Risperidone Long-Acting Therapy Prescribing Patterns and Their Impact on Early Discontinuation of Treatment in a Large Medicaid Population

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Objective: Medicaid claims were examined to determine whether utilization of risperidone long-acting therapy (LAT) was consistent with manufacturer's prescribing information recommendations and what factors were associated with early discontinuation.

Method: Florida Medicaid claims between July 1, 2003, and June 30, 2007, were used. Recipient demographics and diagnoses, provision of oral antipsychotic supplementation during the first 21 days, number of injections received, medication possession ratio, and augmentation/polypharmacy after the first 21 days were assessed. Logistic regression was used to identify factors associated with early discontinuation of risperidone LAT.

Results: There were 3,364 individuals who received 4,546 episodes of risperidone LAT. Most recipients were between 18 and 64 years and had schizophrenia or schizoaffective disorder. Median episode length was 106 days. Median number of injections was 5. Supplementation with oral antipsychotic during the first 21 days was provided in 48% of episodes. Mean dosages were 25 mg or less for 28% of episodes and greater than 75 mg for 7% of episodes. Augmentation/polypharmacy after the first 21 days occurred in 43% of episodes. Early risperidone LAT discontinuation was associated with absence of oral supplementation during the first 21 days ($P < .001$), low ($P = .045$) or high ($P < .001$) initial doses of risperidone LAT, prior inpatient treatment ($P < .001$), having a substance use disorder ($P = .001$), and being male ($P = .036$).

Conclusions: Prescribing practices for risperidone LAT were compared with the recommended protocol. Risperidone LAT was typically used with recommended age and diagnostic groups. However, important discrepancies were identified that could have reduced perceived effectiveness and tolerability of risperidone LAT. Early discontinuation was less likely when the recommendations in the manufacturer's prescribing information regarding dosage and supplementation with oral antipsychotics were followed.

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At least 40% to 50% of patients with schizophrenia exhibit poor adherence to antipsychotic medication regimens.[1–4] The consequences are often increased psychiatric hospitalizations and overall health care service utilization.[5–7] Depot antipsychotic medications offer the potential to improve adherence because a single injection lasts for 2–4 weeks, thereby reducing the burden on patients to fill prescriptions for oral medications and to comply with daily dosing routines.[8,9] Historically, the use of depot medications in the United States has been comparatively low, accounting for an estimated 15% of antipsychotic use for persons with schizophrenia.[10,11] The limited number of available depot medications has been an impediment to wider use. Until recently, fluphenazine decanoate and haloperidol decanoate, 2 first-generation antipsychotics with significant extrapyramidal syndrome burden, have been the primary depot medications available in the United States.[12,13]

The release of risperidone long-acting therapy (LAT) medication in 2003 expanded the options available to clinicians and their patients.[14] Risperidone, a second-generation antipsychotic, had demonstrated efficacy in treating the positive and negative symptoms of schizophrenia with significantly reduced risk of extrapyramidal syndrome and tardive dyskinesia.[15,16] The clinical trials leading to US Food and Drug Administration indication for risperidone LAT in schizophrenia demonstrated its effectiveness compared to placebo, its comparable effectiveness to oral risperidone, and its safety and tolerability for stable patients who switch from the oral to the injectable form.[17–19] Since the clinical trials, research has generally demonstrated that patients who switched to risperidone LAT had symptom improvements[20] and reductions in psychiatric hospital admissions and bed days.[21–23]

However, the pharmacokinetics of the risperidone LAT formulation require adherence to a relatively specific administration protocol. Patients are advised in the manufacturer's prescribing information to take an oral antipsychotic medication for 21 days after the first injection of risperidone LAT because the active drug in the injectable medication does not significantly release into the blood stream until 3 weeks following injection.[24] Injections are to be given on a 14-day schedule and steady-state serum levels are generally not achieved until the fourth injection.[25] Thus risperidone LAT provides its own, albeit different, challenge for clinicians and their patients who must return to their health care provider for injections every 2 weeks for the duration of treatment.

Although risperidone LAT has been on the market for more than 5 years, little research is available on how it is used in real-life, clinical settings. One recent study of its use in the California Medicaid program has raised questions about whether risperidone LAT is used appropriately in ambulatory settings.[26] The average patient in the California study remained on his or her medication for 60.7 days. Thus, the average patient discontinued risperidone LAT only shortly after he or she could have achieved stable blood levels, assuming injections occurred on a 14-day schedule. This finding raises questions about how the medication is used in real-life, clinical settings and whether its patterns of utilization optimize its effectiveness.

The purpose of this article is to explore these questions by addressing the following issues:

1. What are the demographic and diagnostic characteristics of patients who are prescribed risperidone LAT?
2. Is risperidone LAT used appropriately in terms of dosing and appropriate oral supplementation?
   - What are the risperidone LAT doses used, duration of risperidone LAT episodes, and subsequent medication possession ratios (MPRs) of these episodes?
   - Are the 21 days beginning with the first administration of risperidone LAT covered by a sufficient supply of oral risperidone or other antipsychotic medication?
   - How often is risperidone LAT augmented with other antipsychotic medication after the first 21 days of treatment when risperidone LAT monotherapy is recommended?
3. What factors are associated with early discontinuation from risperidone LAT?

METHOD

The study used fee-for-service pharmacy claims generated in the Florida Medicaid Program between July 1, 2003, and June 30, 2007. During this period, pharmacy benefits were paid for on a fee-for-service basis for 50%–55% of enrollees. The remaining enrollees were in health maintenance organizations (HMOs) for which capitation payment mechanisms eliminated pharmacy claims. All claims for antipsychotic medications were identified based on National Drug Code (NDC) numbers and all persons who had 1 or more claims for risperidone LAT during the study period were included as participants in the study. For each person that had a claim for risperidone LAT, demographic characteristics (sex, birth date, and race) were obtained from the Florida Medicaid recipient information database. Also for each person, a behavioral health diagnosis was established by querying the inpatient and outpatient medical claims. All behavioral health diagnoses were extracted from the claims, and the most frequently occurring diagnosis was considered the primary diagnosis.

Medicaid pharmacy claims were analyzed for each person to identify episodes of risperidone LAT. An episode of risperidone LAT was considered to have been initiated on the date of the first injection. Episodes continued as long as subsequent injections were received within 50 days of the last prior injection.* Risperidone LAT episodes were considered terminated if a gap of greater than 50 days occurred between injections. This gap length was chosen to be comparable to research on discontinuation from oral antipsychotics in which episodes are commonly terminated 15 days after the drug supply is exhausted. With risperidone LAT, the drug serum level begins to drop below the therapeutic level approximately 35 days after the last injection.[25]

For each risperidone LAT episode, the number of injections, the number of days between injections, and the mean dosage were calculated; and the initial and final dosages were recorded. A variable similar to the MPR was also calculated for each episode. This was done by assuming that, for each injection, the main release of the drug begins 21 days after the injection, after which a sufficient amount of the drug is released over the next 14 days to maintain a therapeutic blood level. The blood level then drops below the therapeutic level after 35 days following the injection. The length of the risperidone LAT episode was calculated as the number of days from the first injection until 35 days after the last injection. The MPR was the number of days with an assumed therapeutic level divided by the length of the episode minus 21 days (the first 21 days of the episode were excluded from the calculation since the drug is not available during that time).

Claims for antipsychotic medications other than risperidone LAT were analyzed in order to characterize the extent of supplementation with oral risperidone or other antipsychotic medications during the first 21 days of each episode, and during the remainder of the episode to characterize augmentation, in the case of oral risperidone, and polypharmacy, when other antipsychotic medications were involved. For each claim for oral antipsychotic medications, it was assumed that the participant took the medication starting on the date of the claim and continued for the number of days supplied as indicated on the claim. For non–risperidone LAT depot antipsychotic medications, it was assumed that the injection was given on the date of the claim and that the effect of the injection continued for 28 days. Using this approach, we counted the number of days of the first 21 days of each risperidone LAT episode on which the participant received any particular antipsychotic medication other than risperidone LAT. The participant was considered to have received oral supplementation with a medication if they received the medication for 17 days or more of the first 21 days of the episode (MPR $\geq$ 0.8). For the remainder of the risperidone

*Florida Medicaid allows providers to bill for more than 1 injection of risperidone LAT (on different days) on a single claim. Because of this, for claims on which more than 1 injection was indicated, when the subsequent risperidone LAT claim occurred more than 14 days afterward, the multi-injection claim was split into 2 claims, with the second occurring 14 days after the first.

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LAT episode until the date of the last injection, the participants were considered to have received augmentation with oral risperidone or polypharmacy with another antipsychotic medication if they received at least 60 days of the second drug during this period (for persons with at least 75 days from day 21 to the last injection) or if they had an MPR ≥ 0.8 for the second drug during the part of the episode from day 21 to the last injection (for persons with less than 75 days in this period).

Logistic regression utilizing generalized estimating equations was used (PROC GENMOD, SAS version 9.2; SAS Institute Inc, Cary, North Carolina) to identify factors that might be associated with early discontinuation of risperidone LAT. Generalized estimating equations was used because some participants had more than 1 episode of treatment. Early discontinuation was defined as having 4 or fewer risperidone LAT injection events in an episode since steady-state serum levels of the active moiety occur by the fourth injection.[25] Both participant characteristics (demographics and diagnosis) and treatment characteristics (presence or absence of supplementation with oral antipsychotics and initial dosage of risperidone LAT) were examined in the analysis. Since severity of illness and a history of nonadherence to treatment are likely risk factors for early discontinuation, we included several covariates in this analysis—history of substance abuse diagnosis (yes or no), mean number of days per month of inpatient/emergency room behavioral health treatment in the past year, and percentage of days in the past year on which an antipsychotic medication was received.

RESULTS

During the study period, claims for risperidone LAT represented about 1% of all claims for antipsychotic medication in Florida Medicaid. In all, 3,364 individuals experienced 1 or more episodes of risperidone LAT. Table 1 presents the demographic and diagnostic characteristics of this group.

Slightly more recipients were male than female, and almost half were white. The most common age groups were 35–44 and 45–55 years old. Mean age of participants was 44.4 years (SD = 17.1, median = 43). Schizophrenia and schizoaffective disorder were the predominant diagnoses and together represented 69% of all risperidone LAT recipients.

Eighty-nine percent of risperidone LAT episodes were preceded by a non–risperidone LAT antipsychotic prescription within the previous 365 days. Sixty-four percent of these episodes were preceded by 2 or more different non–risperidone LAT antipsychotic medications in the same time frame. During the 60 days immediately preceding risperidone LAT episodes, 48% of patients were prescribed oral risperidone, 20%, quetiapine; 14%, olanzapine; 11%, aripiprazole; and 10%, ziprasidone. During the same time period, 15% had a discontinued risperidone LAT episode and about 13% received first-generation antipsychotic depot medications.

Following discontinuation of risperidone LAT, similar utilization patterns were observed. Forty-nine percent were prescribed oral risperidone, 19% received quetiapine, and approximately 25% received 1 of the other oral second-generation antipsychotic medications. Less than 8% were subsequently placed on other depot medications. (Note: only selected percentages are reported.)

Half of risperidone LAT episodes were less than 106 days in duration. However, the distribution of episode length had a long tail, with 25% of episodes exceeding 240 days. The mean episode length was 184.3 days (SD = 142.0). Similarly, the median number of injections was 5, while the mean was 10.7 (SD = 13.8). Although many risperidone LAT episodes were relatively short, MPRs were greater than or equal to 0.80 in 78% of the episodes involving more than 3 injections (Table 2).

Supplementation with oral risperidone in the 21 days beginning with the first injection actually occurred in 31.4% of risperidone LAT episodes. Supplementation with other antipsychotic medications occurred in 27.8% of risperidone LAT episodes. Some episodes were supplemented with both risperidone and another antipsychotic; thus, 48% of risperidone LAT episodes had supplementation as recommended

Table 1. Characteristics of Risperidone Long-Acting Therapy Recipients (N = 3,364)

Characteristic	n	%
Age, y		
0–17	69	2.0
18–24	349	10.4
25–34	589	17.5
35–44	791	23.5
45–54	788	23.4
55–64	382	11.4
65+	396	11.8
Race		
White	1,640	48.8
Black	994	29.5
Hispanic	393	11.7
Other	337	10.0
Gender		
Male	1,767	52.5
Female	1,597	47.5
Diagnosis		
Schizophrenia	1,674	49.8
Schizoaffective disorder	640	19.0
Other psychotic disorder	159	4.7
Bipolar I disorder	257	7.6
Major depression	124	3.7
Other bipolar/mood disorder	105	3.1
Organic disorders	188	5.6
Other/missing	217	6.5

Table 2. Medication Possession Ratio (MPR) for All Risperidone Long-Acting Therapy (LAT) Episodes and for Risperidone LAT Episodes With More Than 3 Injections

	All Episodes		Episodes With > 3 Injections	
MPR	No. of Episodes	%	No. of Episodes	%
0.4	19	0.4	14	0.5
0.5	100	2.2	79	2.6
0.6	225	5.0	196	6.4
0.7	425	9.3	398	12.9
0.8	920	20.2	890	28.9
0.9	2,857	62.9	1,506	48.8
Total	4,546	100.0	3,083	100.0

Table 3. Doses of Risperidone Long-Acting Therapy by Injection Event

	First Injections		Intermediate Injections		Final Injections		All Injections	
Dose, mg	No. of Injections	%	No. of Injections	%	No. of Injections	%	No. of Injections	%
25	2,122	46.7	12,207	29.9	801	22.8	15,130	31.0
37.5	537	11.8	8,562	21.0	443	12.6	9,542	19.5
50	1,449	31.9	14,881	36.5	1,173	33.3	17,503	35.8
75	194	4.3	3,113	7.6	393	11.2	3,700	7.6
100	214	4.7	1,934	4.7	570	16.2	2,718	5.6
>100	30	0.6	70	0.2	141	4.0	241	0.5
Total	4,546	100.0	40,767	100.0	3,521	100.0	48,834	100.0

Table 4. Mean Doses of Risperidone Long-Acting Treatment per Episode for All Participants and for Participants With Selected Mental Disorders

	Full Sample		Schizophrenia		Schizoaffective		Other Disorder	
Mean dosage, mg	No. of Episodes	%	No. of Episodes	%	No. of Episodes	%	No. of Episodes	%
≤25	1,272	28.0	612	26.4	234	26.5	426	31.8
25.1–37.5	1,067	23.5	532	22.9	211	23.9	324	24.2
37.6–50	1,267	27.9	656	28.3	259	29.3	352	26.3
50.1–75	629	13.8	360	15.5	120	13.6	149	11.1
>75	311	6.8	161	6.9	60	6.8	90	6.7
N (row %)	4,546	100.0	2,321	51.1	884	19.4	1,341	29.5

Table 5. Logistic Regression Model of Early Termination of Risperidone Long-Acting Therapy[a]

		Odds	OR 95% CI		
Effect	Reference	Ratio	Low	High	*P*
Age		1.001	0.997	1.006	.554
Black	White	1.017	0.863	1.198	.841
Other race	White	1.090	0.911	1.305	.345
Female	Male	0.856	0.740	0.990	.036
Schizoaffective disorder	Schizophrenia	0.964	0.795	1.168	.708
Other diagnosis	Schizophrenia	0.977	0.829	1.150	.777
Risperidone supplementation	No risperidone supplementation	0.278	0.238	0.326	<.001
Other antipsychotic supplementation	No other antipsychotic supplementation	0.231	0.194	0.276	<.001
Low first dose	37.5- to 50-mg dose	1.154	1.003	1.327	.045
High first dose	37.5- to 50-mg dose	2.274	1.810	2.855	<.001
Prior inpatient days		1.128	1.072	1.186	<.001
Substance use disorder	No substance use disorder	1.284	1.104	1.492	.001
Prior antipsychotic use (percentage of days)		1.005	0.997	1.012	.207

[a]The number of episodes was 4,239 for this analysis because some participants had missing data for 1 or more covariates.

in the manufacturer's prescribing information. So, 52% of episodes did not have oral antipsychotic supplementation in the first 21 days at an MPR of 0.80 or greater.

Although the majority of risperidone LAT episodes (57%) did not include augmentation or polypharmacy (receipt of a second antipsychotic after the first 21 days), these practices were rather common. Augmentation with risperidone occurred in 28% of episodes and polypharmacy with a non–risperidone antipsychotic agent also occurred in 27% of episodes.

At the time of the study, risperidone LAT came in 25-mg, 37.5-mg, and 50-mg doses. It is possible to administer dosages in excess of 50 mg by combining available prepackaged doses, although this is recommended against in the manufacturer's prescribing information. Table 3 presents information on the dosages of all administrations as well as those associated with the first, intermediate, and last risperidone LAT administrations in an episode. (For instances in which a person received only 1 injection, this is represented in the table as a "first injection" but not as a "last injection"). Table 4 provides data on the mean dosage within all risperidone LAT episodes, as well as the mean dosages received by individuals with schizophrenia, schizoaffective disorder, and all other psychiatric disorders.

Overall, the most frequent dose given in a single administration was 50 mg followed by the 25-mg dose. Almost 14% of risperidone LAT doses were for 75 mg or more and over 6% of all doses were for 100 mg or greater. Dosages differed depending on when they were administered ($\chi^2_{10} = 2{,}617.3$, $P < .0001$). A high percentage of first injections involved 25-mg dosages; intermediate injections had higher percentages of intermediate dosages (37.5 and 50 mg); and final injections had higher percentages of the highest dosages (>50 mg). Twenty-eight percent of all risperidone LAT episodes had a mean dosage equal to or less than 25 mg and more than half fell into the 25.1- to 50-mg range. Almost 7% of episodes had mean dosages exceeding 75 mg. Twenty-six percent of episodes associated with patients with schizophrenia or with schizoaffective disorder received risperidone LAT doses of 25 mg or less compared with 32% for other diagnoses. Patients with schizophrenia and schizoaffective disorder were more likely than those with other diagnoses to have received doses greater than 50 mg (22% vs 18%; $\chi^2_1 = 9.3$, $P < .003$). Also, the mean dosage was higher for persons with schizophrenia and schizoaffective disorder than for those with other diagnoses (41.8 mg vs 39.5 mg; $F_{1,4544} = 8.9$, $P < .003$).

Results of the logistic regression analysis are presented in Table 5. Of the demographic characteristics entered into the analysis, only the effect of gender attained statistical significance (OR = 0.856, $P = .036$), indicating that females were about 15% less likely to discontinue early than males. Age and race were not associated with early discontinuation. Primary diagnosis also was not associated with early discontinuation. Severity of illness was associated with early discontinuation. Persons with a substance abuse diagnosis were more likely to discontinue early (OR = 1.284, $P = .001$), and those with more prior behavioral health inpatient and emergency room treatment days were also more likely to discontinue early (OR = 1.128, $P < .001$). Percentage of days receiving an antipsychotic during the prior year was not associated with early discontinuation. Of the treatment variables entered in the analysis, presence of supplementation with oral antipsychotic medication

during the first 21 days of the episode was associated with a lower probability of early discontinuation for both supplementation with risperidone (OR = 0.278, $P < .001$) and with other antipsychotics (OR = 0.231, $P < .001$). Initial dosage of risperidone LAT was also associated with early discontinuation. Persons who received a low initial dose of risperidone LAT (25 mg) were more likely to discontinue (OR = 1.154, $P < .05$) than persons who received a moderate initial dose (37.5–50 mg), and persons who received a high initial dose of risperidone LAT (75 mg or more) were also more likely to discontinue (OR = 2.274, $P < .001$) than persons who received a moderate initial dose.

DISCUSSION

In general, it appeared that risperidone LAT was used for the recommended age and diagnostic groups. Eighty-six percent of recipients were between 18 and 64 years old during their first risperidone LAT episode. Only 2% were younger than 17, and 12% were 65 or older. The diagnostic distribution of risperidone LAT recipients seems to confirm that it is used for the most severely ill population. Sixty-nine percent of risperidone LAT recipients had schizophrenia or schizoaffective disorder. This contrasts with 32% of all antipsychotic users and 61% of all antipsychotic polypharmacy users reported for the same Medicaid population.[27] There is some evidence that patients who were prescribed risperidone LAT had not previously achieved long-term stability on another antipsychotic medication. Almost two-thirds had been prescribed 2 or more antipsychotics during the 365 days preceding their first risperidone LAT episode during the study period.

Recognizing that the use of depot medications in the United States (~15% for schizophrenia) is considerably lower than in Europe,[10,11,28] we were surprised by the extremely low use of risperidone LAT and the other depot antipsychotics in Florida's Medicaid program. During the study period, slightly less than 1% of all claims for antipsychotic medication were for risperidone LAT. This utilization rate was comparable to those of haloperidol decanoate and fluphenazine decanoate, first-generation depot antipsychotic medications that carry significantly more risk of extrapyramidal syndrome and tardive dyskinesia. This was the case despite the fact that oral risperidone consistently accounted for more than 25% of antipsychotic prescriptions in the Florida Medicaid program during this same time period. It is likely that, among these users of oral risperidone, there were patients with medication adherence problems that would have suggested the use of risperidone LAT. Uncertainty concerning whether risperidone LAT would remain on Florida's Medicaid Preferred Drug List may have suppressed the normal uptake of risperidone LAT that would have occurred in the first 36 months after its release to the market. Another possibility is that the protocol recommended in the manufacturer's prescribing information for risperidone LAT was not well understood or followed, and, as a result, patient and prescriber satisfaction with risperidone LAT may not have been optimized. Such an outcome could have negatively affected the growth in demand for risperidone LAT in the years immediately following its release. Some of the findings reported in this study suggest the latter may be partially responsible for the low utilization of risperidone LAT in Florida's Medicaid program.

Medication possession ratios were rather high in this study; over 82% of episodes met the typical threshold for adherence of MPR ≥ 0.8. However, while MPRs were high, half of all risperidone LAT episodes were less than 106 days in duration (including the initial 21 day inactive period), and 32% involved less than 3 injections. Thus, stable plasma levels and a long-term stable and adherent medication regimen were probably not achieved by many patients initiated on risperidone LAT in Florida's Medicaid program. The delayed release of the risperidone LAT microspheres require physicians initiating patients on risperidone LAT to prescribe oral antipsychotic medication to cover the first 21 days following the first injection. Oral risperidone or another oral antipsychotic is recommended in the manufacturer's prescribing information to facilitate continuity during the early days of treatment. However, only 31% of risperidone LAT episodes had evidence of oral supplementation with risperidone covering 17 or more of the first 21 days of treatment. Supplementation with a different antipsychotic medication occurred for 28% of treatment episodes (some episodes had both risperidone and another antipsychotic). More than half of risperidone LAT episodes were left without adequate oral antipsychotic coverage during the first 21 days of risperidone LAT episodes. The lack of adequate antipsychotic coverage during the first 3 weeks of treatment could have led patients and physicians to question the effectiveness of the medication. Indeed, several studies have cited ineffectiveness as a more frequently cited reason for discontinuation than intolerability.[19,29,30] This conclusion is supported by the logistic regression results that indicate that persons who did not receive oral supplementation at an MPR ≥ 0.8 during the first 21 days of the episode were more than 3 times as likely to discontinue risperidone LAT early than persons who received supplementation.

The data on the dosing of risperidone LAT also raise questions about whether its use in Florida's Medicaid program optimized its tolerability and effectiveness, and, therefore, patient and physician satisfaction. Twenty-eight percent of all risperidone LAT episodes had mean dosages of 25 mg or less. Questions have been raised regarding the tendency for 25-mg doses to produce plasma levels and D_2 occupancy equivalent to 2 mg or less of oral risperidone, which may be subtherapeutic.[31–33] Thus, some of those with mean dosages at or below 25 mg may have experienced an inadequate antipsychotic effect from risperidone LAT. Indeed, persons who received a low initial dose (25 mg) were about 15% more likely to discontinue risperidone LAT early than persons who received a moderate initial dose. In one of the previous clinical trials, no difference was found in efficacy or discontinuation for persons receiving 25 mg vs 50 mg.[17] (A 75-mg dose was also used, which showed lower efficacy and higher

discontinuation.) However, in that study, patients were prestabilized on doses of 2, 4, or 6 mg of risperidone. Only the patients stabilized on 2 mg of risperidone were given the 25-mg dose of risperidone LAT. These patients may have had a lower severity of illness, or have been more responsive to risperidone. Another study that simply assigned patients randomly to 25, 50, or 75 mg of risperidone LAT found that 22% of patients receiving 25 mg of risperidone LAT discontinued due to "insufficient response" compared with 15% and 12% discontinuing for this reason in the 50- and 75-mg groups, respectively.[19]

Additional questions arise regarding the effects of potentially high doses of risperidone LAT alone or in combination with other antipsychotics. Almost 14% of all risperidone LAT administrations involved doses greater than 75 mg, and over 6% were for 100 mg or more. Twenty-one percent of episodes had mean dosages greater than 50 mg (the maximum recommended dose in the manufacturer's prescribing information). More significantly, antipsychotic augmentation and polypharmacy among risperidone LAT patients were relatively common. The manufacturer's prescribing information recommends that other antipsychotics not be coadministered with risperidone LAT following 21 days after the first injection. Yet, 28% of all risperidone LAT episodes were augmented with oral risperidone, and 27% of risperidone LAT episodes involved polypharmacy with a nonrisperidone antipsychotic agent after 21 days following the first injection. Overall, 43% of all risperidone LAT episodes involved augmentation or polypharmacy with some oral antipsychotic. Anticipating that augmentation with oral risperidone and antipsychotic polypharmacy might reflect clinician reluctance to use high doses of risperidone LAT, we looked at the rates of augmentation/polypharmacy associated with mean dosages of risperidone LAT. Contrary to our expectations, the rate of augmentation/polypharmacy was higher for episodes with mean dosages above the median. The consequences of high doses of risperidone LAT and of total antipsychotic doses produced by polypharmacy or augmentation cannot be determined using administrative data. However, one would predict higher incidence of adverse events among affected recipients.

Limitations

As with any study that uses administrative data, there are limitations to this analysis. First, we do not have data from the Medicare part D program or for the 45%–50% of Medicaid beneficiaries enrolled in HMOs. Consequently, medication use is not observed after January 1, 2006, for dually eligible beneficiaries or at any point in the study period for Medicaid enrollees in HMOs. Second, supplementation during the first 21 days of risperidone LAT may be understated if physicians are supplying samples of oral medications to cover that time frame. Third, the assumption that patients who fill prescriptions for oral antipsychotics take all the medication may overstate supplementation if patients were told to discontinue other medications when administered the first risperidone LAT. Fourth, we cannot distinguish whether augmentation with oral antipsychotics denotes polypharmacy or whether physicians prescribe oral antipsychotics to cover gaps in risperidone LAT. This distinction may be particularly important for the simultaneous prescribing of oral risperidone and risperidone LAT after the first 21 days of risperidone LAT.

The results of the logistic regression analysis indicated an association between early discontinuation of risperidone LAT and the absence of oral supplementation during the first 21 days, low initial dose and high initial dose of risperidone LAT. While these findings are supportive of the notion that treatment that is consistent with the protocol in the manufacturer's prescribing information may enhance adherence to risperidone LAT, these findings are correlational. Thus, one cannot rule out the possibility that the findings are reflective of patient or illness characteristics that may increase the likelihood of early discontinuation. We included covariates to attempt to control for severity of illness and prior antipsychotic medication adherence; however, these variables may not fully capture patient or illness characteristics that may increase the likelihood of early discontinuation. For example, persons who fail to fill prescriptions that were written for oral supplementation may well also be less likely to return for additional injections of risperidone LAT. With administrative claims data, it was not possible to discriminate instances in which prescriptions for oral supplementation were not written as opposed to those in which such prescriptions were written but not filled.

CONCLUSIONS

We compared the prescribing practices used for risperidone LAT with key elements of the protocol recommended in the manufacturer's prescribing information. Important discrepancies were identified that could have reduced the perceived effectiveness and tolerability of the new medication and impeded increases in demand for risperidone LAT. Of particular concern is the abbreviated nature of many risperidone LAT episodes. Low initial doses, high initial doses, and absence of supplementation with oral antipsychotic in the first 3 weeks of an episode were associated with early discontinuation. We cannot determine with administrative data if these prescribing practices actually reduced effectiveness and tolerability. Prescribing practices tend to evolve in the years after the release of a new agent, sometimes generating enhanced effectiveness or usage not anticipated at the time the manufacturer's prescribing information is drafted. Detailed medical records reviews are required to determine the actual clinical effects of deviations from the protocol for the use of risperidone LAT. In the present study, data were not available on treatment effectiveness nor on side effects that may have been experienced. In future research, the addition of these types of information would be helpful in determining the extent of the role of prescribing practices in early discontinuation of risperidone LAT.

These findings highlight the importance of encouraging prescribing practices that maximize the effectiveness of these

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medications. With a medication such as risperidone LAT that has a recommended protocol that is significantly different than other antipsychotics, physician education on the unique features of the protocol would seem particularly important. There is also a role for patient education in improving adherence. Patients should be educated on the manufacturer's prescribing recommendations so that they understand the need to obtain and take oral antipsychotic medications for 21 days after the first injection of risperidone LAT. It may also be important to educate the patient as to the expected time course of release of risperidone LAT during the initial phase of treatment to help them understand the importance of oral supplementation.

Drug names: aripiprazole (Abilify), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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