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Evaluation of Prescribing Patterns of Long-Acting Injectable Antipsychotics Within a Community Health System.

Jared Netley PharmD, MPA, BCPS

Jamie Gaul PharmD, BCPS

Chelsea L Ferguson PharmD

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Jared Netley, PharmD, MPA, BCPS, Jamie Gaul, PharmD, BCPS, and Chelsea Ferguson, PharmD

Abstract:

Purpose/Background: Long-acting injectable antipsychotics (LAIAs) are used in the management of schizophrenia, bipolar disorder, and related psychiatric conditions. The efficacy of LAIAs has been established in randomized controlled trials; however, usage of LAIAs outside of randomized controlled trials may not correlate to naturalistic prescribing habits. The purpose of this analysis was to evaluate the prescribing patterns of LAIAs within our health system and identify any inconsistencies between medications' published labeling information and clinical practice.

Methods/Procedures: All patients who received a LAIA at the time of the analysis were included for review. Areas of inconsistency between the prescribed LAIA and each medication's published labeling information were targeted and assessed. Frequency statistics were used to review the following areas for inconsistencies: indication, trial of oral therapy, dose, frequency, and titration method.

Findings/Results: This analysis included 427 patient cases who received a combined 1480 injections during the analysis period. Overall consistency rates between labeling information and prescribed LAIAs within the analysis period were as follows: 71.2% for indication, 67.4% for trial of oral therapy, 94.4% for dose of LAIA, 84.5% for injection frequency, and 93.9% for titration method.

Implications/Conclusions: Inconsistencies were observed between labeling information and clinical practice for LAIAs prescribed within the community health system. Patients who are more symptomatic and have additional psychological comorbidities are commonly excluded from clinical trials. Alternative dosing may be clinically necessary to obtain an adequate response, and this may have been captured in this review. This analysis may be hypothesis generating for future studies on LAIAs.

Key Words: antipsychotic, long-acting injectable, drug use evaluation, pharmacotherapy

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Antipsychotics are the mainstay of therapy for many psychiatric conditions, including schizophrenia and bipolar disorder, and are used for augmentation of other psychiatric conditions. Long-acting depot formulations have existed since the 1960s and provide advantages over oral therapy, including steady release for consistent drug levels and assured medication delivery.[1,2] Monotherapy with long-acting injectable antipsychotics (LAIAs) has been demonstrated in patients with schizophrenia who have historically demonstrated poor adherence to oral antipsychotic regimens.[3]

Long-acting injectable antipsychotics may help address the concern in patients at increased risk for noncompliance secondary to a variety of factors, including poor insight, negative attitude toward medication, previous display of nonadherence, substance abuse, and patients with inadequate discharge planning or aftercare.[4] Previous studies have demonstrated benefits of lowering relapse rates and number of hospitalizations for patients on LAIA therapy.[5,6] In addition to the benefits of improving compliance, frequency of extrapyramidal symptoms was reduced when patients switched from oral therapy to a long-acting injection (LAI), which additionally may help improve compliance.[7,8]

The efficacy of LAIAs has been established in randomized controlled trials; however, the design of randomized controlled trials may not reflect clinical practice. Currently, there is limited evidence available describing the naturalistic prescribing patterns and the clinical impact that can result owing to prescribing variations between labeling information and clinical practice.[9,10] Approved labeled indications, recommendations for oral antipsychotic overlap, titration instructions, and injection intervals vary among the available LAIAs and may be challenging for clinicians to differentiate between products. Improving the understanding and encouraging appropriate prescribing of LAIAs may improve patient outcomes, minimize side effects, and decrease unnecessary healthcare cost. The purpose of this analysis was to evaluate the prescribing patterns of LAIAs within our health system and identify any inconsistencies between medications' prescribing information and clinical practice.

MATERIALS AND METHODS

This analysis was completed as a retrospective chart review within a single health system. The health system comprises of 9 hospitals, including an inpatient behavioral health center and multiple ambulatory care clinics across Northeastern Indiana and Northwestern Ohio. Patients were identified via screening of archived data from the electronic medical records and were included if they had received at least one dose of a LAIA between January 1, 2015, and June 30, 2017. Aripiprazole lauroxil, 3-month paliperidone palmitate, and olanzapine pamoate were included in this initial archive search but, owing to low usage within the health system, were excluded from further evaluation. Medications included in this evaluation were fluphenazine decanoate, haloperidol decanoate, aripiprazole for extended-release injectable suspension, monthly paliperidone palmitate, and risperidone LAI.

The primary outcome of this analysis was to identify areas of inconsistency between published labeling information and clinical practice to identify possible areas of inappropriate use of LAIAs. Areas of prescribing that were reviewed for possible inconsistencies included indication for use, trial of oral antipsychotic agent, prescribed dose, prescribed injection interval, and dose titration method.

Criteria for determining rates of inconsistency were derived from each medication's labeling information published by the drug manufacturer. Table 1 provides the criteria that were reviewed for indication, dose, injection interval, and titration method. When a LAIA was initiated, cases were reviewed for trial of the same oral formulation of the medication being initiated as the LAIA, except for paliperidone, which allows for oral trial of paliperidone or risperidone before converting to injection.

Secondary outcomes of this analysis included duration of LAIA therapy and readmission rate to the inpatient behavioral

From the Parkview Health, Department of Pharmacy, Fort Wayne, IN.
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Reprints: Jared Netley, PharmD, MPA, BCPS, Parkview Health, Department of Pharmacy, 11109 Parkview Plaza Dr, Fort Wayne, IN 46845 (e-mail: Jared.netley@parkview.com).
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TABLE 1. Published Labeling Information Used as Criteria for Clinical Review

	Labeled Indication(s)	Labeled Dose	Labeled Injection Interval	Labeled Method for Titration
Aripiprazole	Schizophrenia, bipolar I disorder	Initial: 400 mg	30 d	If experiencing adverse effects, taper to 300 mg
Fluphenazine	Psychosis	Initial: 12.5–25 mg Maintenance: 12.5–100 mg	21–28 d	Adjust by 12.5 mg increments if dose >50 mg
Haloperidol	Schizophrenia	Initial: 10–20 times oral dose, if >100 mg administer in divided doses 3–7 d apart Maintenance: 50–200 mg	28 d	
Paliperidone	Schizophrenia, schizoaffective disorder	Initial: 234 mg, then 156 mg 7 d later Maintenance: 78–234 mg CrCl 79–50 mL/min: 156 mg, then 117 mg 7 d later, then maintenance 78 mg CrCl <50 mL/min: use not recommended	28 d	First dose is followed 7 d by second initial dose, then maintenance dose 35 d after first injection
Risperidone	Schizophrenia, bipolar I disorder	Initial: 25 mg, may consider 12.5 mg in sensitive patients Maintenance: 12.5–50 mg	14 d	Minimum of 4 wk between dose adjustments

CrCl indicates creatinine clearance.

health center after initiation of a LAIA. Descriptive statistics were used to describe baseline characteristics and frequency of primary and secondary outcomes. All data management and statistics were performed using Excel 2016 (Microsoft Corp, Redmond, WA).

RESULTS

This analysis identified 427 patients who had received a combined 1480 LAI within the health system during the analyzed period. Paliperidone was the most common LAIA given (n = 515), followed by risperidone (n = 485), aripiprazole (n = 328), haloperidol (n = 125), and fluphenazine (n = 27). Additional baseline demographics can be found in Table 2. Observed inconsistency rates for each LAIA reviewed in this analysis are presented in Figure 1.

Prescribing based on published labeled indication(s) was consistent in 71.2% of cases overall. The inconsistency rate for usage of a LAIAs outside of approved indications was 36.4% for patients prescribed risperidone, 34.0% with haloperidol, 31.1% with paliperidone, and 21.0% with aripiprazole. All patients administered fluphenazine met the criterion for published label indication.

Receipt of adequate trial of oral therapy was identified in 67.4% of patient cases overall. Rates for no trial or inadequate trial of oral therapy was 76.9% in patients prescribed fluphenazine, 48.5% with risperidone, 42.0% with haloperidol, 29.5% with aripiprazole, and 23.3% with paliperidone.

The prescribed dose of each LAIA was consistent in 94.4% of cases overall. Inconsistencies between the recommended and prescribed dose were identified in 14.8% prescribed fluphenazine, 11.7% with paliperidone, 7.2% with haloperidol, 1.5% with aripiprazole, and 1.0% with risperidone. Paliperidone was the only LAIA in this evaluation with labeled recommendations for adjustment in renal impairment. In the patients prescribed paliperidone, 4.1% of patients were identified as having an inconsistency due to missed adjustment for renal impairment.

The prescribed injection administration interval was found to be consistent in 84.5% of cases overall. The inconsistency rates between recommended and prescribed injection intervals was found to be 36.9% for patients prescribed aripiprazole, 20.0% with haloperidol, 18.5% with fluphenazine, 5.2% with risperidone, and 4.5% with paliperidone.

The method for titration adjustments was consistent in 93.9% of cases overall, if a dose titration was made. Only 10.2% prescribed paliperidone, and 1.2% prescribed risperidone had inconsistencies in the method used to titrate the patient's medication. All dose titrations made for patients prescribed aripiprazole, fluphenazine, and haloperidol were deemed to be consistent.

For secondary outcomes, 20.2% of patients reviewed were rehospitalized for a psychiatric condition after initiation of a LAIA. Of the patients who had a rehospitalization, 58.9% had 1 readmission, 29.2% had 2 readmissions, and 11.9% had 3 or more readmissions. This analysis identified that 48.4% of patients only had 1 dose of a LAIA administered and/or no additional follow-up administrations within the health system. Of the remaining patients, 70.8% had a LAIA therapy duration less than 90 days, 7.2% had a therapy duration between 90 and 365 days, 12.4%

TABLE 2. Additional Patient Demographics

Index Patient Demographics	n	(%)
Age, mean, y	42	
Sex		
Male	232	(54.3)
Female	195	(45.7)
LAIA prescriber specialty		
Psychiatry	378	(88.6)
Hospitalist (inpatient)	37	(8.7)
Family medicine (outpatient)	12	(2.7)
Concurrent documented substance abuse	117	(27.4)
Concurrent documented cognitive impairment	63	(14.8)
Patients who received >1 LAIA agent during study period	8	(1.9)
Setting of injection administration		
Outpatient clinic	756	(51.1)
Inpatient psychiatric admission	588	(39.7)
Inpatient nonpsychiatric admission	136	(9.2)

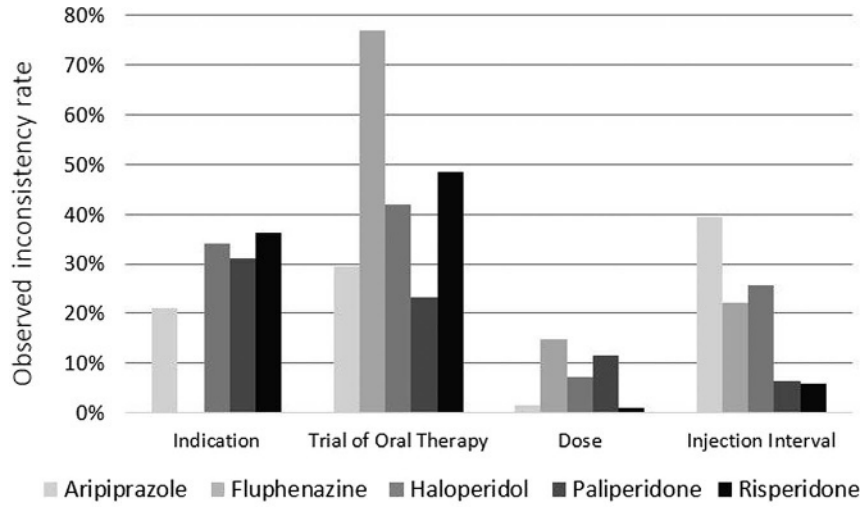

FIGURE 1. Observed rates of inconsistency between medication labeling information and clinical practice.

had a therapy duration between 1 and 2 years, and 9.6% had a therapy duration greater than 2 years.

DISCUSSION

To our knowledge, this is the first retrospective analysis to comprehensively evaluate the prescribing patterns of LAIAs within any health system. This analysis was able to identify inconsistencies between published labeling information and clinical practice for patients who received a LAIA within the health system. As a naturalistic descriptive analysis, the findings of this analysis are not conclusive for any clinical intervention. Data were analyzed and clinically evaluated to determine sources of inconsistency between published labeling information. For future studies, this analysis may be hypothesis generating and clinicians may conduct similar observations to ensure that patients are being managed appropriately within other health systems.

Several areas for inquiry were identified in this analysis. This analysis identified high rates of inadequate trial of oral therapy before administration of a LAIA. Inadequate trial of oral therapy is concerning because of the high risk of adverse effects associated with both first- and second-generation antipsychotics. Meeting the criteria for this analysis only required 1 oral dose to be given before the LAI, although true assessment for tolerability is likely to require multiple doses. Patients who received fluphenazine were identified as having the lowest trial rate of the oral formulation before receiving the LAI. Patients identified commonly received a single injection, which may have been given for acute control of psychotic symptoms. In recent years, availability of fluphenazine tablets, either from shortages or product discontinuation, has created difficulty in trialing patients on oral therapy to initially establish therapeutic efficacy and tolerability. Clinicians should judicially administer fluphenazine LAI in patients who can adequately be trialed on oral therapy or should reserve therapy for patients who have been established on long-acting fluphenazine previously. Injectable fluphenazine hydrochloride may be used for acute control of psychosis with an injectable without concerns for prolonged effect and exposure. Patients who received paliperidone were shown to have the highest rate of adequate trial of oral therapy, which likely correlates to the labeling information, allowing patients to establish tolerability via trial of oral paliperidone or risperidone. Future studies may be beneficial to evaluate the correlation and predictability of tolerance of LAIA therapy for patients who received a different drug as oral therapy than what was initiated as a LAI.

Another area of inquiry identified by this analysis was use of LAIAs outside labeled indications. The more encompassing label indication of "psychosis" for fluphenazine correlated to all patients receiving the injection to meet the criterion. Other LAIAs have finite label indications for schizophrenia and/or bipolar disorder, which resulted in more cases not meeting the criterion and documented as having an inconsistency during this review. Reasons for clinicians' selection of a LAIA may be complex owing to formulary availability, coverage of the injection in the outpatient setting, and patient preference toward adverse effect profile, injection frequency, and product familiarity.

The fundamental reason for inquiry of indication was intended to review cases where LAIAs were erroneously administered and where the usage of an antipsychotic, or additionally if a long-acting formulation, was not indicated. Two off-label indications that were commonly encountered were "major depressive disorders with psychotic features" and "major neurocognitive disorders with behavioral disturbances related to another medical condition." Oral and short-acting injectable antipsychotics may be appropriate in the acute management of these 2 disease states. Primary treatment should target the disease state that is resulting in the presence of the psychotic features. The role of LAIAs primarily serve to chronically manage conditions after tolerance and effectiveness have been established and not for acute control or initial management of psychiatric symptoms. Additional large-scale studies may be beneficial to evaluate the role of LAIAs in off-label indications and to establish when it is clinically indicated to administer a LAI in these conditions, as available literature is currently limited.

Injection frequency of LAI administration varied within the patient population of this evaluation. Notably, this evaluation was limited to LAIAs administered within our health system facilities and omitted injections that may have been given at other health systems leading to an inconsistency rate that may not be truly reflective of the patient sample. However, areas of inconsistency were still able to be identified within the patient population. For example, numerous patients were given aripiprazole at an interval of every 21 days rather than every 28 days, which is likely why it had the highest inconsistency rate for injection intervals. Paliperidone's labeling information recommends that 2 doses be given 1 week apart. In some cases, the

2 doses were given closer than recommended, even when accounting for the ±4 days permitted in the labeling information.

Maintaining appropriate injection frequencies for LAIAs may be beyond the capabilities of clinicians and furthermore may rely on patient compliance and follow-up. Providers may prescribe and schedule injections at the recommended frequency, but patients may require rescheduling owing to personal conflicts (eg, work, family emergencies, lack of transportation) as well as if patients lack follow-up habitually. In addition, for some patients, the effects of the medication may decrease toward the latter part of the injection period if they are a rapid or extensive metabolizer of the medication. Clinicians may have to make patient-specific adjustments to injectable frequency in attempt to maintain adequate therapy. Shorter intervals may be used to ensure that patients maintain adequate response to the medication. Within this analysis, patients discharging from an inpatient facility or who travel long distance to a clinic may have been given their injection early by encompassing it within the current admission/visit to reduce missed doses.

In regard to the observed consistency of dosing within this analysis, fluphenazine and haloperidol had multiple patient cases where a higher initial dose of the LAI was administered than recommended in the labeling information. Some second-generation LAIAs (eg, paliperidone) are initiated with a larger dose(s) to rapidly establish therapeutic plasma concentrations; however, this is not commonly done with first-generation agents owing to adverse side effects and desire to establish tolerability with the long-acting agent. This analysis identified 1 fluphenazine and 1 haloperidol patient who inadvertently received the decanoate formulation instead of the short-acting injectable. Ordering clinicians and ancillary staff should know the pharmacokinetic and indication differences between the formulations and be alerted to the contingency for medication errors. Paliperidone had a higher inconsistency rate for prescribed dose within this analysis, which commonly correlated to omitted dose adjustments for renal impairment, including patients who received paliperidone with a creatinine clearance less than 50 mL/min, for which use is not recommended.

Although patients in this analysis were observed to have received higher doses than recommended, it is clinically important to acknowledge that patients enrolled and studied in clinical trials, and to which the labeling information is based, may not reflect patients in a naturalistic setting. Patients who are more symptomatic and have additional psychological comorbidities are commonly excluded from clinical trials. For these patients, higher doses may be clinically necessary to obtain an adequate response. In addition, patients may have received higher doses as a measure to reduce polypharmacy with oral and LAI therapy. Because monotherapy with a LAI is a goal of therapy, patients may have received a higher dose within this study to achieve this measure; however, complete assessment of polypharmacy was outside the scope of this analysis.

Inconsistencies in titration methods performed by clinicians most often resulted with paliperidone when different doses for initial therapy were used than what was recommended. Initial therapy for paliperidone serves to establish therapeutic plasma levels without the need for additional oral supplementation, and labeling information provides a more structured titration schedule to establish initial therapy with the LAI. If clinicians deviated from the recommended dosing schedule, it was regarded as an inconsistency from labeling information for this analysis.

Within the secondary endpoints evaluated, we believed that the rate of readmissions was reflective of common practice. Previous data have reported rates between 5% and 52.8%,[3] whereas the observed readmission rate for this analysis was 20.2%. This analysis found that approximately half of the patients who had a LAIA administered did not receive an additional injection or did not follow up within the health system. For patients that followed up within the health system, a majority had a LAIA treatment duration less than 90 days. It would be expected that LAIAs would provide improved adherence to therapy, but this was not identified within this analysis. Two factors were identified, which may provide justification for the appearance of short therapy duration within this analysis.

First, as discussed earlier, some patients received a LAIA as inappropriate therapy to control acute psychiatric conditions during an inpatient stay. These patients were only administered 1 injection to control symptoms during the inpatient stay and were not prescribed a LAIA as continued therapy. In addition, some patients captured in this analysis could have been placed under care by a court-ordered involuntary commitment and may have received a single injection of a LAIA to prepare the patient for discharge. This may be done as an attempt to reduce readmission and improve adherence when patients are released from involuntary holds. It is less common in our patient population to encounter court-ordered, involuntary treatment to enforce continued LAIA therapy in the outpatient setting. Second, there are other outpatient mental health facilities within close proximity that patients may have transitioned care to when receiving subsequent administrations. This may have resulted in a falsely lower documented therapy duration than what actually occurred. Future studies and additional resources would be beneficial to determine reasons for decreased adherence and identify methods to improve compliance with medication therapy and to address follow-up barriers.

This analysis has several limitations. As a single health system review, this analysis only captured patients who had a LAIA administered at one of the health systems' hospitals or clinics. Patients who received an injection or transferred care to another outpatient facility were not able to be accounted for. Data collection was limited to information documented or identifiable from the patients' electronic medical record because this analysis was done as a retrospective review. Usage rates were not evenly distributed among LAIAs, which may contribute to patient assistance programs available within the health system, which provides added assistance for paliperidone and risperidone. Lastly, this analysis was not able to account for inconsistencies due to adjustments deemed medically necessary by the clinician, but acknowledgment for possible reasons for inconsistencies was noted within this analysis.

Despite this being a retrospective single-center review, this analysis offers insight into the naturalistic prescribing of LAIAs. This analysis was able to identify areas of inconsistency between medications' labeling information and clinical practice. Clinically, off-label usage and dosing of LAIAs may be commonly done if patient factors and clinical scenarios dictate deviation from labeling information. This analysis offers perspective into the data trends identified within the study population and discusses possible causations for identified inconsistencies and possible correlations to patient care. This analysis may be hypothesis generating for future studies because additional research is needed to better understand how variances in naturalistic prescribing of LAIAs in practice can impact clinical outcomes with common psychiatric conditions.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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