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Risperidone Long-acting Injectable versus Paliperidone Palmitate for Community-dwelling Patients with Schizophrenia

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ABSTRACT

Purpose: Studies indicate that poor medication compliance often hinders positive treatment outcomes in patients with schizophrenia. Risperidone long-acting injectable and paliperidone palmitate theoretically aid compliance as they are given only once every two or four weeks, respectively. Because the two formulations share similar pharmacologic and pharmacokinetic properties, further evaluation is required to determine whether clinically significant differences in patient outcome exist and the impact of these variations. The purpose of this study was to determine whether community-dwelling patients with schizophrenia receiving risperidone long-acting injectable incur improved clinical outcomes or lowered costs than patients receiving paliperidone palmitate.

Methods: A retrospective cohort chart review was conducted on patients who had an encounter at our institution while receiving risperidone long-acting injectable or paliperidone palmitate from January 1, 2011 to December 31, 2012. The primary objective of this study was to determine the total cost of psychiatric-related care for patients receiving paliperidone palmitate versus risperidone long-acting injectable. Secondary objectives included comparisons of hospitalization days and emergency department encounters in patient-days, time to discontinuation, and time to first relapse. A subgroup analysis was conducted on patients receiving injections through a local ambulatory psychiatric facility.

Results: A total of 47 patients were included in the primary analysis with 30 patients included in the ambulatory psychiatric subgroup analysis. Risperidone long-acting injectable patients incurred lower psychiatry-related treatment costs per patient-day than paliperidone palmitate under the total ($p=0.032$) and ambulatory psychiatric subgroup ($p=0.049$) analyses. Ambulatory psychiatric risperidone long-acting injectable patients were found to require fewer psychiatric inpatient days ($p=0.044$) than paliperidone palmitate patients.

Conclusion: Use of risperidone long-acting injectable was associated with significantly fewer psychiatric inpatient days and lower psychiatry-related costs than paliperidone palmitate in our population of community-dwelling patients with schizophrenia.

INTRODUCTION

Affecting approximately 2.4 million Americans, schizophrenia is a lifelong, debilitating thought disorder characterized by positive and negative symptoms [1,2]. Currently, the mainstay of schizophrenia treatment involves heavy reliance on antipsychotic medications. A major goal of antipsychotic treatment generally includes the minimization of symptoms and adverse effects as well as maximization of social functionality and quality of life. Unfortunately, several barriers commonly limit achievement of these goals. Although proven beneficial to patient quality of life and outcomes, antipsychotic medications often involve complex regimens and uncomfortable, sometimes intolerable, adverse effects [3]. If patients prone to paranoia discontinue their oral antipsychotics, reemergence of anxiety may prevent voluntarily resumption of therapy and necessitate inpatient psychiatric treatment [4]. Additionally, patients with schizophrenia commonly lack insight into their mental illness and do not feel that antipsychotic treatment is beneficial. For instance, patients with comorbid schizophrenia and insulin-independent diabetes mellitus rate oral hypoglycemic medications as being significantly more important for overall health maintenance than their prescribed antipsychotics [5].

For these and other reasons, patient adherence to antipsychotic medications is notoriously low and spontaneous discontinuation is common. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) meta-analysis, 74% of patients initiated on oral risperidone discontinued their medication within 18 months [6]. Of the discontinued patients, 37% cited "lack of efficacy" as a reason for discontinuation. A full 41% of the patients who failed to complete 18 months of therapy independently made the decision to discontinue treatment. An outpatient study conducted by the US Department of Veteran's Affairs discovered that approximately 40% of patients receiving at least one antipsychotic drug possessed a medication possession ratio (MPR) of under 0.8. In other words, the frequency of patient-initiated pharmacy refills resulted in 40% of patients receiving fewer than 80% of the doses required for perfect compliance [7].

Presumably due to higher compliance, patients treated with long-acting injectable antipsychotics achieve symptomatic remission at a significantly higher rate than patients relying on oral therapy [8]. For example, risperidone long-acting injectable has been shown to lead to a significantly longer time-to-relapse than daily oral quetiapine [9]. Before-and-after analyses have shown that patients converted from oral to long-acting injectable antipsychotics experience clinically significant reductions in hospitalizations and relapses [10,11]. Previously, total cost comparison studies were only available from European countries with different healthcare systems; however, a recent analysis suggests that total treatment cost savings may exist under the United States system as well [12-14]. As these analyses neither collected nor estimated indirect expenses such as rate of or lost productivity due to unemployment or incarceration, the true overall outcome and treatment cost differences may reasonably be assumed to hold even greater levels of clinical significance.

Unfortunately, these benefits must be factored against the numerous downfalls of long-acting injectable antipsychotics. Under current patents and prices, long acting injectable antipsychotics cost several hundred dollars per month while oral risperidone 1 mg costs under $10 for 28 doses. Patients who revoke consent, experience intolerable side effects, or become otherwise dissatisfied with treatment are unable to quickly rid their bodies of injectable medications and must maintain a therapeutic level of drug in their system for an extended period of time. Because these drugs require administration by a health care professional, patient compliance can easily be tracked; however, it may be argued that this tracking infringes on patient privacy rights.

First generation antipsychotics (FGAs), also known as typical antipsychotics, are infamous for their high rate of extrapyramidal side effects such as tremor, akathisia, bradykinesia, rigidity, and tardive dyskinesia. Risperidone long-acting injectable and paliperidone palmitate, both classified as atypical or second-generation antipsychotics (SGAs), are thought to cause extrapyramidal side effects at a much lower rate. Unfortunately, SGAs carry their own set of negative class effects such as weight gain, hyperlipidemia, and diabetes. Additionally, risperidone and paliperidone, the oral formulations of the antipsychotics compared in this study, inhibit the tuberoinfundibular dopaminergic pathway in the brain to a greater extent than other United States Food and Drug Administration (FDA)-approved SGAs [15]. Due to this inhibition, they are known to cause hyperprolactinemia. This can lead to a variety of hormonal disturbances, particularly infertility, galactorrhea, gynecomastia, and impotence. Although these side effects are believed to be relatively rare, due to the extended duration of action of risperidone long-acting injectable and paliperidone palmitate, the manufacturers strongly recommend that tolerability be established in risperidone and paliperidone-naïve patients prior to initiation of either injectable medication [16,17]. Two oral test doses are required as hypersensitivity reactions frequently do not occur after only one dose.

Administered once every two weeks, risperidone long-acting injectable was the first long-acting atypical antipsychotic approved in the United States and currently carries an FDA-approved indication as a biweekly intramuscular (IM) injection for the treatment of schizophrenia. Because the specific pharmacokinetic properties of this formulation impart a lag time of three weeks between the initial injection and a significant rate of drug release, the manufacturer recommends continuation of oral risperidone (or another antipsychotic) during the first three weeks of treatment [17]. Paliperidone palmitate, administered once every four weeks, is currently indicated for the acute and maintenance treatment of schizophrenia in adults. In contrast with risperidone long-acting injectable, the formulation used in paliperidone palmitate employs an aqueous suspension of nanoparticles. These particles grant increased surface area and cause a rapid release of medication. Consequently, even in patients suffering from

acute illness, oral antipsychotics may be discontinued upon initiation of paliperidone palmitate [18,19]. Initiation consists of 234 mg IM on day one and 156 mg on day eight of treatment. Afterwards, a regular four-week maintenance schedule may commence [16].

Paliperidone (9-hydroxyrisperidone), the major active metabolite of risperidone, acts primarily as an antagonist on D_2 and $5HT_{2A}$ receptors. Paliperidone palmitate, the salt present in long-acting injectable paliperidone, is a very poorly soluble ester of racemic paliperidone that has demonstrated non-inferiority to risperidone long-acting injectable in several trials [20-23]. Best described as a one-compartment model with zero- or first-order absorption, its particles dissolve slowly into the interstitial fluid and are subsequently hydrolyzed into palmitic acid and paliperidone [24]. Although maintenance doses may be administered into either the gluteal or deltoid muscles, the initial two doses of paliperidone palmitate must be given into the deltoid. Its dose should be adjusted in patients with CrCl 50 - 80 mL/min and use is not recommended in patients with severe renal impairment (CrCl < 50 mL/min). It must be noted that paliperidone palmitate has not been studied in patients with moderate hepatic impairment; however, previous trials involving oral paliperidone have failed to demonstrate clinically significant metabolic changes. Even though lower initial plasma concentrations were noted in patients with a high body mass index (BMI ≥ 25 kg/m^2), this was concluded to be secondary to unintended administration into adipose tissue. No dose adjustment is recommended; nevertheless, it is suggested that administration to individuals with higher BMIs be performed with needles of a length appropriate for muscle tissue penetrance [24]. When switching to paliperidone palmitate from another long-acting injectable antipsychotic, paliperidone palmitate may be initiated on the day that the previous long-acting injectable would otherwise be due. In these patients, the one-week initiation regimen is not required.

As risperidone long-acting injectable and paliperidone palmitate are extremely similar, psychiatrists have questioned the clinical pharmacists at our institution as to whether any minor differences exist which potentially make one a more appropriate selection for the average patient with schizophrenia and a history of medication noncompliance. Unfortunately, a thorough literature review revealed a dearth of comparative data not compiled or extrapolated from separate trials and the question ultimately remained unsolved. This study represents our institution's attempt to add to the pool of knowledge on this topic and aid in the resolution of this dilemma.

Several different primary hypotheses were considered during the background research phase of study design. Prior to study initiation, preliminary medication acquisition reports predicted a study population size highly unlikely to grant a level of power sufficient for the detection of previously unobserved differences in any frequently studied efficacy- or safety-related endpoints. Due to this finding and the known baseline difference in acquisition cost between products, it was decided that the primary endpoint would be pharmacoeconomic in nature and that the primary hypothesis would be in favor of risperidone long-acting injectable. Total cost of psychiatry-related treatment was deemed to be the measurement allowing paliperidone palmitate the best opportunity to overcome the baseline difference in acquisition cost; subsequently, this became the primary endpoint of the study and the relative superiority of risperidone long-acting injectable under this measurement became the primary hypothesis. Secondary endpoints included rates of placement into various residential programs allowing for differing levels of independence, drug and administration cost, unplanned encounter cost, overall cost of all medical care, duration of therapy, time to first relapse overall and per encounter type, the frequency, risk, and acuity of all-cause and psychiatric-related emergency department encounters, and the frequency, duration, and risk of general and psychiatric inpatient admissions.

METHODS

Study design. This multi-facility retrospective chart review was conducted from January 1, 2011 until April 1, 2013 at a community hospital, an inpatient psychiatric hospital, and an outpatient psychiatric treatment center which, combined, provide the majority of mental health care in Battle Creek, Michigan. The protocol was approved by the Institutional Review Board at Bronson Methodist Hospital and the study was conducted in compliance with national regulations on good clinical practices and in accordance with the Declaration of Helsinki (as revised in 2000). Potential participants were found by using Trinity Health's drug utilization reporting software to search for relevant medication histories, medication administration records, and discharge prescriptions. These reports identified patients who were active users of risperidone long-acting injectable or paliperidone palmitate during an encounter with either our general medical or inpatient psychiatric hospital between January 1, 2011 and December 31, 2012. As paliperidone palmitate is a recent addition to the U.S. market, it was felt that these dates would limit bias from stable risperidone long-acting injectable patients but still provide ample time for differences to emerge. All accepted patients were followed until study drug discontinuation or April 1, 2013. Patients receiving injections at federally-funded Summit Pointe ambulatory psychiatric facility were additionally followed through Summit Pointe for the purpose of acquisition of more accurate data with regards to living arrangements, employment, compliance, and initiation and discontinuation dates.

Study participants. Patients were accepted into the study if they carried a diagnosis of schizophrenia or psychotic disorder of a non-physical nature and were receiving treatment with risperidone long-acting injectable or paliperidone palmitate at the time of an encounter with our general medical or inpatient psychiatric hospital. Patients were excluded if they were under the age of 18 years, found to have initiated the particular study drug trial prior to January 1, 2011, or were found to have severe dementia, developmental disorder, neurological damage secondary to a cerebrovascular accident, traumatic brain injury, or a significant and life-limiting comorbid physical medical condition.

Cost measures. Total cost of psychiatry-related treatment, the primary outcome, was defined as the average summative cost per patient-day of medication, medication administration, psychiatric-related emergency department encounters, inpatient psychiatric admissions, and inpatient hospital admissions secondary to psychiatry-related injuries. Drug prices were based on our institution's group purchasing organization (GPO) acquisition prices during April, 2013. Cost of care information was collected by a hospital financial analyst and confirmed by a hospital senior administrator. Acuity adjustments based on current procedural terminology (CPT) codes were applied to total final costs where possible. Because cost was determined on a patient-day basis, cost in any given category was spread amongst entire cohorts to assess cost of therapy on a per-population basis and compensate for differences in sample size and duration of therapy.

Length of treatment. Whenever possible, length of treatment was calculated as the number of days between the initial dose and final dose of the study drug. When the date of first injection was unavailable, the first dose of study drug was recorded as the date of the first recorded day of therapy. When the date of the last injection was not available, it was recorded as the date that therapy was noted to have discontinued. If no such note or estimate was available, the conclusion of treatment was recorded as April 1, 2013, the end date of data collection.

Unplanned encounters. Unplanned encounters, defined as unscheduled inpatient or outpatient encounters with our emergency department, general medical hospital, or inpatient psychiatric hospital, were recorded. Frequency, length of stay, and time to first relapse were analyzed both as a whole and individually per encounter type. Additionally, emergency department encounters were classified as being psychiatric or non-psychiatric in nature and further stratified by acuity rating. Inpatient admissions involving the first dose of a study drug were considered to have taken place prior to drug initiation and thus were entirely excluded from analysis.

Statistical analysis. All patients identified with a qualifying study drug trial were included in the primary analysis. A subgroup analysis was conducted on all patients noted to receive injections through our local ambulatory psychiatric facility. Data were analyzed by use of the student t-test for metric data and chi square testing for nominal data as appropriate.

RESULTS

Study participants. Of the 78 risperidone long-acting injectable and 39 paliperidone palmitate results identified, 50 risperidone long-acting injectable and 21 paliperidone palmitate entries were determined to not meet study criteria for the following reasons: initiation of study drug prior to January 1, 2011 (n=18); disqualifying comorbid condition (n=7); discontinuation of study drug prior to initial hospital discharge (n=12); and duplicate or erroneous entries (n=31). Three patients were identified with qualifying trials of both drugs and were included as separate patients in both groups. Overall, twenty-nine risperidone long-acting injectable and eighteen paliperidone palmitate patients were found to meet the inclusion criteria and were ultimately accepted into the study.

Demographic and clinical characteristics of the study population are summarized in **Table 1.** The twenty-nine risperidone long-acting injectable and eighteen paliperidone palmitate patients in the total study population represent a total of 8,420 and 6,562 days of therapy, respectively, while the eighteen risperidone long-acting injectable and twelve paliperidone palmitate patients in the ambulatory facility cohort represent 4,448 and 4,676 days. A trend towards younger patients was noted in the ambulatory facility risperidone long-acting injectable cohort. Although specific diagnosis-related information was not collected from the local ambulatory psychiatric facility, it was available almost exclusively in these patients. For this reason, only diagnoses for those patients have been reported.

Cost measures.

Table 1: Clinical characteristics and demographics

	PP (All)	RLAI (All)	All (All)	p	PP (AP)	RLAI (AP)	All (AP)	p
Demographics								
n	18 (38%)	29 (62%)	47 (100%)		12 (40%)	18 (60%)	30 (100%)	
Age	47.6 ± 13.6	46.4 ± 18.6	46.9 ± 16.9	0.818	47.4 ± 9.5	37.9 ± 14.2	41.7 ± 13.3	0.059
Male (%)	11 (61%)	16 (55%)	27 (57%)	0.739	7 (58%)	11 (61%)	18 (60%)	0.975
Still on study drug	13 (72%)	16 (55%)	29 (62%)	0.529	8 (67%)	8 (44%)	16 (53%)	0.920
Followed by ambulatory facility	12 (67%)	18 (62%)	30 (64%)	0.804	-	-	-	-
Employed/in school	-	-	-	-	1 (8%)	3 (38%)	4 (6%)	-
Axis I + II diagnoses								
Schizophrenia, paranoid type	-	-	-	-	3 (25%)	3 (17%)	6 (20%)	0.668
Schizoaffective disorder					8 (67%)	6 (33%)	14 (47%)	0.231

Bipolar with psychotic features	-	-	-	-	1 (8%)	4 (22%)	5 (17%)	0.332
Mood disorder NOS					0 (0%)	3 (17%)	3 (10%)	0.146
Psychotic disorder NOS	-	-	-	-	0 (0%)	2 (11%)	2 (7%)	0.235
Antisocial personality disorder					3 (25%)	2 (11%)	5 (17%)	0.398
Borderline personality disorder	-	-	-	-	0(0%)	1(6%)	1(3%)	0.401
Substance abuse					3 (25%)	3 (17%)	6 (20%)	0.668
PTSD	-	-	-	-	0 (0%)	1 (6%)	1 (3%)	0.401
Living arrangement during final follow-up								
Home	-	-	-	-	7 (58%)	12 (67%)	19 (63%)	0.777
Ambulatory psychiatric housing					1 (8%)	2 (11%)	3 (10%)	0.814
Adult foster care	-	-	-	-	3 (25%)	2 (11%)	5 (17%)	0.365
Homeless					1 (8%)	1 (6%)	2 (7%)	0.445
County jail	-	-	-	-	0 (0%)	1 (6%)	1 (3%)	0.386

All=total study population; PP=paliperidone palmitate; AP=Ambulatory psychiatric facility cohort; RLAI=Risperidone long-acting injectable. ± represents standard deviation.

Drug and Administration Cost

In April 2013, paliperidone palmitate could be purchased by this institution for a base drug cost of $798.71 per month and risperidone long-acting injectable for $532.46 per month. Taking into account materials and labor, the cost of administration was estimated to be $25 per injection giving paliperidone palmitate and risperidone long-acting injectable administration costs of $25 and $50 per month and base expenses of $29.42 and $20.80 per patient-day, respectively.

Unplanned Encounter Cost

All-cause emergency department encounters cost the total study population approximately $3.52 per patient-day and the ambulatory psychiatric subgroup $5.19 per patient-day with psychiatric-related emergency department encounters accounting for $1.91 and $2.70 of this amount. No significant differences were found between groups. See **Table 2** for a detailed breakdown of these costs.

Table 2: Cost of treatment

	PP (All)	RLAI (All)	All (All)	p	PP (AP)	RLAI (AP)	All (AP)	p
Base costs								
Drug + Administration	$193,042.32	$175,154.04	$368,196.37		$137,559.57	$92,527.93	$230,087.50	
Cost per patient-day	$29.42	$20.80	$24.58		$29.42	$20.80	$25.22	
Any emergency department								
Total cost	$25,071.00	$27,639.00	$52,710.00		$23,258.00	$24,080.00	$47,338.00	
Cost per patient-day	$3.82	$3.28	$3.52		$4.97	$5.41	$5.19	
Psychiatric emergency department								
Total cost	$16,795.00	$11,810.00	$28,605.00		$15,662.00	$8,931.00	$24,593.00	
Cost per patient-day	$2.56	$1.40	$1.91		$3.35	$2.01	$2.70	
Psychiatric inpatient admissions								
Total inpatient cost	$61,369.06	$56,032.62	$117,401.68		$61,369.06	$36,020.97	$97,390.03	
Cost per patient-day	$9.35	$6.65	$7.84		$13.12	$8.10	$10.67	
Any inpatient admissions								
Total inpatient cost	$113,326.96	$142,629.12	$255,956.08		$113,326.96	$122,617.47	$235,944.43	
Cost per patient-day	$17.27	$16.94	$17.08		$24.24	$27.57	$25.86	
Total cost								
Total cost of treatment	$331,440.28	$345,422.16	$676,862.45		$274,144.53	$239,225.40	$513,369.93	
Total cost per patient-day	$50.51	$41.02	$45.18	0.106	$58.63	$53.78	$56.27	0.148
Psychiatric treatment								
Cost of psych-related therapy	$271,206.38	$242,996.66	$514,203.05		$214,590.63	$137,479.90	$352,070.53	
Psych cost per patient-day	$41.33	$28.86	$34.32	0.032	$45.89	$30.91	$38.59	0.049

All: Total Study Population; PP: Paliperidone Palmitate; AP: Ambulatory Psychiatric Facility Cohort; RLAI: Risperidone Long-acting Injectable. ±represents standard deviation.

Overall Cost

Including medication acquisition, medication administration, and unplanned inpatient or outpatient encounters, the entire study population accumulated a gross system-wide expense totaling $676,862. Of this, paliperidone palmitate patients cost an average of $50.51 per patient-day and risperidone long-acting injectable patients cost $41.02 (p=0.106). The ambulatory psychiatric facility cohort accumulated a total of $513,370 worth of treatment with paliperidone palmitate patients costing $58.63 per patient-day and risperidone long-acting injectable patients costing $53.78 per patient-day (p=0.148). Although a trend existed within both analyses in favor of lower treatment costs among risperidone long-acting injectable patients, no significant differences were found.

Psychiatric Treatment Cost

Analysis of the primary study outcome of total cost of psychiatric treatment (i.e.: psychiatry-related emergency department encounters, inpatient psychiatric admissions, and baseline drug/administration costs) revealed that paliperidone palmitate patients in the total population accrued expenses averaging a total of $41.33 per patient-day while risperidone long-acting injectable patients accumulated an average daily cost of $28.86, significantly less expensive (p=0.032). This cost reduction remained significant even post isolation of the ambulatory psychiatric cohort. Ambulatory psychiatric facility patients cost an average of $38.59 per patient-day with paliperidone palmitate and risperidone long-acting injectable patients costing $45.89 and $30.91 per patient-day, respectively (p=0.049).

Length of Treatment

Duration of therapy

On average, patients were on their particular study drug for under a year with averages of 319 ± 225 days in the overall study population and 304 ± 231 days in the ambulatory psychiatric facility cohort. A trend was found towards shorter length of treatment in the ambulatory psychiatric risperidone long-acting injectable cohort. However, no significant differences were found between groups (p=0.105). Further details can be found in **Table 3.**

Table 3. Length of treatment and time to relapse.

	PP (All)	RLAI (All)	All (All)	p	PP (AP)	RLAI (AP)	All (AP)	p
Time to discontinuation								
Length of therapy	365 ± 226	290 ± 220	319 ± 225	0.282	390 ± 230	247 ± 214	304 ± 231	0.105
Days to next unplanned								
Any emergency department	165 ± 160	214 ± 229	195 ± 207	0.445	150 ± 170	141 ± 195	145 ± 183	0.892
Psych-related emergency dept	189 ± 180	233 ± 221	217 ± 209	0.493	187 ± 199	173 ± 191	178 ± 193	0.846
Psych inpatient stay	305 ± 228	224 ± 190	255 ± 209	0.209	300 ± 237	185 ± 186	231 ± 215	0.161
General inpatient stay	342 ± 217	281 ± 215	304 ± 219	0.369	355 ± 220	232 ± 204	282 ± 220	0.144
Any unplanned encounter	155 ± 161	163 ± 183	160 ± 174	0.886	136 ± 171	103 ± 148	116 ± 151	0.575
Psych-related unplanned	180 ± 182	181 ± 176	181 ± 177	0.974	173 ± 203	133 ± 142	149 ± 165	0.537
Disregarding any encounters within 30 days of start								
Any emergency department	199 ± 167	255 ± 213	236 ± 205	0.389	130 ± 77	195 ± 189	178 ± 173	0.332
Psych-related emergency dept	245 ± 201	272 ± 213	263 ± 209	0.687	204 ± 185	223 ± 199	220 ± 192	0.802
Psych inpatient stay	286 ± 226	302 ± 220	295 ± 223	0.819	269 ± 235	266 ± 220	267 ± 224	0.975
General inpatient stay	324 ± 222	296 ± 217	304 ± 219	0.694	329 ± 229	257 ± 213	282 ± 220	0.418
Any unplanned encounter	188 ± 171	255 ± 213	233 ± 206	0.306	112 ± 74	195 ± 189	173 ± 175	0.219
Psych-related unplanned	234 ± 207	272 ± 213	259 ± 211	0.574	186 ± 191	223 ± 199	214 ± 195	0.636
Patients with at least one encounter within 30 days of start								
Any emergency department	5 (28%)	6 (21%)	11 (23%)	0.712	4 (33%)	5 (28%)	9 (30%)	0.785
Psych-related emergency dept	5 (28%)	3 (10%)	8 (17%)	0.194	4 (33%)	2 (11%)	6 (20%)	0.182
Psych inpatient stay	1 (6%)	3 (10%)	4 (9%)	0.540	1 (8%)	2 (11%)	3 (10%)	0.814
General inpatient stay	0 (0%)	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	0 (0%)	-
Any unplanned encounter	5 (28%)	8 (28%)	13 (28%)	0.910	4 (33%)	6 (33%)	10 (33%)	1.000
Psych-related unplanned	5 (28%)	5 (17%)	10 (21%)	0.519	4 (33%)	3 (17%)	7 (23%)	0.355

All: Total Study Population; PP: Paliperidone Palmitate; AP: Ambulatory Psychiatric Cohort; RLAI: Risperidone Long-Acting INJECTABLE. ± represents standard deviation

Time to first relapse: There was a slight trend in both the overall (p=0.194) and ambulatory psychiatric (p=0.182) analyses towards paliperidone palmitate patients being more likely to require a psychiatric-related emergency department encounter within the first 30 days of treatment. There also existed a slight trend towards fewer days until the next inpatient psychiatric and general admission in the ambulatory psychiatric risperidone long-acting injectable group. There were no significant differences or trends found regarding time to first all-cause or psychiatric-related emergency department encounter.

Unplanned encounters.

Emergency department visits

Of the 75 separate all-cause emergency department encounters recorded, 33 visits were from paliperidone palmitate and 42 were from risperidone long-acting injectable patients. The ambulatory psychiatric paliperidone palmitate and risperidone long-acting injectable cohorts accounted for 31 and 37 of these encounters, respectively. No significant differences were found; however, the ambulatory psychiatric paliperidone palmitate cohort trended towards having a higher risk of requiring at least one psychiatric-related emergency department encounter during treatment (p=0.113). See **Table 4** for further details.

Table 4. Patient encounters.

	PP (All)	RLAI (All)	All (All)	p	PP (AP)	RLAI (AP)	All (AP)	p
Patients with at least one encounter after initiation								
Any emergency department	9 (50%)	9 (31%)	18 (38%)	0.386	9 (75%)	8 (44%)	17 (57%)	0.276
Psych-related emergency dept	8 (44%)	6 (21%)	14 (30%)	0.190	8 (67%)	5 (28%)	13 (43%)	0.113
Psych inpatient stay	4 (22%)	4 (14%)	8 (17%)	0.564	4 (33%)	3 (17%)	7 (23%)	0.355
General inpatient stay	2 (11%)	2 (7%)	4 (9%)	0.683	2 (17%)	2 (11%)	4 (13%)	0.683
Any unplanned encounter	9 (50%)	10 (34%)	19 (40%)	0.512	9 (75%)	8 (44%)	17 (57%)	0.276
Psych-related unplanned	8 (44%)	8 (28%)	16 (34%)	0.414	8 (67%)	6 (33%)	14 (47%)	0.190
Any emergency department								
Total number of encounters	33	42	75	0.972	31	37	68	0.350
Patient-days per visit	199	201	200	-	151	120	134	-
Average acuity	2.9	3.2	3.0	0.120	2.9	3.2	3.1	0.144
Psych-related emergency dept								
Total number of encounters	20	16	36	0.155	19	12	31	0.263
Patient-days per visit	328	526	416	-	246	371	294	-
Average acuity	2.7	2.9	2.8	0.326	2.7	2.9	2.8	0.497
Psych inpatient								
Total number of admissions	8	9	17	0.786	8	4	12	0.285
Inpatient days	46	42	88	0.109	46	27	73	0.044
Any inpatient								
Total number of admissions	11	9	20	0.313	11	8	19	0.562
Inpatient days	55	57	112	0.258	55	42	97	0.283

All: Total Study Population; PP: Paliperidone Palmitate; AP: Ambulatory Psychiatric Facility Cohort; RLAI: Risperidone Long-Acting Injectable. ± represents standard deviation

Acuity of emergency department visits

All-cause emergency department encounters tended to be classified as medium acuity with an average rating of 3.0 on a 5 point scale. There was a trend towards higher acuity ratings during all-cause emergency department encounters in paliperidone palmitate patients under both primary (p=0.120) and ambulatory psychiatric (p=0.144) analyses. This trend did not remain once psychiatric-related emergency department encounters were isolated. No differences in this category reached significance.

Total inpatient admissions

Members of the paliperidone palmitate and risperidone long-acting injectable groups required eleven and nine all-cause inpatient admissions, respectively. Of these, all eleven paliperidone palmitate and eight of nine risperidone long-acting injectable admissions were from patients followed by the local ambulatory psychiatric facility. No significant differences or trends were found with regard to number of all-cause inpatient admissions or length of time spent inpatient.

Inpatient psychiatric admissions

Patients in the ambulatory psychiatric paliperidone palmitate cohort trended towards faster readmissions (p=0.285) and were discovered to require significantly more days of inpatient psychiatric treatment than patients in the ambulatory psychiatric risperidone long-acting injectable cohort (p=0.044). No trend in readmission rates was found in the total study population; however, there existed a trend towards more days spent inpatient among the total paliperidone palmitate cohort (p=0.109). Time spent inpatient on a per-admission basis was not found to be significantly different under any analysis.

Discussion

This study demonstrated an association between risperidone long-acting injectable use and lower psychiatric-related treatment costs within both the overall and ambulatory psychiatric populations. Additionally, the ambulatory psychiatric cohort further showed an association between risperidone long-acting injectable use and fewer inpatient psychiatric treatment days. This may be interpreted as a sign that risperidone long-acting injectable is superior to paliperidone palmitate regarding both clinical and pharmacoeconomic outcomes.

There exist several potential explanations for the discovery that the ambulatory psychiatric paliperidone palmitate cohort

experienced significantly higher treatment costs per patient-day, required significantly more psychiatric inpatient days, and trended towards being more likely to require a psychiatry-related emergency department encounter both within the first 30 days of treatment and during follow-up as a whole. Although not found to be significant, ambulatory psychiatric paliperidone palmitate patients experienced twice as many psychiatric inpatient admissions as risperidone long-acting injectable patients (p=0.285). As length of stay per inpatient admission was not found to be different between groups, the significant difference in psychiatric inpatient days potentially signals an overall true difference in number of admissions. Given an increase in sample size, this number may have been found to be statistically significant.

Although not recorded as an end point, several patients in the paliperidone palmitate group were noted to have histories of failed trials with risperidone long-acting injectable. This suggests that patients receiving paliperidone palmitate may have had more treatment-resistant disease and thus lowered outcome expectations. The trend towards younger age among ambulatory psychiatric risperidone long-acting injectable patients supports this assertion as schizophrenia is known to be a progressive illness. A history of paliperidone palmitate or risperidone long-acting injectable failed trials was originally recommended as an exclusion criterion in this study. While investigating justification for this recommendation, several recent studies were found suggesting that, due to greater compliance, patients with extensive histories of failed trails of oral risperidone may experience success on long acting formulations of risperidone or paliperidone [25,26]. Because proponents of paliperidone palmitate argue that less frequent administration leads to better adherence and as the most commonly noted reason for conversion of risperidone long-acting injectable to paliperidone palmitate was poor compliance, the decision was ultimately made to include patients with a history of failed study drug trials. This may have led to a difference between groups with regards to disease severity.

As injectable antipsychotics are nearly always administered during office visits, patients in the ambulatory psychiatric cohort were well followed with very accurate documented dates of initiation and discontinuation. Because members of this subgroup very likely reside in or around the Battle Creek area, it may be assumed that they would be likely to come to our institution for their healthcare needs. Due to the overall lack of inpatient psychiatric treatment options, our inpatient psychiatric facility serves many out-of-county patients. As such, the ambulatory psychiatric cohort represented only 64% of the total study population. Data overall were limited not only in terms of number of participants but also in terms of follow-up length and access to follow-up data. This forced several compromises to be made to maintain an appropriate sample size.

The definition of "community-dwelling", originally defined as residing at home alone or with family and friends, was broadened to include patients living in assisted living facilities and adult foster care centers who have contact with the outside community (i.e.: patients not undergoing long-term inpatient hospitalization or serving a prison sentence). This definition captured several elderly risperidone long-acting injectable patients who were admitted to our inpatient psychiatric hospital from nursing facilities beyond our institution's typical geographic reach. These patients, who were the primary cause of the sharp difference in age between the ambulatory psychiatric and overall risperidone long-acting injectable cohorts, were unlikely to have the renal function required for paliperidone palmitate. This may have skewed data in the total population with regards to renal function and follow-up probability. As neither of these factors were measured as secondary end points, it is possible that the groups as a whole were skewed in this regard.

CONCLUSION

Risperidone long-acting injectable was found to be associated with significantly lower psychiatry-related costs than paliperidone palmitate under all analyses and was additionally associated with fewer inpatient psychiatric days in the ambulatory psychiatric cohort. These findings add to the pool of knowledge and provide further evidence of the non-superiority of paliperidone palmitate. Risperidone long-acting injectable may be assumed to be superior to paliperidone palmitate with regards to overall cost of psychiatric care and non-inferior with regards to all other clinical and pharmacoeconomic outcomes measured in this study. Based on these results, preference for risperidone long-acting injectable over paliperidone palmitate is recommended for the first-line treatment of similar patients with schizophrenia or psychotic disorder of a non-physical nature who require initiation of injectable antipsychotics. Further research is required before making recommendations as to the treatment of patients who have previously failed trials of injectable atypical antipsychotics.

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DISCLOSURE

The authors report no actual or potential conflicts of interest with regards to the design or implementation of this study.

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