21.4)	25 (22.9)	20 (18.3)
30–39	40 (21.3)	35 (26.7)	24 (22.0)	29 (26.6)
40–49	45 (23.9)	25 (19.1)	28 (25.7)	24 (22.0)
50–59	46 (24.5)	28 (21.4)	21 (19.3)	25 (22.9)
60–69	13 (6.9)	11 (8.4)	5 (4.6)	8 (7.3)
70–79	2 (1.1)	3 (2.3)	2 (1.8)	2 (1.8)
80–89	–	–	–	–
Year of index [n (%)]				
2009	46 (24.5)	30 (22.9)	31 (28.4)	27 (24.8)
2010	92 (48.9)	54 (41.2)	50 (45.9)	45 (41.3)
2011	50 (26.6)	47 (35.9)	28 (25.7)	37 (33.9)
Length of exposure to the switched-to drug (mean) (days)	227.0	116.1	239.4	122.2

who switched to an oral AP. A notable difference in the length of exposure was seen after a switch from RLAI between the two cohorts. Patients receiving PP had 239 days of exposure on average, as compared with an average of 122 days of exposure for the matched oral AP cohort.

Propensity score modeling

Table 3 shows the five covariates used within the model and a comparison of the average for each covariate before and after matching. In general, covariates used in the model became balanced or remained balanced after matching. After adjustment, some covariates that were not used within the model (e.g. number of inpatient admissions, number of ED visits) became more balanced. However, 202 of the 5852 (3.45%) covariates remained unbalanced after matching (standardized difference > 0.25) between those who switched to PP and those who switched to an oral AP, including manic and bipolar mood disorders and disturbances (40 vs. 59%), patient use of valproate (20 vs. 42%), and patient diagnosis of bipolar I disorder (36 vs. 58%).

Time-to-event analysis for relapse

Patients who switched from RLAI to PP had fewer relapse-related events (26 vs. 32 events) and longer time to an event (mean of 70 vs. 47 days) after a switch than patients who switched to an oral AP. This resulted in a significantly lower risk for schizophrenia-related hospitalizations (HR 0.54; 95% CI 0.32–0.92; $P=0.024$) in favor of a switch to PP (Fig. 2). The proportionality test failed to confirm an interaction ($P>0.05$). The two sensitivity analyses that used broader and narrower outcome definitions yielded similar results. When the outcome was defined by hospitalizations with a specific primary diagnosis of schizophrenia, the number of events decreased (26–15 vs. 32–26 events), but the HR remained significantly reduced (HR 0.37; 95% CI 0.19–0.70; $P=0.003$). When the outcome definition was broadened to include all-cause hospitalization, the total

Table 3 Covariates used within the Bayesian logistic regression model to build propensity scores for analysis of switching from injectable risperidone to injectable paliperidone versus switching from injectable risperidone to oral antipsychotic

Description	Unmatched			Matched		
	Injectable risperidone to injectable paliperidone	Injectable risperidone to oral antipsychotic	SD	Injectable risperidone to injectable paliperidone	Injectable risperidone to oral antipsychotic	SD
Age at index (years) (mean)	42.03	41.71	0.0238	40.55	42.17	0.1230
Number of concomitant medications (mean)	5.05	6.18	0.2725	5.09	5.65	0.1425
Number of outpatient visits (mean)	181.71	189.79	0.0484	196.58	193.28	0.0181
Number of schizophrenia admissions/ED visits (mean)	1.96	3.54	0.3829	2.63	2.69	0.0158
Days receiving antipsychotic treatment (mean)	769.27	690.76	0.1980	689.53	706.12	0.0479

ED, emergency department; SD, standardized difference.

number of events increased from 26 to 42 events for patients who switched from RLAI to PP and from 32 to 43 events for patients who switched from RLAI to an oral AP (HR 0.66; 95% CI 0.43–1.02; $P = 0.062$).

Discussion

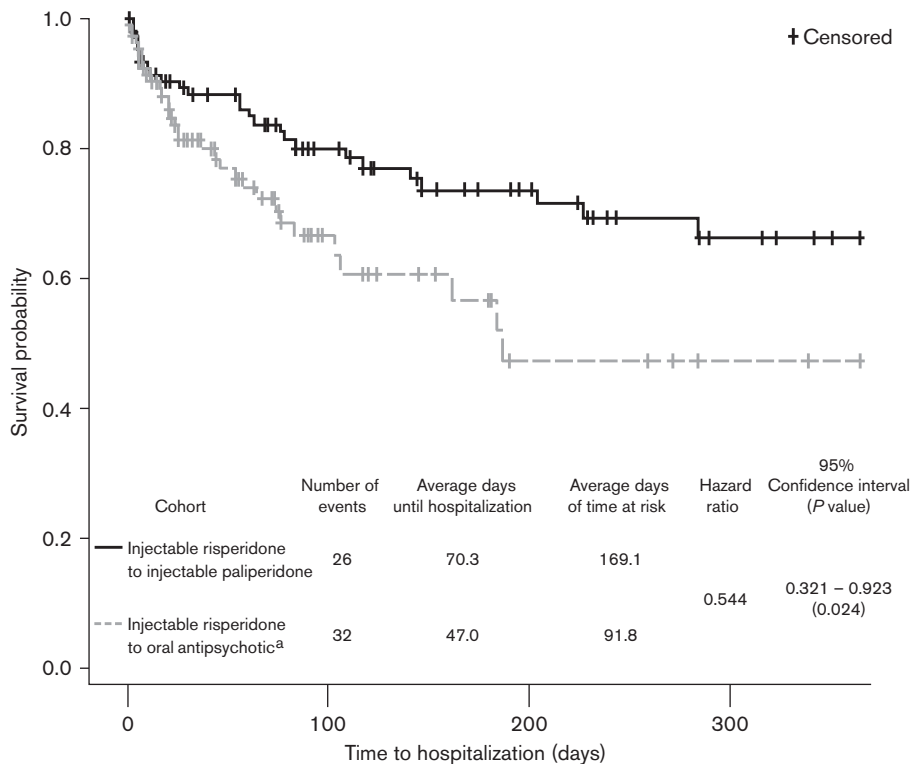
This retrospective analysis of a claims database failed to confirm any potential concerns that problems in dose optimization following a switch from RLAI to PP LAI might be associated with greater risk for relapse than problems following a switch from RLAI to oral medications. On the contrary, as measured by time to schizophrenia-related hospitalizations, switching from RLAI to the longer-acting PP resulted in significantly better outcomes, as measured by time to symptom relapse in this real-world environment. More than a quarter of the patients in this multistate Medicaid claims database who were being treated with PP had switched from RLAI. Given the frequency of this initiation approach, it seems unlikely that concerns about dose optimization following a switch to PP will substantially interfere with its practical introduction to patients.

Although the number of schizophrenia-related hospitalizations observed during the study period was nearly identical for both treatment groups (26 events in the PP cohort vs. 32 events in the oral AP cohort), the number of

observed events was skewed by the longer time at risk within the PP group. As a result, time to relapse was prolonged by more than 50% when similar patients were switched to PP as compared with oral APs. This is supported by the findings of several prior reports on data from the electronic Schizophrenia Treatment Adherence Registry (e-STAR), which found a beneficial effect of atypical long-acting APs in reducing hospitalizations after patients were switched from oral therapies (Olivares *et al.*, 2008, 2009a, 2009b). Despite the positive findings seen in e-STAR, clinical studies have failed to demonstrate significant treatment differences between LAI and oral APs (Schooler, 2003; Kane *et al.*, 2010; Macfadden *et al.*, 2010; Rosenheck *et al.*, 2011a). This apparent lack of difference in efficacy between LAI and APs may be explained by the explanatory nature of controlled clinical trials, and it highlights the need for more pragmatic studies that better reflect real-world clinical practice settings (Rosenheck *et al.*, 2011b; Fusar-Poli *et al.*, 2013; Kirson *et al.*, 2013). With these issues taken into account, the generalizability and impact of the present study appear to be enhanced by the fact that it was conducted using a matched group of persons treated in a naturalistic, real-world environment.

The longer periods of stability observed in persons who switched to PP in this study have important implications

Fig. 2



Propensity score-matched cohort Kaplan–Meier estimates of time to hospitalization for analysis of the switch from injectable risperidone to injectable paliperidone versus injectable risperidone to oral antipsychotic. ^aReference group.

for clinical outcomes and can be expected to positively affect patients' social, educational, and work lives. Relapses are extremely disruptive to patients' lives and are burdensome to families, friends, caregivers, and coworkers. The resulting economic, social, and healthcare burdens lead to loss of employment, disruption of education, broken relationships, and loss of support systems that are crucial to long-term treatment success. Not infrequently, such periods are associated with substance abuse and involvement with the criminal justice system, which compound existing problems. In contrast, prolonged clinical stability can allow the building of successful relationships and the development of new skills that are necessary for productive, happy lives.

This retrospective analysis review of a healthcare claims database has several limitations. The MMMD used in this analysis was not a randomly selected sample and is not necessarily representative of the overall US population. However, it does reflect the experience of a large group of patients with schizophrenia residing in select US states. They are likely to be representative of persons receiving AP medication treatment. Another consideration is that claims data are based on financial claims filed for reimbursement. Therefore, disease coding may reflect financial incentives for reimbursement rather than clinically verified events. Claims for illness-related events that are not addressed by the US healthcare system are not included. In the USA, many patients with psychiatric conditions are managed within the criminal justice system. Indeed, many patients with schizophrenia are more likely to be incarcerated than hospitalized. These outcomes have not been captured by this work. Finally, we were unable to determine the reason for a switch in medication. As a result, it cannot be determined whether the improvement in outcome following a medication switch was because of improvement in effectiveness and/or safety of the medication or whether it was the result of selection of patients who are more likely to benefit from a longer-acting LAI than from oral medications.

This claims database study of real-world patients with schizophrenia suggests that switching from RLAI to PP may be associated with a lower risk for schizophrenia-related hospitalization and longer duration of therapy, compared with switching from RLAI to an oral AP agent. Given the potential sources of error in observational studies, these results cannot be viewed as definitive and should be confirmed by additional evaluations.

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All authors are responsible for the study design, data collection, and writing. Erica Voss is responsible for the statistical analyses. All authors critically reviewed and revised the manuscript and have approved the final manuscript for submission.

Conflicts of interest

Erica A. Voss, Patrick B. Ryan, Paul E. Stang, and David Hough are employees of Janssen Research & Development, LLC, and are Johnson & Johnson stockholders. Larry Alphas is an employee of Janssen Scientific Affairs, LLC, and a Johnson & Johnson stockholder.

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