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Evaluation of oral antipsychotic supplementation of select second-generation long-acting injectable antipsychotics in an acute-care psychiatric setting

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Abstract

Introduction: Long-acting injectable (LAI) antipsychotics were developed to increase medication adherence in patients with schizophrenia. The US Food and Drug Administration (FDA)-approved LAI dosing provides guidance regarding oral antipsychotic supplementation. Previous studies have concluded concomitant use of oral and LAI antipsychotics requires further investigation. The aim of this study was to examine oral antipsychotic supplementation among patients receiving select second-generation LAIs.

Methods: Patients were included if they were admitted to an inpatient psychiatric unit and received a second-generation LAI. The primary outcome was to determine the percentage of patients receiving oral antipsychotic supplementation prescribed in accordance with FDA recommendations. Secondary outcomes described oral supplementation prescribed in an inconsistent manner with FDA recommendations and identified patient-specific predictors associated with oral supplementation prescribed consistent with FDA recommendations.

Results: Of the 422 patients evaluated, 376 patients met inclusion criteria. Oral supplementation was prescribed in a manner consistent with FDA recommendations in 30% of patients. The following predictors were associated with oral supplementation prescribed in accordance with FDA recommendations: LAI initiation (odds ratio 1.868, 95% confidence interval 1.120-3.125) and the use of the once-monthly paliperidone LAI (odds ratio 20.278, 95% confidence interval 10.472-39.873).

Discussion: In the patient population evaluated, oral supplementation of LAI antipsychotics were prescribed in 30% of patients in a manner consistent with FDA recommendations. Of the patients who were prescribed oral antipsychotic supplementation inconsistent with FDA labeling, 223 patients were prescribed oral supplementation longer than the recommended duration and 8 patients received oral supplementation for a shorter duration than recommended.

Keywords: long-acting injectable antipsychotic, oral antipsychotic supplementation, second-generation antipsychotic

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Introduction

Long-acting injectable (LAI) antipsychotics were developed to increase medication adherence in patients with schizophrenia.[1-3] All LAI antipsychotics are indicated for schizophrenia. Furthermore, aripiprazole monohydrate and risperidone LAIs are indicated for bipolar I disorder, and once-monthly paliperidone LAI is indicated for schizoaffective disorder.[4-9] Benefits of LAIs in schizophrenia include improved medication adherence, reduced relapse rates, and fewer hospitalizations.[10-16] Second-generation LAIs, notably risperidone and once-monthly paliperidone, have been found to be cost-effective for the treatment of schizophrenia as compared with oral formulations or first-generation LAI antipsychotics.[3,11,12,17,18]

The US Food and Drug Administration (FDA) labeling provides specific guidance regarding oral supplementation when initiating LAIs.[4-9] Establishing tolerability to the oral dosage form is recommended before initiating treatment with all LAIs.[4-9] The FDA-approved dosing for aripiprazole monohydrate LAI recommends oral therapy for 14 days after initiation.[4] Risperidone and aripiprazole lauroxil FDA-approved dosing recommends oral therapy for 21 days following the first injection.[5,6] An alternative FDA-approved initial dosing strategy for aripiprazole lauroxil is to administer one 30-mg oral aripiprazole dose plus 1 intramuscular aripiprazole lauroxil 675-mg dose in addition to the aripiprazole lauroxil LAI dose.[7] Once-monthly paliperidone and olanzapine pamoate FDA-approved dosing recommends discontinuation of oral antipsychotics at LAI initiation.[8,9]

Although clinical practice may deviate from approved dosing, several concerns arise from off-label use. Antipsychotic polypharmacy may result if the oral antipsychotic is not discontinued after the recommended time frame. Increased adverse effects, including a higher rate of metabolic syndrome, dry mouth, and use of anticholinergic agents to prevent or treat extrapyramidal symptoms, have been reported secondary to antipsychotic polypharmacy.[19-21] Increased cost of therapy due to multiple medications is another potential concern.[9] Conversely, subtherapeutic antipsychotic therapy may occur if oral supplementation is not continued throughout the recommended time frame, possibly leading to a decline in symptom control.[22]

Boaz et al[22] evaluated the use of risperidone LAI compared with FDA recommendations. The study found that 48% of the 3364 participants were prescribed oral supplementation for the first 21 days as recommended; however, oral supplementation continued after 21 days in 43% of participants. The study characterized factors associated with early risperidone LAI discontinuation, including absence of oral supplementation for the first 21 days, substance use disorder diagnosis, and male sex. Overall, the study identified discrepancies in risperidone LAI prescribing practices that may have reduced perceived effectiveness and tolerability.[22]

Aggarwal et al[23] evaluated concomitant use of oral and LAI antipsychotics, including fluphenazine decanoate, haloperidol decanoate, and risperidone over a 1-year time period. Among 124 patients receiving LAIs, 46% received combination oral and long-acting therapy. Hispanic ethnicity and alcohol abuse or dependence showed greater use of concurrent oral and injectable therapy. The study concluded concomitant use of oral and LAI antipsychotics occurred frequently and merits further investigation.[23]

Doshi et al[24] evaluated concomitant oral antipsychotic prescriptions with routine use of LAIs, including haloperidol decanoate, fluphenazine decanoate, once-monthly paliperidone, and risperidone at posthospital discharge in an observational, retrospective cohort study. A total of 340 patients were included, and 75.9% of patients were given concurrent oral antipsychotic prescriptions in the 6 months posthospital discharge. Once-monthly paliperidone had the lowest and risperidone had the highest rates of concurrent oral antipsychotic prescribing. The authors concluded further study is required to characterize concomitant use of oral and LAI antipsychotics.[24]

Whereas previous studies[22-24] have indicated that fluphenazine, haloperidol, risperidone, and once-monthly paliperidone LAIs require further investigation into the rates of concomitant oral and LAI therapy, no studies were identified that evaluated oral supplementation with aripiprazole monohydrate, aripiprazole lauroxil, or olanzapine pamoate LAIs. There may be patient-specific predictors associated with oral supplementation prescribed in a manner consistent with FDA recommendations. Therefore, the objective of this study was to examine oral supplementation among patients receiving select second-generation LAIs.

Materials and Methods

This was a retrospective, single-center chart review completed at a community teaching hospital with 55 inpatient psychiatric beds. The study was approved by the health system's institutional review board. Pharmacy records were accessed to identify patients who were admitted to psychiatry and received at least 1 dose of aripiprazole monohydrate, risperidone, or once-monthly paliperidone LAI between December 1, 2009, and November 30, 2014. Exclusion criteria included age less than 18 years and pregnancy. Aripiprazole monohydrate

TABLE: Patient demographics of the current study

Variable	No. (%) Patients, n = 376
Age <65 y	362 (96.2)
White	237 (63)
Length of stay ≥10 d	208 (55.3)
Male	203 (54)
Psychiatric diagnoses	
Bipolar disorder	26 (6.9)
Borderline personality disorder	44 (11.7)
Major depressive disorder	7 (1.9)
Schizophrenia	349 (92.8)
Substance use disorder	201 (53.5)

LAI was evaluated for 18 months, which corresponded to its availability on the US market. Data collection included 12 months (December 1, 2013, to November 30, 2014) for paliperidone LAI secondary to frequent prescribing at the health system. Risperidone LAI was evaluated for the entire study period. The olanzapine pamoate, aripiprazole lauroxil, and 3-month paliperidone LAIs were not evaluated due to nonformulary status at the health system. First-generation LAI antipsychotics were not evaluated due to infrequent prescribing at the health system.

The primary outcome was to determine the percentage of patients receiving oral antipsychotic supplementation in a manner consistent with FDA recommendations. Two secondary outcomes were evaluated. The first was to determine the percentage of patients receiving oral antipsychotic supplementation prescribed in a manner inconsistent with FDA recommendations in terms of the amount of time on oral therapy (ie, longer than recommended, shorter than recommended, or oral antipsychotic added to maintenance LAI therapy). If patients were discharged prior to the recommended time frame for oral supplementation, the discharge medication reconciliation form, discharge medication list, and discharge summary were evaluated for instructions to discontinue oral therapy after the recommended interval. If no documentation was included in the hospital medical record, the patient was determined to have oral supplementation prescribed inconsistent with recommendations. Additionally, patient-specific predictors were evaluated to identify associations with oral supplementation prescribed in a manner consistent with recommendations. These predictors included age, sex, race, third-party coverage, prescriber, length of stay, LAI received, LAI initiation, and psychiatric diagnoses, including schizophrenia spectrum and other psychotic disorders, bipolar disorders, major depressive disorder, borderline personality disorder, and substance use disorders.

All data were collected via electronic medical records and recorded in Microsoft Excel® (Redmond, WA). Patients received a numerical identifier to maintain confidentiality. Primary and secondary outcomes were analyzed using descriptive statistics. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for each patient-specific predictor to determine if an association with oral antipsychotic supplementation prescribed consistent with FDA recommendations was present.

Results

During the study period, 422 patients were evaluated for inclusion in the study, and 46 patients were excluded. Reasons for exclusion included patient not admitted to an inpatient psychiatric unit (25 patients), LAI prescribed but not administered (20 patients), and pregnancy (1 patient). Therefore, 376 patients were included for analysis. Baseline demographics are described in the Table. Aripiprazole monohydrate, once-monthly paliperidone, and risperidone LAIs were prescribed in 5.3% (n = 20), 44.5% (n = 167), and 50.2% (n = 189) of patients, respectively.

Primary Outcome

Oral antipsychotic supplementation was prescribed in a manner consistent with FDA recommendations in 30% (n = 113) of patients included in the study. Of the 30% who were prescribed oral supplementation in accordance with FDA recommendations, 88% (n = 99) received once-monthly paliperidone LAI, 7% (n = 9) received risperidone LAI, and 5% (n = 5) received aripiprazole monohydrate LAI.

Secondary Outcomes

Oral supplementation was prescribed inconsistent with FDA recommendations in 70% (n = 263) of patients. Of these patients, 69% (n = 182), 26% (n = 68), and 5% (n = 13) of patients were prescribed risperidone, once-monthly paliperidone, and aripiprazole monohydrate LAIs, respectively. Oral supplementation was prescribed longer than the recommended duration in 85% (n = 223), shorter than the recommended duration in 3% (n = 8), and prescribed in addition to maintenance LAI therapy in 12% (n = 32) of patients.

Patient-specific predictors associated with oral supplementation prescribed in a manner consistent with FDA recommendations include LAI initiation during the inpatient admission (OR 1.868, 95% CI 1.12-3.125) and use of the once-monthly paliperidone LAI (OR 20.278, 95% CI 10.472-39.873). No other patient-specific predictors were

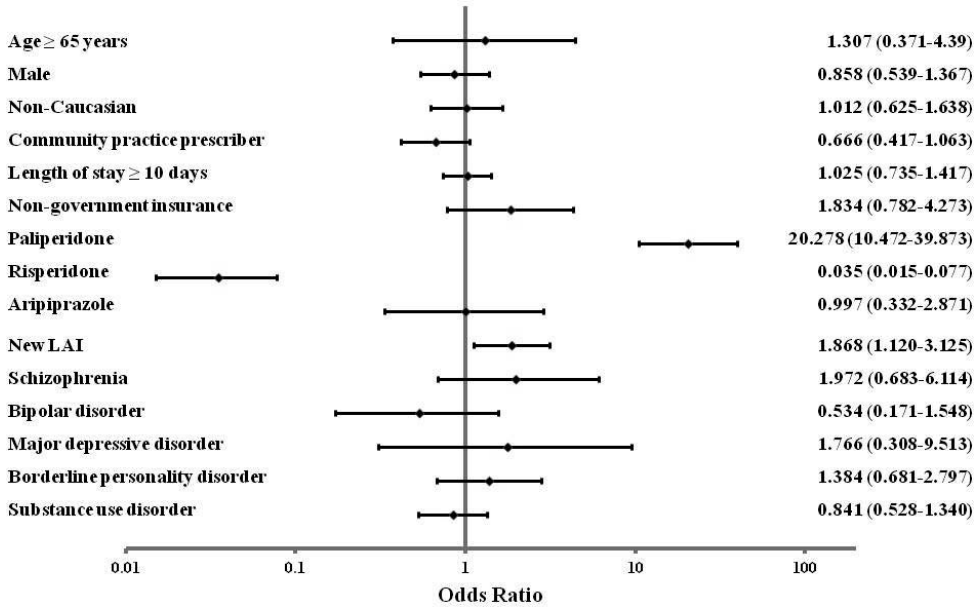

FIGURE: Patient-specific predictors of oral supplementation prescribed consistent with Food and Drug Administration recommendations (error bars represent 95% confidence intervals and schizophrenia includes schizophrenia spectrum and other psychotic disorders; LAI = long-acting injectable)

associated with oral supplementation prescribed in a manner consistent with FDA recommendations (Figure).

Discussion

Most patients included in this study did not receive oral antipsychotic supplementation in a manner consistent with FDA recommendations. These results are similar to previous studies[22-24] on concomitant use of oral and LAI antipsychotics. Oral supplementation was prescribed for longer than FDA recommendations in most cases.

Long-acting injectable initiation during an inpatient admission and the use of once-monthly paliperidone LAI were the two patient-specific predictors associated with oral antipsychotic supplementation prescribed in a manner consistent with FDA recommendations. Unlike patients initiated on LAIs, patients receiving maintenance LAI therapy who are admitted to an inpatient psychiatric unit were more likely to be prescribed additional oral therapy. This practice may be in attempt to augment treatment secondary to refractory symptoms. The use of once-monthly paliperidone LAI and consistent FDA-recommended oral supplementation could be because oral supplementation is not necessary once paliperidone LAI therapy is initiated. Furthermore, length of stay did not impact the ability to evaluate oral supplementation of paliperidone LAI. Additionally, it is possible that the recommendation is easier to follow, and therefore, prescribers may be more likely to prescribe according to FDA recommendations.

Use of risperidone LAI was not found to be a predictor of recommended oral antipsychotic supplementation. Several factors may have contributed to this finding. Many patients were discharged prior to completion of the 21-day recommended time frame for oral supplementation. It is possible that a subset of patients were instructed to discontinue oral therapy as an outpatient. If this occurred, the discontinuation instructions were not documented in the medical record, and these patients were included in the oral supplementation prescribed longer than recommended group. Additionally, risperidone LAI was the first available second-generation LAI, and prescribers may have gained more clinical experience with its use and subsequently developed individualized prescribing practices.

Use of aripiprazole monohydrate LAI was also not found to be a predictor of recommended oral antipsychotic supplementation. Due to its low usage, limited conclusions can be made regarding current prescribing practices. Similar to risperidone LAI, many patients prescribed aripiprazole monohydrate LAI were discharged prior to completion of the 14-day recommended time frame for oral supplementation, which may have impacted results.

This study has limitations that should be considered when interpreting the results. It was a single-center study, and the results may not be applicable to other institutions. The reliability of medical records due to the retrospective chart review design may have influenced the results. Many patients were discharged prior to the end of the recommended time frame for oral supplementation, and

the study could not account for patients who may have continued or discontinued oral therapy appropriately as an outpatient. Patients were included for evaluation if they received a second-generation LAI during an inpatient psychiatric admission. If a patient was not due to receive a maintenance injection while hospitalized, the patient was not evaluated. Therefore, the true incidence of oral supplementation added to maintenance therapy may be underrepresented. Also, the length of time that each medication was evaluated differed, and it is possible prescribing practices evolved over time. Oral antipsychotics may have been prescribed for indications independent of the LAI; for example, the oral antipsychotic may have been prescribed for an off-label use, such as insomnia. Finally, doses of oral and LAI antipsychotics were not collected. Although antipsychotic dosing may influence the use of oral supplementation, this analysis focused on prescriber adherence to the FDA's recommendation for oral supplementation duration.

In conclusion, oral supplementation of LAI antipsychotics was prescribed in a manner consistent with FDA recommendations in 30% of included patients. Oral supplementation is most often prescribed for a longer duration than what is recommended. Two patient-specific predictors, LAI antipsychotic initiation during an inpatient psychiatric admission and use of the once-monthly paliperidone LAI, were each associated with oral supplementation prescribed consistent with recommendations. Overall, this study enhances the limited literature available regarding oral antipsychotic supplementation of LAIs.

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