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Appropriate use of single-dose injectable aripiprazole lauroxil in the treatment of schizophrenia

Rachael C. Davis, BS[1]; Jianing Xu, MS[2]; Daniel B. Hall, PhD[3]; Xianyan Chen, PhD[4]; Michaelyn M. Moretz[5]; Henry N. Young, PhD[6]; Joshua Caballero, PharmD, BCPP, FCCP[7]

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Abstract

Introduction: Single-dose injectable aripiprazole lauroxil (SDIAL) is used with long-acting injectable (LAI) aripiprazole lauroxil in the treatment of schizophrenia. SDIAL can be used to either initiate treatment or supplement during maintenance when follow-up doses are not given within labeling recommendations. The primary objective was to determine the usage and appropriateness of SDIAL between the initiation and the maintenance supplementation use in a Medicaid database. The secondary objective was to determine the overall associated costs with the potentially inappropriate use of LAI aripiprazole lauroxil.

Methods: International Classification of Diseases, 10th edition codes were used to identify adult patients with schizophrenia and related disorders (18-64 years) who received SDIAL and/or LAI aripiprazole lauroxil between 2018 and 2020 using MarketScan Medicaid databases. The appropriateness of SDIAL was determined by package insert labeling timelines for treatment initiation and maintenance supplementation. Two authors independently reviewed each SDIAL claim for appropriateness. Descriptive statistics were used to analyze the data.

Results: After excluding possible billing errors, a total of 582 claims were identified for SDIAL. Of these, 21% were potentially inappropriate, with a higher proportion occurring during the maintenance phase. Overall, potential inappropriate use resulted in costs over $307 000.

Discussion: It appears that prescribers should be better educated on the appropriate use of SDIAL during maintenance supplementation.

Keywords: long-acting injectable antipsychotics, aripiprazole lauroxil, schizophrenia

[1] Pharmacy Student, College of Pharmacy, University of Georgia, Athens, Georgia, ORCID: https://orcid.org/0009-0007-1645-9560; [2] PhD Student, Department of Statistics, Franklin College of Arts and Sciences, University of Georgia, Athens, Georgia, ORCID: https://orcid.org/0000-0002-3891-8867; [3] Professor and Director, Statistical Consulting Center, Department of Statistics, Franklin College of Arts and Sciences, University of Georgia, Athens, Georgia, ORCID: https://orcid.org/0000-0003-2543-2400; [4] Assistant Professor, Department of Epidemiology and Biostatistics, Franklin College of Arts and Sciences, University of Georgia, Athens, Georgia, ORCID: https://orcid.org/0000-0002-1806-0883; [5] Pharmacy Student, College of Pharmacy, University of Georgia, Athens, Georgia, ORCID: https://orcid.org/0009-0007-9729-5480; [6] Department Head and Kroger Professor, Department of Clinical and Administrative Pharmacy, College of Pharmacy, University of Georgia, Athens, Georgia, ORCID: https://orcid.org/0000-0002-4803-3288; [7] (Corresponding author) Associate Professor, Department of Clinical and Administrative Pharmacy, College of Pharmacy, University of Georgia, Athens, GA, joshua.caballero@uga.edu, ORCID: https://orcid.org/0000-0003-4406-2425

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Introduction

Adherence to antipsychotic medications for patients with schizophrenia may play a role in improving quality of life and preventing recurrent hospitalizations.[1] Research shows the majority of neurodegenerative damage associated with schizophrenia occurs within the first five years of onset.[2] Once patients experience a single relapse, the probability of a future relapse increases. Frequent relapses further extend the time until the patient reaches remission and allow further neuro-degenerative damage to escalate. Therefore, decreasing the

relapse rate and improving adherence are critical. The relapse rate in patients with schizophrenia on oral antipsychotics is approximately 82% within 5 years.[3] Studies examining adherence rates among oral antipsychotic users suggest that 40% to 60% are considered partially or totally nonadherent.[4-6] In general, data show approximately 74% of patients with schizophrenia discontinue treatment before 1.5 years.[7] As a result, identifying strategies to improve medication adherence in schizophrenia may be needed.

Long-acting injectable (LAI) antipsychotics are used to treat patients with mental illnesses such as schizophrenia, bipolar disorder, and other psychiatric disorders. LAI antipsychotics may offer the advantage of prolonged and sustained drug release, allowing for consistent therapeutic concentrations. As a result, LAI antipsychotics may be candidates for nonadherent patients or those prone to relapse. Data suggest LAI antipsychotics may be a viable solution to improving patient adherence and decreasing relapse rates.[8-10] For example, 1 meta-analysis study suggested LAI antipsychotics prevented hospitalization (16 studies, $N = 4066$; risk ratio = 0.43; 95% CI = 0.35, 0.53; $P < .001$) vs. oral antipsychotics.[8] A small study suggested a significant advantage for patients on an LAI antipsychotic who experienced a higher average proportion of days with medication (76%) compared with patients on an oral antipsychotic regimen (32%; $P < .001$).[10] In summary, LAI antipsychotics may decrease the daily burden associated with oral medications and increase medication adherence by promoting the convenience of a single injection ranging between several weeks to several months.

Aripiprazole lauroxil is a LAI antipsychotic indicated for the treatment of schizophrenia in adults. Depending on the dose, LAI aripiprazole lauroxil can be administered to patients at 4, 6-, or 8-week intervals.[11] At the start of treatment, patients currently have 2 options to initiate treatment with LAI aripiprazole lauroxil. One is an oral aripiprazole dose for 21 consecutive days, with the first LAI aripiprazole lauroxil dose.[12,13] Another initiation option is using single-dose injectable aripiprazole lauroxil (SDIAL).[12,13] SDIAL is a 1-time 675 mg injection approved by the FDA in 2018 with the goal of improving adherence by bypassing the need for oral overlap. It is given in combination with a single 30-mg oral dose of aripiprazole before or at the same time as starting LAI aripiprazole lauroxil. SDIAL may also be administered to patients who missed a follow-up scheduled LAI aripiprazole lauroxil dose within the dosing timeframe required to reinitiate LAI aripiprazole lauroxil.[14] As a result, SDIAL may reduce the reinitiation period by allowing patients to receive a single injection to remain on schedule.

While LAI aripiprazole lauroxil is proposed to improve adherence, patients may miss follow-up appointments that require rescheduling and following manufacturing guidelines for maintenance treatment. The dosing window and whether SDIAL is needed to establish treatment continuation during follow-up visits vary depending on the LAI aripiprazole lauroxil dose.[14] The different time frames between doses may lead to confusion regarding administration. Therefore, inappropriate subsequent SDIAL doses given during the maintenance phase may impact adherence or outcomes. Data are lacking on how often SDIAL is properly used when initiating treatment. There are also no data reporting if the inappropriate use of SDIAL may impact costs. Therefore, the primary objective of this study was to determine the usage and appropriateness of SDIAL between initiation and maintenance supplementation use. The secondary objectives were to determine differences in demographic characteristics between appropriate and potentially inappropriate use and associated costs with the potentially inappropriate use of SDIAL.

Methods

Study Design and Data Sources

For the purpose of this study, data claims were used from Merative® MarketScan® Multi-State Medicaid Databases (referred to hereafter as the MarketScan Medicaid Database) between January 1, 2018, and December 31, 2020. The MarketScan Medicaid Database contains longitudinal records of prescription drug claims and services for millions of inpatient and outpatient enrollees. The database provides valuable insights into the treatment patterns across diverse patient populations. Medical claims obtained included the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) diagnosis codes. Regarding pharmaceutical claims, data included National Drug Code numbers for dispensed SDIAL and LAI aripiprazole lauroxil. University institutional review board approval was obtained.

Study Population and Cohort Assignment

MarketScan Medicaid Database was used to identify patients between the ages of 18 and 64 receiving SDIAL with or without LAI aripiprazole lauroxil between January 2018 and December 2020. Based on previous studies evaluating LAI antipsychotics in schizophrenia using claims databases, qualifying patients had 1 or more inpatient or 2 or more outpatient claims containing an ICD-10-CM diagnosis code for schizophrenia (F20.x), schizotypal (F21), or schizoaffective (F25.x).[15-17] The index date was established as the date of their first LAI aripiprazole lauroxil prescription, which had to occur subsequent to the initial diagnosis. A refill date was defined as the fill date plus the coverage period, which varies by LAI aripiprazole lauroxil dose (eg, 4-8 weeks). Package insert (ie, SDIAL labeling) timelines determined the appropriateness of SDIAL administration on both treatment initiation (ie, 10-day timeframe) and maintenance supplementation (ie, 6- to 12-week timeframe).[14] Miscellaneous potential inappropriateness was identified as SDIAL given as a single dose without any LAI

TABLE: SDIAL supplementation recommendation after missed doses of aripiprazole lauroxil[a]

Dose of Last LAI Aripiprazole Lauroxil	Length of Time Since Last LAI Aripiprazole Lauroxil Injection, Weeks		
441 mg	≤6	>6 and ≤7	>7
662 mg	≤8	>8 and ≤12	>12
882 mg	≤8	>8 and ≤12	>12
1064 mg	≤10	>10 and ≤12	>12
Recommended supplementation dosage	No supplementation	Administer SDIAL	Administer SDIAL and single-dose oral aripiprazole 30 mg

LAI = long-acting injectable; SDIAL = single-dose injectable aripiprazole lauroxil.
[a]Adapted from aripiprazole lauroxil (Aristada) website and Aristada Initio package insert.

antipsychotic, given with another LAI antipsychotic, or used outside ± 90 days of LAI aripiprazole lauroxil use. Therefore, 3 categories of potentially inappropriate use were defined as follows: initiation, maintenance supplementation, and miscellaneous. The appropriateness of SDIAL was determined by cross-referencing data from identified patients. An initial fill was determined by the first LAI aripiprazole lauroxil dose received, while a maintenance supplemental dose was identified as a subsequent dose after initiation of LAI aripiprazole lauroxil (ie, second dose or greater). To ensure accuracy, 2 authors (MM, JC) independently reviewed each claim for appropriateness. Afterward, they met to discuss any differences and determine the appropriate classification. Demographic characteristics were determined via descriptive statistics. Differences in demographic characteristics between appropriate and potentially inappropriate SDIAL use were evaluated using nonparametric tests (ie, Pearson's χ^2 test, Wilcoxon rank sum test, and Fisher's exact test) with a P value $< .05$. Demographics characteristics included age at first diagnosis, sex, race/ethnicity, and plan type. The average wholesale price (AWP) was determined using appropriate pricing resources (ie, drugs.com price guide).

Results

Initially, a total of 599 claims were identified. After excluding for potential billing errors ($n = 17$), a total of 582 claims were identified for SDIAL and further analyzed. Complete demographic information were available for 531 patients. Overall, the mean age was approximately 37.6 ± 12 years, and 59% were male. The distribution of race/ethnicity was 49% White, 46% Black, approximately 3% Hispanic, and approximately 2% other. Approximately, 56% of the sample were on a health maintenance organization plan and 44% were on comprehensive plans. Of the 582 claims, 459 (79%) SDIAL doses were appropriately used and included 458 during initiation phase and 1 during maintenance phase. There were 123 (21%) SDIAL claims that were potentially inappropriate, which included 47 occurring during initiation, 47 during maintenance supplementation, and 29 miscellaneous occurrences. The miscellaneous uses included 19 cases of use without any LAI antipsychotic administered within 12 months, 6 cases of use with a LAI antipsychotic used between 4 and 6 months, and 4 cases in which another LAI antipsychotic (ie, haloperidol decanoate, aripiprazole monohydrate, paliperidone palmitate, or risperidone microspheres) was used within 3 weeks of SDIAL use. No differences in demographic characteristics (eg, age, race/ethnicity, sex, plan type) were noted between appropriate and inappropriate use. Based on AWP pricing ($2499/SDIAL 675 mg/2.4 mL unit), total potential inappropriate use resulted in costs of $307 377.

Discussion

To our knowledge, this is the first study exploring the real-world usage of SDIAL during initiating and maintaining LAI aripiprazole lauroxil. Overall, it appears SDIAL was potentially inappropriately administered in 9% of cases (47/506) during initiation and 98% of cases (47/48) during the maintenance phase. Given the disparity of potential inappropriate use, the results suggest more education is needed regarding the maintenance phase because a higher proportion of potentially inappropriate use occurred during this phase. The potentially inappropriate use during the maintenance phase may be due to the different timeframes between doses, which may cause confusion among prescribers and healthcare practitioners. For treatment initiation, SDIAL is used concurrently on the same day or *within 10 days before* LAI aripiprazole lauroxil is administered (regardless of the dose).[14] However, proper administration of SDIAL during maintenance is dependent on the LAI aripiprazole lauroxil current dose and the length of time since it was last administered. The Table displays routine and missed dosage administration schedules. Additionally, there were 29 potentially inappropriate miscellaneous uses of SDIAL. These cases either fell outside ± 90 days of LAI aripiprazole lauroxil administration or were given as a random dose with no dose of LAI aripiprazole lauroxil. A possible explanation may be that prescribers were planning on initiating LAI aripiprazole lauroxil but, after giving SDIAL, did not for multiple reasons (eg, transition of care, patient attrition, LAI aripiprazole lauroxil procurement issues). Despite the low incidence, for initiation, practitioners should be reminded that LAI aripiprazole lauroxil should be given within 10 days after SDIAL administration. LAI aripiprazole lauroxil should be secured beforehand and possibly administered

concurrently with SDIAL on the first day to mitigate the risk of missing the initial administration window.

At this time, data are lacking if the potentially inappropriate use of SDIAL leads to negative consequences (eg, greater discontinuation rates, adverse effects). However, SDIAL, when used appropriately, has been shown to successfully reduce symptoms of schizophrenia.[18] More recently, a real-world study focusing on the proper use of SDIAL with aripiprazole lauroxil showed reductions in the emergency room and inpatient admissions.[19] The study compared healthcare resource usage 6 months before versus 6 months after receiving LAI aripiprazole lauroxil with SDIAL initiation.[19] Overall, mental health–related emergency room visits and inpatient admissions decreased by approximately 25% ($P < .001$).[19] Additionally, results from exploratory self-administered satisfaction surveys stated patients using SDIAL had an overall high satisfaction, stable quality of life, and decreased caregiver burden.[18] Outside of localized pain/redness at the injection site, the reported safety profile of SDIAL is consistent with known adverse reactions of LAI aripiprazole lauroxil.[14] However, studies addressing other acute side effects of SDIAL administration are lacking.

Overall, the effectiveness of LAI antipsychotics can be further explored by comparing LAI agents that require oral overlap initiation with those that do not. Based on individual manufacturer recommendations, oral overlap is recommended for specific LAI antipsychotics to rapidly achieve or maintain a concentration within the therapeutic window.[20,21] For example, LAI aripiprazole monohydrate, risperidone microspheres, and fluphenazine decanoate typically require oral overlap, while LAI olanzapine pamoate, paliperidone palmitate, and risperidone subcutaneous do not.[20,21] Currently, Aripiprazole lauroxil is the exception with both initiation strategies.[11,14] Additionally, confusion may occur between both LAI aripiprazole formulations. Currently, LAI aripiprazole monohydrate requires a 14-day oral overlap of aripiprazole after the first injection.[22] Upon initiation of LAI aripiprazole lauroxil, patients and providers may choose between a 21-day oral overlap or an SDIAL with a single-dose 30-mg oral dose of aripiprazole.[11,12] A comparison between the SDIAL and the oral overlap treatment group showed blood plasma levels to be comparable at day 21.[12] However, the assigned oral overlap group experienced a decline in aripiprazole concentrations after day 21. Aripiprazole blood plasma concentrations in the SDIAL group did not experience a decline until day 30.[12] Therefore, the SDIAL appears to provide an extended period of coverage compared with the oral overlap. Regardless, efficacy was not significantly different during the study period when using the SDIAL or 21-day aripiprazole oral starting regimen. Also, while these studies were done in a controlled environment, the potentially inappropriate use of SDIAL found in our "real-world" scenario can affect concentrations, leading to suboptimal efficacy or side effects that may impact discontinuation. However, future studies are needed to corroborate findings.

Limitations

Limitations of this study may include but are not limited to coding errors (eg, omission, commission) and reporting bias. We attempted to mitigate this concern by excluding potential billing errors. In our study, we excluded 17 claims due to SDIAL being dosed twice on the same day ($n = 3$) and SDIAL given 1 day *after* LAI aripiprazole lauroxil ($n = 14$) administration as opposed to the same date or within 10 days prior. However, this was done to account for the possibility that a claim may have been processed 1 day late when LAI aripiprazole lauroxil was administered correctly. Therefore, the data present a conservative measure evaluating SDIAL appropriateness.

Additionally, the severity of schizophrenia could not be identified because of obtaining a diagnosis via billing codes. The discontinuation between appropriate and inappropriate use was not possible because of small sample sizes, which would lack power. As such, reasons for discontinuing could not be appropriately determined based on the nature of available data. This could be addressed if there was access to a longer study period to obtain a larger data set. Additionally, the nature of inappropriate use has been defined as "potential" given package insert recommendations were used, which may not always be followed given the specific needs of individual patients. Similar to other data,[19] this study did not evaluate the use of oral aripiprazole 30 mg during initiation. However, the study objective was to identify the proper use of SDIAL and not address efficacy or adherence after LAI aripiprazole lauroxil initiation. Finally, as with all claims data, the possibility of the SDIAL being administered but not billed could be a limiting factor, thereby limiting the sample size.

Conclusion

At this time, it appears that healthcare providers should be better educated on the appropriate use of SDIAL, especially for supplementation during the maintenance phase. Future studies may evaluate whether potentially inappropriate use may impact discontinuation rates due to the lack of efficacy or lead to more unwanted side effects.

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