

## Treatment of Schizophrenia With Long-Acting Fluphenazine, Haloperidol, or Risperidone

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**Objective:** This study compares 3 cohorts of patients with schizophrenia before, during, and after initiating treatment with fluphenazine decanoate (FD), haloperidol decanoate (HD), or long-acting injectable risperidone (LAR). **Methods:** Administrative data are analyzed from California Medicaid (Medi-Cal) beneficiaries with schizophrenia who initiated FD, HD, or LAR treatment. Patients were required to have been continuously enrolled in Medi-Cal for 180 days before and 180 days after the start of the new episode of long-acting antipsychotic therapy. **Results:** There were few demographic and clinical differences among patients initiating FD, HD, and LAR. During the 180 days before starting long-acting injections, most patients initiating FD (53.5%), HD (58.5%), and LAR (61.2%) received oral antipsychotic medications for <80% of the days in this period (medication possession ratio: <0.80). The mean duration of depot treatment episodes was 58.3 days (SD = 53.6) for FD, 71.7 days (SD = 56.4) for HD, and 60.6 days (SD = 48.8) for LAR ( $F = 18.3$ ,  $df = 2$ , 2694,  $P < .0001$ , HD > FD). Few patients who started on FD (5.4%), HD (9.7%), or LAR (2.6%) continued for at least 180 days. Most patients in each group (FD [77.4%], HD [78.9%], and LAR [75.5%]) received oral antipsychotic medications during the 45 days after discontinuing long-acting injections. Coprescription with antidepressants, mood stabilizers, and benzodiazepines was common. **Conclusions:** Patients treated with long-acting antipsychotic injections tend to have complex pharmacological regimens and recent medication nonadherence. A great majority of

patients initiating long-acting antipsychotic medications discontinue use within the first few months of treatment.

**Key words:** schizophrenia/depot antipsychotic medications/community treatment

Long-acting antipsychotic medication injections are thought to help improve medication adherence in schizophrenia.<sup>1</sup> Theoretical advantages of long-acting antipsychotic injections over oral medications include guaranteed delivery of medication, reliable monitoring of treatment adherence, and an increased opportunity for the treatment team to intervene as soon as a patient misses a dose.<sup>2,3</sup> Clinical research<sup>4,5</sup> and expert opinion<sup>6</sup> support use of long-acting injection antipsychotic medications as maintenance treatment for patients with a history of medication nonadherence.

Approximately 15% of schizophrenia patients in maintenance antipsychotic treatment receive depot preparations.<sup>7,8</sup> In one recent study, 29.9% of patients with schizophrenia and a recent history of antipsychotic nonadherence were currently being prescribed a long-acting injection antipsychotic medication.<sup>9</sup> In the United States, psychiatrists tend to select long-acting injection medications for patients who have persistent psychotic symptoms<sup>10,11</sup> and who frequently receive more than one concurrent antipsychotic medication.<sup>11,12</sup> Use of depot antipsychotic medications may be increased among African Americans<sup>11,13</sup> and patients with substance use problems.<sup>13</sup>

Three antipsychotic medications are currently available in the United States as long-acting injections: fluphenazine decanoate (FD) or enanthate, haloperidol decanoate (HD), and long-acting injectable risperidone (LAR). These medications differ from one another in their pharmacokinetic<sup>14–16</sup> and side-effect<sup>17</sup> profiles. Little is known about the characteristics and service use patterns of patients who are treated with these medications in community practice.

In the current report, we use a large administrative database to compare and contrast the characteristics of schizophrenia patients starting FD, HD, and LAR and assess the continuity of their antipsychotic treatment.

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We also describe the use of oral antipsychotic and other psychotropic medications, treatment for selected comorbid conditions, and service use before, during, and after treatment with long-acting antipsychotic medications.

## Methods

Statewide service use and pharmacy claims from the California Medicaid (Medi-Cal) program were analyzed to assess characteristics of patients with schizophrenia who were initiating long-acting antipsychotic injections. The samples were drawn from 4 consecutive years of Medi-Cal data (2001–2004).

Medi-Cal beneficiaries, 18–64 years of age, with at least 1 inpatient or 2 outpatient claims for schizophrenia (ICD: 295),<sup>18</sup> were selected. Patients were also required to have been prescribed FD, HD, or LAR and to have been Medi-Cal enrollees for at least 180 days before and after starting FD, HD, or LAR. For each patient, a 360-day period including 180 days before and 180 days after the first FD, HD, or LAR injection defined their study period. Because prescription data were not available during episodes of inpatient treatment, patients with 90 or more days of total inpatient treatment or a hospital admission of greater than 14 days during their 360-day period were excluded ( $n = 461$ ).

Analyses were conducted of patients before, during, and after depot treatment. The before depot treatment period included the 180 days before the first long-acting injection. The period during depot treatment started on the date of the first injection and continued until there was a gap of more than twice the standard injection treatment interval (ie, 14 days for LAR, 21 days for FD, and 28 days for HD injections). For example, a patient who received an injection of LAR followed by a second LAR injection 14 days later but who missed the next 2 injections was considered to have received a 28-day depot treatment episode. However, if there were 10 days between the first and second LAR injection, the depot treatment episode would be considered to be 38 days (14 + 10 + 14 days) in duration. A standard injection interval approach was used rather than relying on the “days supplied” variable that has uncertain validity.<sup>19</sup> Because the actual injection schedule may not follow these standard intervals, we also examined the mean number of injections and period from first to last injection. A 45-day period after the depot treatment episode was also studied. Patients were excluded from postdepot treatment analysis if their depot treatment extended to within 45 days of the end of available data.

Patients were characterized with respect to age, gender, and race/ethnicity<sup>20,21</sup> and by whether they had been treated for diabetes, obesity, and hyperlipidemia during the predepot treatment period.<sup>22</sup> Because comorbid substance use disorder and depression and anxiety disorders may influence the risk of medication nonadherence,<sup>23,24</sup>

the groups were also characterized with respect to treatment of these disorders. On the basis of the largest number of claims, patients were considered to have schizophrenia, schizoaffective disorder, or schizophreniform disorder. Services use including emergency department visits, hospital admissions for the treatment of a mental disorder, and the number of outpatient visits for mental disorders and general medical disorders was also examined.

Patients were classified by whether or not they filled one or more prescription for an antidepressant, anxiolytic/hypnotic, and mood stabilizer medication before, during, and after depot treatment. We also determined the proportion of patients that received any oral antipsychotic medication, a second-generation oral antipsychotic medication, and an oral form of the depot antipsychotic medication. Other measures of antipsychotic medication treatment included the proportion of patients with depot treatment of at least 180 days, the mean duration of continuous depot antipsychotic use, the mean antipsychotic medication possession ratio (MPR), and the proportion of patients with an antipsychotic MPR below 0.80. MPR is the proportion of days supplied of medication during a treatment period. An MPR of less than 0.80 is commonly accepted as evidence of medication noncompliance.<sup>3,25</sup>

We used chi-square analyses to measure the strength of associations between each categorical independent variable and each long-acting antipsychotic medication group and analysis of variance for continuous independent variables. When the omnibus test statistic was statistically significant ( $P < .05$ , 2 tailed), post hoc pairwise group comparisons were performed with chi squares for 2-level categorical variables and Tukey's HSD test ( $P < .05$ ) for continuous variables. A series of logistic regression models were fit with each binary service use characteristic as a dependent variable, initial treatment with HD or FD (LAR reference group) as the independent variable, and duration of treatment episode as a covariate. Similar analyses were performed with a multiple linear regression models for continuous variables.

The mean and median duration of long-acting antipsychotic treatment episodes were calculated for the 3 antipsychotic groups overall and stratified by age group, sex, and racial groups (white, other). Confidence intervals (CIs) were calculated around the means. Accelerated failure time regressions based on the Weibull distribution were performed overall and separately by demographic traits controlling for these characteristics, use of other mental services, and prescription of other psychotropic medications. In these analyses, the dependent variable was time to discontinuation of depot treatment episode. These regressions yield a survival time ratio (STR). It is a ratio of the adjusted median time to depot discontinuation between antipsychotic treatment groups with LAR as the reference group.

**Table 1.** Background Characteristics of Patients With Schizophrenia During the 180-d Period Before Starting FD, HD, or LAR

Characteristic	FD Patients, % (N = 948)	HD Patients, % (N = 1631)	LAR Patients, % (N = 116)	Statistics			Group Differences <sup>a</sup>
				F	df	P	
Age, mean (SD)	41.2 (10.4)	39.9 (11.0)	39.4 (11.6)	4.8	2, 2692	.008	FD > HD
Number of health care visits							
Mental health, (SD)	11.3 (26.6)	7.9 (21.4)	5.1 (7.2)	8.1	2, 2692	.0003	FD > HD, LAR
General medical, (SD)	37.9 (36.1)	31.4 (30.6)	29.4 (31.4)	12.9	2, 2692	.0001	FD > HD, LAR
	(%)	(%)	(%)	$\chi^2$	df	P	
Sex				3.8	2	.15	
Male	59.5	58.6	50.0				
Female	40.5	41.4	50.0				
Race				19.7	4	.003	
White	51.4	44.7	48.3				
African American	20.0	20.5	16.4				
Hispanic	4.6	7.0	11.2				
Other	24.0	27.8	24.1				
Schizophrenia subtype <sup>b</sup>				1.8	4	.77	
Schizophrenia	73.4	74.6	69.8				
Schizoaffective	25.5	24.5	29.3				
Schizophreniform	1.1	0.9	0.9				
Treatment of selected disorders <sup>c</sup>							
Obesity	4.6	4.8	1.7	2.3	2	.31	
Hyperlipidemia	9.8	8.0	11.2	3.4	2	.18	
Diabetes mellitus	8.8	10.4	7.8	2.3	2	.32	
Substance use disorder	15.3	15.5	11.2	1.5	2	.46	
Depressive disorder	17.4	17.0	24.1	3.8	2	.15	
Anxiety disorder	7.3	7.2	7.8	0.1	2	.97	
Acute mental health care (%)							
Emergency visit	28.6	28.8	28.4	.02	2	.99	
Hospital admission	1.0	1.6	0.9	2.1	2	.35	

Note: Data from 2001 to 2004 Medi-Cal. FD denotes fluphenazine decanoate, HD denotes haloperidol decanoate, and LAR denotes long-acting risperidone.

<sup>a</sup>Group differences,  $P < .05$ .

<sup>b</sup>Based on the most frequently listed primary diagnosis.

<sup>c</sup>Obesity (ICD-9-CM: 278.0, 783.6, V77.8), hyperlipidemia (272.0–272.4), diabetes mellitus (250), substance use disorder (291, 292, 303–305), depressive disorders (296.2, 296.3, 300.4, 311), and anxiety disorders (300.0, 300.2, 300.3, 304, 308.3).

## Results

### Prior to Depot Treatment Episode

A majority of patients were started on HD (60.5%), with fewer patients started on FD (35.2%) or LAR (4.3%). LAR became available to Medi-Cal recipients in December 2003. Because of the requirement for at least 180 days of data following the first injection, only patients who started LAR from December 2003 to September 2004 were included in the analysis.

Patients who initiated FD were significantly older and were more likely to be white in race than patients who initiated HD (table 1). As compared with patients starting FD, those who started HD or LAR made significantly fewer mental health visits and visits for the treatment general medical disorders during the 180 days before their first injection (table 1).

Over 90% of patients in each group received an oral antipsychotic medication during the 180 days before their

first injection (table 2). Treatment with second-generation oral antipsychotic medications was common in all 3 groups, especially among patients who were subsequently started on LAR. Most patients in each group were prescribed a mood stabilizer during the 180 days before their first injection. Prescriptions for antidepressants and anxiolytics/hypnotics were also common during this period (table 2).

A majority of patients in each group received 2 or more different oral antipsychotic medications at some point during the 180 days before their first injection. Patients were commonly treated with the oral form of the antipsychotic medication that they subsequently received as a long-acting injection. Although LAR patients were significantly more likely than HD or FD patients to have received aripiprazole prior to their injection (table 2), this association fell below the level of significance after adjusting for treatment year (odds ratio [OR] for FD: 1.2, 95% CI: 0.6–2.4; and OR for HD: 1.3, 95% CI: 0.6–2.5).

**Table 2.** Pharmacological Treatment of Patients With Schizophrenia During the 180-d Period Before Starting FD, HD, or LAR

Treatment	FD Patients, % (N = 948)	HD Patients, % (N = 1631)	LAR Patients, % (N = 116)	Statistics			Group Differences <sup>a</sup>
				$\chi^2$	df	P	
Any oral antipsychotic	92.9	91.1	96.6	6.1	2	.046	LAR > HD
Any oral atypical antipsychotic	84.6	85.5	95.7	10.4	2	.006	LAR > HD, FD
Selected oral antipsychotics							
Fluphenazine	34.5	3.7	9.5	45.5	2	>.0001	FD > LAR > HD
Haloperidol	13.8	42.2	23.3	227.9	2	>.0001	HD > LAR > FD
Risperidone	32.8	38.9	70.7	63.8	2	>.0001	LAR > FD, HD
Aripiprazole	3.8	4.6	16.4	36.0	2	>.0001	LAR > FD, HD
Clozapine	10.4	10.6	10.3	0.1	2	.98	
Olanzapine	45.2	41.8	36.1	4.9	2	.09	
Quetiapine	32.2	31.7	32.8	0.1	2	.94	
Ziprasidone	13.1	11.1	14.7	3.1	2	.22	
2+ Oral antipsychotics	65.1	64.0	75.0	5.5	2	.07	
Antipsychotic, MPR <sup>b</sup> <0.80	53.5	58.5	61.2	6.9	2	.03	HD > FD
Antipsychotic gap >30 d	22.7	24.5	29.5	2.8	2	.24	
Other psychotropic medications							
Antidepressant	50.2	47.7	56.0	3.9	2	.14	
Anxiolytic/hypnotic	47.2	45.4	56.9	6.1	2	.048	LAR > FD, HD
Mood stabilizer	56.3	56.1	60.3	0.8	2	.67	
Antipsychotic MPR, mean (SD)	0.64 (0.32)	0.61 (0.32)	0.63 (0.29)	F	df	P	
				1.6	2, 2612	.19	

Note: Data from 2001 to 2004 Medi-Cal. FD denotes fluphenazine decanoate, HD denotes haloperidol decanoate, and LAR denotes long-acting risperidone. All analyses are based on 180-d period before the start of first depot injection.

<sup>a</sup>Group differences,  $P < .05$ .

<sup>b</sup>MPR denotes medication possession ratio and is defined as the proportion of days of medication over the 180-d treatment period.

Discontinuous use of oral antipsychotic medications was common before the first depot injection. The mean oral antipsychotic MPR during the 180-day period before starting depot medications was approximately 0.6 for all 3 groups, and most patients had oral antipsychotic MPRs below 0.80 (table 2).

#### Depot Treatment Episode

Fewer than 1 in 10 depot patients continued on long-acting injections for 180 days following the first injection (table 3). The mean duration of depot treatment episodes was significantly longer for HD patients than for FD patients (table 3). The period from first to last injection of the treatment episode was also significantly longer for patients treated with HD than FD, while the mean depot MPR over the first 90 days was significantly greater for patients treated with HD than either FD or LAR. At the same time, patients treated with LAR, which has the shortest recommended dosing interval, received a significantly larger number of injections during their depot treatment episodes than patient treated with FD or HD (table 3).

During depot treatment, a substantial proportion of the patients also received antidepressant medications, anxiolytics/hypnotics, and mood stabilizers (table 3) as well as oral antipsychotic medications (table 4). The

oral antipsychotic medication was frequently the oral formulation of the depot medication.

After controlling for several background characteristics, the overall median length of depot treatment or STR was significantly greater for LAR and HD than FD (table 5). In stratified analyses, the duration of LAR treatment episodes was significantly greater than FD episodes for males, patients 45–64 years, and patients who were other than white in race (table 5). Among patients who were white in race, the STR was significantly greater for HD than LAR (table 5).

#### Following Depot Treatment Episode

During the 45-day period following depot antipsychotic discontinuation, more than three-quarters of each group received oral antipsychotic medications. The oral antipsychotic medication was commonly the oral formulation of the antipsychotic medication that patients previously received as an injection (table 6). A significantly larger proportion of post-LAR than post-FD patients had oral antipsychotic MPRs <0.80 during the period following long-acting injection treatment.

As compared with patients who discontinued HD, those who discontinued FD were significantly more likely to be treated with an antidepressant or anxiolytic/hypnotic medication during the period following long-acting

**Table 3.** Characteristics of Schizophrenia Patients During Treatment With FD, HD, or LAR

Characteristic	FD Patients, % (N = 948)	HD Patients, % (N = 1631)	LAR Patients, % (N = 116)	Statistics			Group Differences <sup>a</sup>	
				$\chi^2$	df	P		
Depot for $\geq 180$ d	5.4	9.7	2.6	20.0	2	<.0001	HD > LAR, FD	
Injection episode, d [mean (SD)]	58.2 (53.6)	71.7 (56.2)	60.5 (48.8)	18.3	2, 2692	<.0001	HD > FD	
First to last injection, d [mean (SD)]	38.7 (54.5)	45.8 (58.7)	47.7 (49.2)	5.0	2, 2692	.007	HD > FD	
Number of injections [mean (SD)]	2.8 (2.4)	2.9 (2.4)	4.4 (2.9)	24.2	2, 2692	<.0001	LAR > FD, HD	
First 90 d, depot MPR <sup>b</sup> [mean (SD)]	0.40 (.19)	0.49 (0.22)	0.40 (0.19)	62.6	2, 2692	<.0001	HD > LAR, FD	
							FD/LAR, OR (95% CI) <sup>c</sup>	HD/LAR, OR (95% CI) <sup>c</sup>
Other psychotropic medications (%)								
Antidepressant	35.4	36.0	34.5	0.18	2	.91	1.1 (0.7–1.6)	1.0 (0.7–1.5)
Anxiolytic/hypnotic	35.1	36.6	36.2	0.57	2	.77	1.0 (0.6–1.4)	1.0 (0.6–1.4)
Mood stabilizer	46.6	50.2	31.0	17.1	2	.0002	2.0 (1.3–3.0)	2.1 (1.4–3.2)
Acute mental health care (%)								
Emergency visit	10.1	8.2	3.4	7.1	2	.03	3.2 (1.1–8.9)	2.3 (.8–6.4)
Hospital admission	0.6	0.4	0	1.5	2	.47	N/A	N/A

Note: Data from 2001 to 2004 Medi-Cal. FD denotes fluphenazine decanoate, HD denotes haloperidol decanoate, and LAR denotes long-acting risperidone. All analyses are based on long-acting injection treatment episode.

<sup>a</sup>Group differences,  $P < .05$ .

<sup>b</sup>MPR denotes medication possession ratio and is defined as the proportion of days of depot medication during the first 90 d after the first injection.

<sup>c</sup>Results for categorical variables are presented as odds ratios (ORs) followed by 95% confidence intervals (CIs). These results are from separate logistic regressions for each row controlling for treatment duration with antipsychotic agent as the dependent variable with LAR as the reference group. Results for continuous variables are presented as significant pairwise comparisons for Tukey's HSD ( $P < .05$ ).

injection treatment. Patients who discontinued FD or HD were significantly more likely than LAR patients to be subsequently treated with a mood stabilizer (table 5).

## Discussion

The current findings suggest that early discontinuation of depot antipsychotic medication is quite common in the community treatment of schizophrenia. After 180 days, only 9.7% of HD patients, 5.4% of FD patients, and 2.6% of LAR patients were continuing to receive the same long-acting antipsychotic medication. The longer typical injection interval for HD (28 days) as compared with FD (21 days) or LAR (14 days) appeared to contribute to the significantly higher proportion of HD patients continuing depot treatment for at least 6 months. Although patients starting HD or FD tended to receive a similar number of injections during their treatment episode, the period from the first to last injection was significantly longer for patients receiving HD than FD. In analyses that controlled for several background patient characteristics, treatment with HD or LAR was associ-

ated with significantly longer episodes of depot treatment than treatment with FD. The reasons for these differences are unclear but may involve medication-related differences in drug tolerability, effectiveness, injection intervals, or other factors.

The current findings reveal substantially lower rates of continuity with depot antipsychotic treatment than has been reported from patients in research studies. In one prospective British study of 100 patients starting LAR, 51% discontinued during the first 6 months.<sup>26</sup> The most common reasons for discontinuation were that the medication was considered ineffective by the prescribing physician (47%), refused by the patient (35%), or not tolerated by the patient (18%).<sup>26</sup> In randomized controlled trials with conventional long-acting antipsychotic injections, discontinuation rates have ranged from as low as 12.5% over 36 weeks<sup>27</sup> and 19% over 24 weeks<sup>28</sup> to 50.5% at 52 weeks.<sup>29</sup> Because randomized controlled trials involve carefully selected subjects who consent to extended assessments and care under controlled conditions, significantly lower discontinuation rates are to be anticipated than in usual practice conditions. In community

**Table 4.** Oral Antipsychotic Medication Treatment of Patients With Schizophrenia During the First 90-d After Starting FD, HD, and LAR

Oral Medication	FD Patients (%)	HD Patients (%)	LAR Patients (%)	Statistics		
				$\chi^2$	df	P
<b>Any oral antipsychotic</b>						
0–30 d ( $n_1 = 419, n_2 = 794, n_3 = 75$ )	92.8	91.1	89.3	1.6	2	.44
31–60 d ( $n_1 = 321, n_2 = 669, n_3 = 49$ )	91.6	86.6	77.6	10.0	2	.007
61–90 d ( $n_1 = 212, n_2 = 509, n_3 = 27$ )	92.0	85.7	70.4	12.0	2	.002
<b>Second generation antipsychotic</b>						
0–30 d ( $n_1 = 419, n_2 = 794, n_3 = 75$ )	83.3	81.2	82.7	0.8	2	.67
31–60 d ( $n_1 = 321, n_2 = 669, n_3 = 49$ )	84.1	75.9	69.4	10.8	2	.004
61–90 d ( $n_1 = 212, n_2 = 509, n_3 = 27$ )	84.4	74.1	66.7	10.6	2	.005
<b>Oral form of depot antipsychotic</b>						
0–30 d ( $n_1 = 419, n_2 = 794, n_3 = 75$ )	42.5	44.7	64.0	12.0	2	.002
31–60 d ( $n_1 = 321, n_2 = 669, n_3 = 49$ )	33.0	35.7	46.9	3.7	2	.16
61–90 d ( $n_1 = 212, n_2 = 509, n_3 = 27$ )	32.6	33.8	48.2	2.6	2	.27

Note: Data from 2001 to 2004 Medi-Cal. FD denotes fluphenazine decanoate, HD denotes haloperidol decanoate, and LAR denotes long-acting risperidone. All analyses are based on long-acting injection treatment episode. Results are percentages of patients within each category prescribed any oral antipsychotic, second generation antipsychotic, or oral form of the depot antipsychotic during the 3 time periods. The number of patients in the denominators are represented as  $n_1 =$  FD patients,  $n_2 =$  HD patients, and  $n_3 =$  LAR patients.

practice, patients may be selected for long-acting antipsychotic injections because of problems with adherence with oral antipsychotic medications.

In the current study population, there were several similarities between schizophrenia patients who initiated FD, HD, or LAR injections. A majority of patients starting each of the preparations had oral antipsychotic MPRs during the period before the first injection below 0.80, suggestive of nonadherence with oral antipsychotic medications.<sup>3</sup> Previous research has linked medication

nonadherence to initiation of depot antipsychotic medications.<sup>30</sup> Clinical characteristics related to medication nonadherence, including substance use disorders<sup>23,24</sup> and emergency mental health treatment,<sup>31,32</sup> were also common among patients who started each of the depot medications.

In relation to the general population, adults with severe psychiatric disorders have elevated rates of several medical disorders, including heart disease,<sup>33,34</sup> diabetes,<sup>35,36</sup> and obesity.<sup>37,38</sup> Among patients with schizophrenia starting

**Table 5.** Mean and Median Depot Treatment Duration of Patients With Schizophrenia Starting Fluphenazine Decanoate (FD), Haloperidol Decanoate (HD), and Long-Acting Risperidone (LAR)

Group	Mean, Days (SD)			Median, Days			STR <sup>a</sup> (95% CI)		
	FD	HD	LAR	FD	HD	LAR	FD	HD	LAR
<b>Injection</b>									
Total	58.2 (53.6)	71.7 (56.2)	60.5 (48.8)	21	28	49	0.81 (0.70–0.93)	1.09 (0.95–1.25)	1.00
<b>Sex</b>									
Male	56.2 (57.8)	71.6 (55.9)	64.3 (50.2)	21	29	56	0.78 (0.63–0.95)	1.11 (0.91–1.36)	1.00
Female	61.3 (54.6)	71.7 (57.3)	56.8 (47.5)	21	28	46	0.86 (0.71–1.05)	1.06 (0.87–1.28)	1.00
<b>Age</b>									
18–44 (y)	59.1 (53.8)	70.0 (55.4)	55.6 (43.7)	21	28	47	0.64 (0.73–1.04)	1.14 (0.96–1.36)	1.00
45–64 (y)	57.1 (53.5)	74.4 (58.1)	69.1 (56.1)	21	31	54	0.71 (0.56–0.90)	.95 (0.79–1.25)	1.00
<b>Race</b>									
White	59.4 (53.1)	73.5 (56.7)	58.3 (48.3)	21	35	45	0.81 (0.68–1.01)	1.24 (1.02–1.51)	1.00
Other	56.9 (53.9)	70.2 (56.1)	62.7 (49.5)	21	28	54	0.81 (0.67–0.99)	0.99 (0.81–1.20)	1.00

Note: Data are from the California Medicaid program, 2001–2004. CI, confidence interval.

<sup>a</sup>STR denotes survival time ratio. It is a ratio of the adjusted median time to depot discontinuation between antipsychotic treatment groups with LAR as the reference group. The STRs are adjusted for patient age, sex, race, use of inpatient and emergency mental health services, outpatient mental health treatment, outpatient general medical treatment, and treatment with antidepressants, mood stabilizers, anxiolytic/hypnotics, and oral antipsychotic medications.

**Table 6.** Mental Health Treatment of Patients With Schizophrenia During the 45 Days After Discontinuing FD, HD, or LAR

Medication	FD Patients, % (N = 816)	HD Patients, % (N = 1301)	LAR Patients, % (N = 102)	Statistics			Group Differences <sup>a</sup>
				$\chi^2$	df	P	
Any oral antipsychotic	77.4	78.9	75.5	1.1	2	.57	
Oral antipsychotic medications							
Fluphenazine	24.0	1.7	4.9	279.7	2	<.0001	FD > LAR > HD
Haloperidol	6.0	23.5	7.8	118.1	2	<.0001	HD > FD, LAR
Risperidone	20.1	21.6	43.4	28.4	2	<.0001	LAR > FD, HD
Olanzapine	30.0	30.0	23.5	1.9	2	.39	
Quetiapine	21.4	19.1	13.7	4.2	2	.12	
Ziprasidone	6.5	6.1	4.9	0.4	2	.80	
Aripiprazole	2.0	3.1	5.9	6.0	2	.049	LAR > FD
Clozapine	7.8	7.6	5.9	0.5	2	.78	
Other psychotropic medications							
Antidepressant	38.2	33.9	39.2	4.7	2	.10	FD > HD
Anxiolytic/hypnotic	34.9	29.8	36.3	7.1	2	.03	FD > HD
Mood stabilizer	46.6	45.5	35.3	2.7	2	.26	FD, HD > LAR
Antipsychotic gap of >30 days among oral users	5.5	6.6	9.1	1.8	2	.41	
Antipsychotic MPR <sup>b</sup> <0.80	35.9	38.7	48.0	6.2	2	.046	LAR > FD
Acute mental health care (%)							
Emergency visit	8.1	6.2	6.9	2.9	2	.23	
Hospital admission	0.6	0.6	0	0.6	2	.73	

Note: Data from 2001 to 2004 Medi-Cal. FD denotes fluphenazine decanoate, HD denotes haloperidol decanoate, and LAR denotes long-acting risperidone.

<sup>a</sup>Group differences,  $P < .05$ .

<sup>b</sup>MPR denotes medication possession ratio and is defined as the proportion of days of any antipsychotic medication treatment during the 45 days after depot injection treatment.

the 3 long-acting injections, there were no significant differences in the proportion who had recently received treatment for diabetes, obesity, or hyperlipidemia. However, prior to depot initiation, patients who started FD made significantly more general medical visits than those who started the other 2 antipsychotic medications. The reasons for this difference are not clear.

The 3 patient groups received broadly similar adjunctive psychopharmacological treatments during the 180 days before their first antipsychotic injection. After starting depot injections, most patients received oral antipsychotic medications and many received more than one oral antipsychotic medication. Prescriptions of other psychotropic medications, especially mood stabilizers and antidepressants, were also common. In one large European observational study of outpatients with schizophrenia, a substantial proportion of patients received anxiolytic/hypnotics (29.8%) at the time of starting conventional long-acting injection antipsychotics, but relatively few received antidepressants (9.5%) or mood stabilizers (6.8%).<sup>39</sup> Although such point estimates would be expected to be lower than cumulative estimates over 180 days as presented in the current study, it is nonetheless striking that such a great disparity exists between the high rates of anxiolytic/hypnotic, antidepressant, and mood stabilizer coprescription in the California sample

and the low rates in the European sample. As compared with schizophrenia patients in Europe, proportionately fewer patients in the California Medicaid program are treated with long-acting antipsychotic medications. It is possible that higher levels of psychiatric comorbidity within the California sample contribute to their higher rates of psychotropic coprescription.

A recent literature review found no convincing evidence to support or disprove the efficacy of antidepressant treatment for depressive symptoms in adults with schizophrenia.<sup>40</sup> Evidence for an augmenting effect of mood stabilizers in the antipsychotic treatment of schizophrenia is similarly mixed.<sup>41,42</sup> Given that concurrent medication administration increases the risk of adverse drug reactions,<sup>43</sup> efforts to reduce psychotropic coprescription might help improve tolerability and adherence of antipsychotic medications.<sup>44</sup>

Treatment with mood stabilizers was significantly less common among patients during treatment with LAR than during treatment with FD or HD. It is possible that this difference reflects inherent mood stabilizing properties of risperidone<sup>45,46</sup> or less mood instability in patients selected for LAR therapy.

Following discontinuation of long-acting antipsychotic medications, most patients continue to receive oral antipsychotic medications. This suggests that problems with

continuity of long-acting injection medications do not necessarily generalize to patient rejection of oral antipsychotic medications. A longer period of follow-up after discontinuation of long-acting antipsychotic medications would permit a more complete assessment of the frequency with which these patients are restarted on long-acting medications.

This study has several limitations. First, although pharmacy claims measure oral psychotropic medication utilization with reasonable accuracy,<sup>47,48</sup> oral prescription fills are only a proxy for actual medication use. Second, because patients who receive LAR likely differ from those selected for the older depot medications, group comparisons are vulnerable to selection biases. Medicaid data provide no information concerning several factors such as clinical efficacy, medication tolerability, adverse effects, patient medication preferences, illness insight, and family support that may influence antipsychotic selection. Without random assignment, it is possible that group differences in outcome are a consequence of pretreatment group differences rather than the treatments themselves. Third, LAR was approved by the Food and Drug Administration during the study period. As a result, our data provide information on LAR early in its market cycle. Over time, as reimbursement factors change and clinicians gain greater training in administration of LAR microspheres, patient selection for LAR may change. Similar channeling biases have been demonstrated in selection of antipsychotic medications.<sup>49</sup> Fourth, in order to help ensure complete prescription data retrieval, patients with extensive inpatient treatment before starting depot were excluded. This exclusion may limit the generalizability of the findings. Fifth, the results may underestimate the duration of treatment episodes that were initiated during an inpatient stay. Sixth, the posttreatment follow-up involved a small number of patients over a short time period. Finally, the results may not extend to patients who are not covered by the Medicaid program.

Patients with schizophrenia who initiate long-acting antipsychotic injections commonly exhibit evidence of nonadherence with oral antipsychotic medications in the months before their first injection. Patients starting HD, FD, and LAR also commonly receive prescriptions for other classes of psychotropic medications. Treatment with long-acting antipsychotic medications is often brief, usually lasting no longer than 7–10 weeks. Detailed clinical research is needed to determine the role of medication-related factors, such as dosing, tolerability, and efficacy, as well as other key clinical and psychosocial factors that contribute to the early discontinuation of depot antipsychotic medications. More importantly, research is needed to develop intervention strategies that will enhance the continuity of depot antipsychotic therapy in community treatment.

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