COLLEGE OF PHARMACY
UNIVERSITY OF UTAH

L. S. SKAGGS PHARMACY INSTITUTE

UTAH MEDICAID DUR REPORT
OCTOBER 2024

ADHERENCE TO LONG-ACTING INJECTABLE OR ORAL ANTIPSYCHOTICS

A RETROSPECTIVE UTILIZATION REVIEW

Report finalized: September 2024
Report presented: October 2024

Drug Regimen Review Center

Monet Luloh, PharmD, Clinical Pharmacist
Jacob Crook, MStat, Data Analyst
Lauren Heath, PharmD, MS, Clinical Pharmacist
Valerie Gonzales, PharmD, Clinical Pharmacist
Kristin Knippenberg, MFA, Administrator and Editor
Joanne LaFleur, PharmD, MSPH, Director and Associate Professor

University of Utah College of Pharmacy, Drug Regimen Review Center

CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

APA	American Psychiatric Association
CI	Confidence interval
DoD	Department of Defense
DUR	Drug Utilization Review
EDS	Entered days' supply
ER	Extended-release
FDA	US Food and Drug Administration
FFS	Fee-for-service
FGA(s)	First-generation antipsychotic(s)
GRMI	General recommended maintenance interval
ICD-10	International Classification of Diseases, 10th Revision
LAI(s)	Long-acting injectable(s)
MPR	Medication possession ratio
ODT	Orally disintegrating tablet
PDC	Proportion of days covered
PDL	(Utah Medicaid) Preferred Drug List
RCT(s)	Randomized controlled trial(s)
RR	Risk ratio
SGA(s)	Second-generation antipsychotic(s)
SMD	Standardized mean difference
SRMA	Systematic review and meta-analysis
TI	Therapeutic interval
US	United States
VA	Department of Veteran's Affairs

1.0 INTRODUCTION

Schizophrenia is a serious, heterogeneous, chronic psychiatric disorder characterized by disruptions in perceptual, motor, cognitive, and emotional functioning.[1,2] Core features include positive symptoms (eg, delusions, hallucinations, disorganized speech), negative symptoms (eg, avolition, alogia, diminished emotional expression), and cognitive symptoms (eg, memory or attention impairment, difficulty expressing thoughts).[1,3] *Schizoaffective disorder* is a distinct psychiatric condition that is characterized not only by symptoms common with schizophrenia, such as hallucinations and delusions, but also major depressive or manic episodes.[4]

Antipsychotics are the mainstay pharmacological treatment for treating schizophrenia and are often used to treat schizoaffective disorder*.[2,3,5-7] Antipsychotics can mitigate positive symptoms and prevent relapse of schizophrenia.[2,8] However, treatment response is profoundly influenced by adherence.[2] Medication non-adherence is common among patients with schizophrenia[8]; some evidence suggests an estimated non-adherence prevalence of up to 55%.[9] Factors contributing to non-adherence are multifarious, some medication-related, such as missing or inconsistently taking doses due to trouble managing complex regimens or due to unpleasant side effects.[10] The potential adverse outcomes of poor adherence to antipsychotics for schizophrenia are severe, including increased risk of relapse or rehospitalization, emergence of aggressive or suicidal behaviors, and death.[10]

Antipsychotics are categorized into 2 subclasses: first-generation antipsychotics (FGAs; also referred to as "typical" antipsychotics) and second-generation antipsychotics (SGAs; also referred to as "atypical" antipsychotics)†.[10] Available antipsychotic dosage forms depend on the active ingredient, but generally include oral dosage forms (eg, tablets, capsules) typically administered daily, and/or long-acting injectables (LAIs) administered approximately every 2 weeks to every 6 months, depending on the product.[1,10-23] The variety of antipsychotic dosage forms provides flexibility in treatment options to accommodate patient preferences and clinical needs. The particular dosage form prescribed may play a role in adherence for some patients, and switching dosage forms as needed is one option for increasing adherence and therapeutic continuity.[10] For example, patients who have difficulty managing oral regimens due to frequent daily dosing may elect switching to a formulation with a longer dosing interval, such as an LAI, to potentially improve treatment adherence.[24]

The **primary objectives** of this data-driven report are to a) assess the utilization rate of LAIs, according to their status on the Utah Medicaid Preferred Drug List (PDL; see **Table 1**), and b) measure adherence to oral and LAI antipsychotics among Utah Medicaid adults with schizophrenia or schizoaffective disorder. To inform these data analyses, we also summarize recommendations from recent United States (US) schizophrenia treatment guidelines related to interventions to promote adherence (eg, switching to an LAI from oral therapy). Notably, this report complements a previous Drug Utilization

* Paliperidone and clozapine (to reduce suicidal behavior) are the only antipsychotics specifically approved for schizoaffective disorder.

† Some more recently approved antipsychotics are sometimes also referred to as third-generation antipsychotics, but we included them among SGAs for the purposes of this report.

Review (DUR) report on high-dose antipsychotic therapy and multiple antipsychotic use in adults, completed in September 2024.[25]

Table 1 shows the preference status of LAI antipsychotic products according to the PDL published August 1, 2024.[26]

Table 1. Preference Status of LAI Antipsychotics on the Utah Medicaid PDL as of August 2024[a,26]

Preferred LAI antipsychotics			Non-preferred LAI antipsychotics	
Abilify Asimtufii	Abilify Maintena	Aristada	Rykindo	Uzedy
Invega Hafyera	Invega Sustenna	Invega Trinza	Risperdal Consta and its generic (risperidone LAI)	
Perseris	Zyprexa Relprevv			

[a] *LAI antipsychotics preferred by Utah Medicaid contain aripiprazole (as Abilify Asimtufii and Abilify Maintena), aripiprazole lauroxil (as Aristada), paliperidone palmitate (as Invega Hafyera, Invega Sustenna, and Invega Trinza), risperidone (as Perseris), and olanzapine (as Zyprexa Relprevv); non-preferred LAI antipsychotics are the risperidone LAIs, Risperdal Consta and its generic, Rykindo, and Uzedy. All LAIs with placement on the PDL are SGAs; FGA LAIs are not classified on the PDL.*

Abbreviations: FGA(s), first-generation antipsychotic(s); LAI, long-acting injectable; PDL, Preferred Drug List; SGA(s); second-generation antipsychotic(s)

According to prescribing information, the LAIs listed on the PDL are indicated for adults only (or have not been studied in the pediatric population[‡]) and must be administered by a healthcare provider.[11-21] Therefore, preferred and non-preferred products are limited to Utah Medicaid patients aged at least 18 years old; prior authorization is required for use in younger individuals. Utah Medicaid also indicates that LAIs on the PDL are to be dispensed directly to the provider rather than the patient.[26]

2.0 METHODS

We reviewed 2 US schizophrenia guidelines, one each from the American Psychiatric Association (APA; 2020) and the Department of Veteran's Affairs/Department of Defense (VA/DoD; 2023), for recommendations or guidance on the adherence to oral or LAI antipsychotics in adults with schizophrenia or schizoaffective disorder.[1,10] Consistent with our previously completed 2024 DUR report on antipsychotics in adults,[25] we selected the same guidelines for review.

2.1 Utilization of LAI antipsychotics, by PDL preference status

For the utilization data analysis of preferred versus non-preferred LAI antipsychotic products, we classified preferred/non-preferred status of LAIs according to the August 2024 PDL (see **Table 1**). Utah Medicaid outpatient pharmacy fee-for-service (FFS) claims were queried for utilization of preferred or non-preferred LAI products in the latest 12-month period from August 2023 through July 2024 among

[‡] Package insert statements may be based on the research status at the time of approval and primarily express that the product has not been formally approved for the pediatric population. Yet, it is possible that some subsequent studies involving the pediatric population have been conducted since the approval (ie, this statement in the package insert may be outdated).

Utah Medicaid patients (no age or diagnosis restrictions). Outpatient pharmacy claims of LAI antipsychotics account for approximately 99% of all Utah Medicaid LAI claims based on a November 2023 Utah Department of Health and Human Services report.[27]

We determined the total claims and number of unique patients with a claim for a preferred or non-preferred LAI product overall, and by product type and age group (adult versus pediatric). Among patients with at least 1 claim for a preferred or non-preferred LAI, we identified the proportion of patients with a diagnosis claim for schizophrenia, schizoaffective disorder, or bipolar disorder, as coded by International Classification of Diseases, 10th Revision (ICD-10) codes (F20.XX, F25.X, and F31.XX, respectively) during the latest 18-month timeframe (starting 6 months before the assessment of LAI utilization).

2.2 Adherence to oral and LAI antipsychotics

Products of interest for our adherence analyses were mono- or combination-ingredient oral or LAI antipsychotics approved by the US Food and Drug Administration (FDA) for schizophrenia or schizoaffective disorder (specific oral dosage formulations of eligible antipsychotics included in the oral adherence analysis are listed in **Appendix A**). We excluded loxapine oral inhalation powder as it is used for acute treatment, and bulk ingredients.[28] Notably, some antipsychotics may be approved for additional indications and/or available in other dosage forms not addressed by this report (eg, short-acting injectable, transdermal patch). **Table 2** provides an overview of the antipsychotics queried for the adherence data analyses, by oral and LAI formulation.

We classified the antipsychotics listed in **Table 2** into **regimens**, as follows:

- Oral antipsychotics were grouped into the same regimen if they had the same active ingredient (regardless of brand or generic name) and dosage form, and irrespective of dosage strength[§].
    - *Example:* fills for Abilify 10 mg and 20 mg oral tablets were considered as the same regimen, as it is the same active ingredient and dosage form.
- LAI antipsychotics were grouped into the same regimen if they had the same brand name (or generic equivalent) for SGAs or generic name for FGAs, and respective to their dosing intervals[**] (see **Appendix B**).
    - *Example:* Zyprexa Relprevv 300 mg and the 405 mg products were considered as the same regimen for the purposes of our analyses, as they have the same dosing intervals; whereas Zyprexa Relprevv 150 mg and the 210 mg products were their own regimen apart from Zyprexa Relprevv 300 mg or 405 mg because they have different dosing intervals (ie, covering a different number of days).

[§] For products described as a concentrate in the database, a single descriptor was chosen (ie, solution) to represent concentrates and solutions as the same regimen per drug molecule, as the difference in name is related to the dosage strength.

[**] Some LAI antipsychotics have different dosing intervals based on the dosage strength, which could affect medication adherence.

Table 2. Queried Antipsychotics for the Adherence Data Analyses

Oral antipsychotics by active ingredient[a,b]			
First-generation			
• Chlorpromazine	• Fluphenazine	• Haloperidol	• Loxapine
• Molindone	• Perphenazine	• Perphenazine/Amitriptyline	• Prochlorperazine
• Thioridazine	• Thiothixene	• Trifluoperazine	
Second-generation			
• Aripiprazole	• Asenapine	• Brexpiprazole	• Cariprazine
• Clozapine	• Iloperidone	• Lumateperone	• Lurasidone
• Olanzapine	• Olanzapine/samidorphan	• Paliperidone	• Quetiapine
• Risperidone	• Ziprasidone		
Long-acting injectable antipsychotics by active ingredient (brand, as applicable)[b]			
First-generation			
• Fluphenazine decanoate		• Haloperidol decanoate	
Second-generation[11-21]			
• Aripiprazole (Abilify Asimtufii; Abilify Maintena) • Aripiprazole lauroxil (Aristada; Aristada Initio) • Olanzapine (Zyprexa Relprevv) • Paliperidone palmitate (Invega Sustenna; Invega Trinza; Invega Hafyera) • Risperidone (Risperdal Consta, generic; Rykindo; Perseris; Uzedy)			

[a] *Eligible antipsychotic oral dosage forms included capsules, tablets, and/or solutions, among others; all oral dosage forms for an antipsychotic of interest were eligible for inclusion. For the specific oral dosage forms of each oral antipsychotic included in our adherence analysis, see* ***Appendix A****.*

[b] *Drug bulk ingredients were excluded.*

2.2.1 Data collection and calculating adherence

We queried Utah Medicaid claims data for eligible patients between August 2023 and July 2024 (ie, observation period). **Eligible patients** met the following criteria:

a. adults (≥18 years of age) with an ICD-10 code for schizophrenia (F20.XX) or schizoaffective disorder (F25.X) among any Utah Medicaid FFS claim;
b. ≥2 Medicaid FFS outpatient pharmacy claims for the same oral or LAI regimen (except for Invega Hafyera, for which we required ≥1 claim) within the observation period; and
c. At least 2 months of continuous Utah Medicaid eligibility starting from the first fill of an eligible antipsychotic during the observation period.

The proportion of days covered (PDC) was calculated to quantify adherence to antipsychotic regimens. PDC is the preferred method for measuring chronic medication adherence according to the Pharmacy Quality Alliance.[29] **PDCs were calculated by dividing the total number of "days covered" by a medication regimen by the total number of Medicaid-eligible days from the first fill date in the medication regimen (index claim) until the date of the first occurrence of one of the following: a) a**

regimen switch, b) a regimen discontinuation, c) the end of Medicaid coverage, or d) the end of the observation period. The "days covered" by a medication regimen was defined as follows:

- For oral dosage forms (ie, oral adherence analysis), the "days covered" from a fill was assigned based on the entered days' supply (EDS)[††] within the claim record for the fill.
- For LAI dosage forms, 2 adherence analyses were completed with "days covered" based on the general recommended maintenance interval (GRMI; Analysis 1), or the therapeutic interval (TI; Analysis 2); see **Table 3**.
    - Analysis 1: The GRMI is the dosing interval recommended by the package insert (product labeling), which does not account for early- or late-dose allowances that may also be outlined in the package inserts. For example, Abilify Maintena is recommended for administration on a monthly basis; thus the days covered per GRMI is 30 days for this product. For LAI products with more than 1 possible GRMI specified by prescribing information, we selected the longest interval.
    - Analysis 2: As LAI antipsychotics may maintain sufficient circulating plasma levels to sustain a treatment response for longer than the GRMI, we performed **a separate LAI analysis calculating the PDC with respect to the TI.** The TI represents the longest duration that the injection may be therapeutically effective as inferred based on the point at which the product labeling recommends that the patient must receive supplementation with an oral product or LAI injections (in addition to the next dose) to restore therapeutic levels. Only LAI antipsychotics with this late-dose/supplementation information specified in their product labeling were included in Analysis 2.

To assign the number of days covered according to the GRMI or TI described in product labeling, we used either the numerical number of days specified in the product labeling or, if more general terms such as weekly or monthly were used in the product labeling, we used either increments of 7 days for weekly-based dosing intervals or increments of 30 days for monthly-based dosing intervals. Similar to assigning a "days covered" per LAI fill, assigning a days' supply to LAI antipsychotics has been used previously in a quality measure developed by the Health Services Advisory Group with the Centers for Medicare and Medicaid Services for assessing LAI adherence.[30] **Table 3** outlines the GRMI and TI (if available) for each LAI antipsychotic.

[††] Unlike for oral antipsychotics, we did not use EDS on a pharmacy claim to represent the number of days covered for LAIs because there is more nuance and potential for inconsistency or inaccuracies with that field in the claim's record for LAIs.

Table 3. Dosage Strength and Administration Interval(s) for Included LAI antipsychotics

LAI product (brand name, as applicable)	Dosage strength (mg)	GRMI (days)[a,b]	Interval range (days)[c]	TI (days)[a,d]
Fluphenazine decanoate[31]	25	28[e]	NA	42[e]
Haloperidol decanoate[32]	50 and 100	30	28–30	NA
Aripiprazole (Abilify Asimtufii)[19]	720 and 960	60	46–98	98
Aripiprazole (Abilify Maintena)[18]	300 and 400	30	26–42	42[f]
Aripiprazole lauroxil (Aristada)[11]	441	30	14–42	42
	662	30	14–56	56
	882	42	14–56	56
	1064	60	14–70	70
Olanzapine (Zyprexa Relprevv)[12]	150 and 210	14	NA	NA
	300	28	NA	NA
	405	28	NA	NA
Paliperidone palmitate (Invega Sustenna)[17]	39 to 234	30	23–42	42
Paliperidone palmitate (Invega Trinza)[15]	273 to 819	90	76–120	120
Paliperidone palmitate (Invega Hafyera)[14]	1092 and 1560	180	166–201	201
Risperidone (Risperdal Consta)[16]	12.5 to 50	14	NA	NA
Risperidone (Rykindo)[20]	12.5 to 50	14	NA	NA
Risperidone (Perseris)[13]	90 and 120	30	NA	NA
Risperidone (Uzedy)[21]	50 to 250	60	NA	NA

[a] *For LAI products with monthly dosing intervals that did not specify an exact number of days in their labeling, we assigned 30 days for each month in the dosing interval (eg, 1 month = 30 days, 2 months = 60 days). When the package insert specified a weekly-based interval, we multiplied it by 7 to calculate the total number of days (eg, a 6-week interval = 42 days).*

[b] *For LAI products with more than 1 possible GRMI specified by prescribing information, we selected the longest interval. The GRMI does not account for early- or late-dose allowances.*

[c] *This column shows the possible maintenance administration interval range, accounting for early- and late-dose allowances if explicitly provided in the package insert.*

[d] *TI represents the longest duration that the injection may be therapeutically effective as inferred based on the point at which product labeling recommends that the patient must receive supplementation with an oral product or LAI injections (in addition to the next dose) to restore therapeutic levels. This was calculated for those products with this information specified by prescribing information.*

[e] *Although a specific administration interval is not provided in the prescribing information for fluphenazine decanoate, labeling suggests tailoring the dosing interval to the patient's response; maintenance dosing intervals of 4–6 weeks may be sufficient for many patients.*

[f] *Prescribing information for Abilify Maintena explicitly mentions starting concomitant oral supplementation when >5 weeks (if second or third doses are missed) or >6 weeks (if fourth or subsequent doses are missed) have elapsed since the last injection. For feasibility and the purposes of our adherence analysis, we used the 6-week threshold for the TI.*

Abbreviations: GRMI, general recommended maintenance interval; LAI, long-acting injectable; NA, not applicable; TI, therapeutic interval

PDCs for antipsychotic oral or LAI regimens were calculated 2 different ways: at the "population level" and "patient level". "Population level" PDCs were calculated by summing up all of the contributing days covered per patient then dividing it by the sum of the observation days from each patient, whereas "patient level" PDCs were used to determine the percentage of patients with a PDC ≥0.6 or ≥0.8 for each antipsychotic regimen. PDC calculations were performed using claims data from eligible patients and oral or LAI claims during the observation period. Refer to **Table 4** for an overview of the PDC calculations.

Table 4. PDC Calculations for Oral or LAI Antipsychotic Adherence

• Calculated at the *population-level* for antipsychotic oral or LAI regimens by summing up all the contributing days covered per patient then dividing it by the sum of the observation days from each patient. • Calculated at the *patient-level* to determine the percentage of patients with a PDC ≥0.6 or ≥0.8 for each antipsychotic regimen.	
Numerator[a,b]	Total number of days covered by fills for the antipsychotic regimen, using: • **Oral antipsychotic products**: pharmacy-entered days' supply (EDS) in the claim record for the fill, with carryover of the days' supplied for successive fills of the same regimen • **LAI antipsychotic products:** general recommended maintenance interval (GRMI) or therapeutic interval (TI; see **Table 3**)
Denominator[a,b]	Observation days were defined as the total number of Medicaid-eligible days after the first fill in the medication regimen (index claim) until the date of the first occurrence of one of the following: a) a regimen switch (see definition below or **Table 5**), b) regimen discontinuation (see definition below or **Table 5**), c) the end of Medicaid coverage, or d) the end of the observation period

[a] *Notably, among patients who filled the same regimen more than once during the observation period (eg, patient discontinued the regimen for ≥30 days and later re-initiated the same regimen), only data from the first regimen period contributed to the PDC calculation.*

[b] *If a patient switched regimens (see definition of a switch below) during the observation period, both regimen periods contributed to the PDC calculation for the respective antipsychotic regimen.*

Abbreviations: EDS, entered days' supply; GRMI, general recommended maintenance interval; LAI, long-acting injectable; PDC, proportion of days covered; TI, therapeutic interval

Switches to a new regimen were defined when a claim for an antipsychotic differing from the prior regimen occurred after a gap of ≥30 consecutive days with no fills for the prior regimen following the last day covered by the prior regimen. Generally, a regimen switch could include a change to a different LAI or oral regimen; however, there are some exceptions:

- Given that oral antipsychotic therapy of the same molecule can be used to supplement LAI injections for very late/missed LAI doses (in order to recover/maintain therapeutic levels),[11,18,19] we considered patients to be continuing their LAI regimen if they filled an oral antipsychotic of the same molecule between 2 claims of the same LAI type (eg, oral aripiprazole filled between 2 claims of Abilify Asimtufii). However, if a fill for the same LAI did not reoccur within 30 days after the last day

covered by the oral therapy, it was considered a switch or discontinuation. Regarding paliperidone-based LAIs (Invega Sustenna, Invega Trinza, Invega Hafyera), in addition to oral paliperidone, oral risperidone was considered the same oral antipsychotic molecule as permitted per labeling.[14,15,17]

- Fills of Aristada Initio (given as a one-time injection) were allowed between 2 claims of Aristada, as the initial injection of Aristada can be given on the same day or up to 10 days after Aristada Initio.[33] Additionally, Aristada Initio can be used for re-initiation following a missed dose of Aristada.[33]

A **regimen discontinuation** was defined as 30 consecutive days with no fills for that particular regimen after the last day covered of the previous fill (in absence of a switch).

For the PDC calculation, only gap days were counted as "non-adherent" (ie, days in which it was assumed that the patient did not have antipsychotic supply/coverage, which lowers the PDC). Gap days are the days between the expected refill date (based on either the GRMI or TI [for LAIs, depending on the analysis] or EDS [for orals]) and the actual refill date that occurred within the assessed gap length(s) (30, 60 or 90 days) for scenarios not meeting criteria for a regimen discontinuation or switch. For patients considered to have discontinued or switched regimens, days after the end of the supply/coverage of the initial regimen were not counted as "non-adherent".

A **sensitivity analysis** was performed for recalculating the GRMI PDCs for oral and LAI regimens using a gap length of 60 and 90 days, rather than 30 days, in the definitions of regimen switches and regimen discontinuations.

Table 5 summarizes key definitions used in this report.

Table 5. Key Definitions

Definitions	
Entered days' supply (EDS)	The entered days' supply from the pharmacy, as shown in the claim record
Gap days	Days between the expected refill date and actual refill date that occurred within the assessed gap length(s) (30, 60 or 90 days). The expected refill date is according to the GRMI or TI for that particular LAI antipsychotic regimen (depending on the analysis) or the EDS for oral products.
General recommended maintenance interval (GRMI)	The recommended maintenance dosing interval for LAI antipsychotics per labeling (see **Table 3**)
Proportion of days covered (PDC)	Calculated to quantify adherence to antipsychotic regimens; see **Table 4** for how PDCs were calculated to measure oral or LAI antipsychotic adherence
Regimen discontinuation[a]	Defined as 30 consecutive days with no fills for that particular regimen after the last day covered of the previous fill (including any oversupply for oral regimens only) and in absence of a regimen switch
Regimen group	• **Oral antipsychotics** were grouped into the same regimen based on having the same active ingredient and dosage form, and irrespective of dosage strength; for example, all strengths of Abilify and generic aripiprazole oral tablets were grouped into 'aripiprazole tablet' regimen. • **LAI antipsychotics** were grouped into the same regimen based on the brand name (or generic equivalent) for SGAs or generic name for FGAs, and respective to dosing intervals (GRMI or TI depending on the analysis). See **Appendix B** for a summary of LAI regimen groups.
Regimen switch[a]	A claim for an antipsychotic differing from the prior regimen and occurring after a gap of ≥30 consecutive days with no fills for the prior regimen following the last day covered (including any oversupply for oral regimens only) by the prior regimen • **Oral regimens:** switching to a different antipsychotic regimen group (including a different oral regimen or change to an LAI regimen) • **LAI regimens:** switching to a different LAI regimen group or a switch to a different oral antipsychotic molecule
Same oral antipsychotic molecule	Products with the same active ingredient (except for paliperidone/risperidone; see below) • Oral risperidone was considered the same molecule of paliperidone-based LAIs (Invega Sustenna, Invega Trinza, Invega Hafyera), in addition to oral paliperidone
Therapeutic interval (TI)	The longest duration that the injection may be therapeutically effective as inferred based on the point at which the product labeling recommends that the patient must receive supplementation with an oral product or LAI injections (in addition to the next dose) to restore therapeutic levels

[a] *Sensitivity analysis for recalculating the GRMI PDCs for oral and LAI regimens was performed using a gap length of 60 and 90 days, rather than 30 days.*

Abbreviations: EDS, entered days' supply; FGAs, first-generation antipsychotics; GRMI, general recommended maintenance interval; LAI, long-acting injectable; PDC, proportion of days covered; SGAs, second-generation antipsychotics; TI, therapeutic interval

3.0 SCHIZOPHRENIA AND ANTIPSYCHOTIC NON-ADHERENCE

Antipsychotic non-adherence is common among patients with schizophrenia or schizoaffective disorder,[8,34] potentially due to several reasons including, but not limited to, patients perceiving they do not have a condition that requires treatment or are feeling well; unpleasant side effects (eg, weight gain, akathisia); and beliefs, ambivalence, or suspiciousness about medications that results in patients discontinuing treatment.[10,24] A 2005 randomized controlled trial (RCT) to compare the effectiveness of certain oral antipsychotics found that overall 74% of patients with schizophrenia (1,061 out of 1,432) receiving an oral antipsychotic (olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone) discontinued the medication during the first 18 months of treatment, generally due to intolerable side effects or perceived inefficacy.[35] However, this population benefited when they tried a different antipsychotic during a subsequent phase of the trial.[10]

It is estimated that approximately 50% of patients with schizophrenia have additional psychiatric comorbidities (eg, substance use disorder, depression),[36] which may impact adherence.[10] Other contributing factors to poor adherence may include challenges related to medication management, such as difficulty managing complex medication regimens; however, adherence may also be influenced by other aspects, including financial or transportation barriers.[10]

Prevalence of medication non-adherence among patients with schizophrenia varies,[2] but some evidence estimates it is as high as 55%.[9] Potential serious adverse outcomes of poor adherence include increased risk of relapse or rehospitalization, emergence of aggressive or suicidal behaviors, and death.[10] It is estimated that 40% of all schizophrenia relapses are attributable to antipsychotic non-adherence (eg, PDC <80%).[37]

In addition to requiring less frequent administration compared to oral antipsychotics, several pharmacokinetic characteristics of LAI antipsychotics may also promote adherence or minimize the impact of a missed dose on antipsychotic plasma concentrations. Because LAI antipsychotics are absorbed slowly from their injection site, there is a smaller difference between peak and trough plasma levels, which could theoretically lessen some adverse events compared to some oral antipsychotics.[38] Furthermore, the sustained plasma concentrations achieved with LAI antipsychotics may offer a longer window for patients to administer treatment after a missed dose before significantly impacting antipsychotic plasma levels, reducing the risk of symptom recurrence or relapse.[37] Nonetheless, it should be considered that the pharmacokinetic characteristics of oral antipsychotics are heterogeneous. For example, oral aripiprazole and oral paliperidone extended-release have favorable peak-to-trough plasma ratios,[38] and cariprazine and its active metabolites have relatively long elimination half-lives (up to 2−3 weeks for a metabolite)[39] that might minimize the impact of occasional missed doses on plasma levels. Some patients may also prefer to take an oral antipsychotic.

4.0 GUIDELINE RECOMMENDATIONS

Recommendations from US schizophrenia treatment guidelines from the VA/DoD (2023) and APA (2020) with respect to maintenance or switching antipsychotic regimens, and recommendations for interventions to improve antipsychotic adherence are discussed in the following subsections; see **Table 6** for a summary of select formal (ie, graded) recommendations related to antipsychotic use.

Table 6. Select Guideline Treatment Recommendations on Antipsychotic Use in Patients with Schizophrenia (Strength; LOE)

Practice guideline for the treatment of patients with schizophrenia[a] **(American Psychiatric Association [APA]; 2020)[10]** Target population for recommendations: patients with schizophrenia, and potentially patients with schizophrenia spectrum disorders
All of the following recommendations should be applied as part of a patient-centered treatment plan, incorporating both evidence-based pharmacological and nonpharmacological interventions for schizophrenia: • **Continual antipsychotic use is recommended in patients with schizophrenia who have experienced symptom improvement while taking an antipsychotic medication (1A)** ○ Benefits include sustaining symptom relief; decreasing the risk of relapse, rehospitalization, and mortality; and enhancing overall quality of life and functioning. ○ Benefits and risks of long-term antipsychotic use should be evaluated with the patient throughout the course of treatment, and dosage adjustments or changes in medications to ensure tolerability may be performed, as appropriate. • **Patients with schizophrenia who have experienced symptom improvement while on an antipsychotic medication are suggested to continue receiving the *same* antipsychotic (2B)** ○ Switching to a different antipsychotic from one that has been associated with symptom improvement may result in early treatment discontinuation, clinical destabilization, worsened treatment tolerability, and increased symptoms. ○ Although it is optimal to continue the same antipsychotic, there may be reasons to consider switching antipsychotics, such as medication availability, side effects, or patient preferences. • **LAI antipsychotics are suggested for patients who prefer this treatment modality or have a history of poor or uncertain adherence (2B)** ○ Relative to oral antipsychotic formulations, LAIs reduce the likelihood of missed doses and allow providers to promptly address missed injections or office visits. ○ Particular scenarios for which to consider LAIs include when adherence is suspected to be uncertain or poor, such as for patients a) who are poorly adherent or unresponsive to oral antipsychotics; b) who are transitioning between health care settings; or c) have limited treatment awareness or a comorbid substance use disorder. ○ To assure tolerability and response to LAI therapy, patients generally must undergo a trial of an oral formulation of the same antipsychotic prior to initiation of the first LAI injection with that active ingredient.
Clinical practice guideline for management of first-episode psychosis and schizophrenia[b] **(Department of Veterans Affairs [VA]/Department of Defense [DoD]; 2023)[1]** Target population for recommendations: adults with schizophrenia, schizophrenia spectrum disorders, schizoaffective disorder, schizophreniform disorder, or first-episode psychosis
• **Maintenance treatment with an antipsychotic is recommended in patients with schizophrenia who have responded to treatment, as it can prevent hospitalization and relapse[c] (strong, in favor; moderate)** ○ Potential benefits of antipsychotic treatment outweighed the potential harms of withholding such medications (eg, an elevated likelihood of self-harm or harm to others, diminished quality of life, distress due to untreated symptoms). • **For patients with schizophrenia who are unresponsive or intolerant to an initial antipsychotic, it is suggested to consider a trial of an alternative antipsychotic[c] (weak, in favor; very low)** ○ Before switching agents, adherence to therapy should be determined, unless the change in therapy is due to intolerable side effects. • **To improve medication adherence in patients with schizophrenia, it is suggested to offer an LAI antipsychotic (weak, in favor; very low)** ○ Although patient preferences vary, some patients may prefer an LAI antipsychotic to an oral formulation due to the convenient administration frequency and the elimination of pill burden. ○ While frequent clinic visits associated with LAI use may be burdensome for some patients, they offer the benefit of regular provider interaction. • **Insufficient evidence for the use of shared decision-making or motivational interviewing strategies to improve medication adherence in patients with schizophrenia (either for or against; very low)**

[a] *APA guideline recommendation strength/LOE: Recommendation strength: 1, recommended option, benefits clearly outweigh harms; 2: suggested option, benefits outweigh harms, although there is a degree of uncertainty — patient preferences and values should be taken into consideration. LOE: letter ratings denote the level of confidence that the measured effect is the true effect; A, high confidence; B, moderate confidence; C, low confidence.*

[b] *VA/DoD guideline recommendation strength/LOE: Recommendation strength: strong, generally denotes high or moderate confidence that the benefits outweigh the harms; weak, lower confidence that the benefits outweigh the harms; LOE: based on the GRADE approach, with the overall rating determined by the critical outcome with the lowest evidence rating.*

[c] *Antipsychotic selection should take into account patient-specific factors and the side effect profiles of the various agents.*

Abbreviations: APA, American Psychiatric Association; DoD, Department of Defense; GRADE, Grading of Recommendation, Assessment, Development, and Evaluation; LAI(s); long-acting injectable(s); LOE, level of evidence; VA, Department of Veterans Affairs

4.1 General antipsychotic management of schizophrenia

The VA/DoD (2023) and APA (2020) strongly recommend maintenance antipsychotic treatment in patients with schizophrenia who have either responded to treatment in general (VA/DoD) or experienced symptom improvement while taking an antipsychotic medication (APA).[1,10] Benefits of continual antipsychotic treatment (eg, decreasing the risk of relapse, rehospitalization, and mortality)[10] are considered to outweigh potential harms associated with either withholding antipsychotics (eg, an elevated likelihood of self-harm or harm to others, distress due to untreated symptoms) or antipsychotic-related side effects for most patients.[1]

The APA suggests that patients continue the *same* antipsychotic associated with symptom improvement rather than switching to a different antipsychotic,[10] which we infer to be a product with a different active ingredient. Changing antipsychotics may result in early treatment discontinuation, clinical destabilization, worsened treatment tolerability, and increased symptoms.[10] Although it is optimal to continue the same antipsychotic for most patients, there may be reasons to consider switching from one antipsychotic to another, such as medication availability, side effects (eg, tardive syndromes, metabolic effects), or patient preferences. If using an LAI antipsychotic is desired for patients using an oral product that lacks a corresponding LAI formulation, switching antipsychotics is required.[10] The VA/DoD weakly recommends considering an alternative antipsychotic in patients with schizophrenia who are unresponsive or intolerant to an initial antipsychotic.[1]

Before switching agents, adherence to therapy should be determined, unless the change in therapy is due to intolerable side effects.[1] Switching antipsychotics necessitates careful monitoring due to the potential risk of relapse or withdrawal symptoms, clinical destabilization, or reduced adherence.[1,10] Instead of switching agents, augmentation with a second antipsychotic or other agent (eg, antidepressant) may be an option for patients with an insufficient response to other approaches[10]; however, this approach may hinder adherence if the multi-drug regimen is too cumbersome for the patient to manage.[1]

Regarding the use of psychosocial interventions to improve medication adherence, no recommendation was provided by the APA guideline.[10] The VA/DoD guideline more explicitly described that there was insufficient evidence to recommend either for or against the use of shared decision-making or motivational interviewing strategies to improve medication adherence in patients with schizophrenia.[1] Additionally, evidence for the impact of caregiver-directed psychosocial interventions for improving medication adherence was inconclusive, although such interventions may improve patient and caregiver wellbeing and are strongly recommended by the VA/DoD. Notably, other non-pharmacologic interventions for schizophrenia (eg, housing support, yoga) may positively impact medication adherence.[1]

4.2 LAI antipsychotic recommendations and supportive evidence

Both reviewed guidelines suggest offering LAI antipsychotics to patients with schizophrenia, either to generally improve medication adherence or based on patient preference.[1,10] Although discussions about initiating an LAI antipsychotic often pertain to patients who are poorly adherent to oral antipsychotics, patients who are unresponsive to oral antipsychotics or transitioning between health

care settings (eg, discharge from an inpatient facility) may also be considered for LAI antipsychotic therapy as medication adherence may also be affected for these patients.[10] Additionally, early consideration of an LAI antipsychotic may be warranted in patients with limited treatment awareness or a comorbid substance use disorder, as they may be at an increased risk of poor adherence.[10]

Long-term oral antipsychotic use may be a burden for some patients, making adherence challenging.[1,10] Therefore, some patients may opt for an LAI formulation over daily oral antipsychotic use due to the convenient administration frequency and the elimination of pill burden.[1] When informed through shared decision-making that discusses the risks and benefits of LAIs, many patients prefer LAIs to oral antipsychotics (although patient preferences may vary), particularly those with prior experience using an LAI antipsychotic.[10] While frequent clinic visits associated with LAI use may be burdensome for some patients, they also offer the benefit of regular provider interaction that may reduce the likelihood of missed doses and allow providers to promptly address missed injections/office visits.[1,10]

To assure tolerability and response to an LAI, patients naïve to treatment with the LAI's active ingredient should undergo a trial of an oral formulation of the same molecule antipsychotic[‡‡] prior to LAI initiation.[1,10] Compared to oral antipsychotics, side effects with LAI antipsychotics may be experienced for a longer duration owing to their longer duration of action, but generally the safety profile is comparable between oral and LAI formulations of the same antipsychotic.[10]

Several potential barriers to using LAI formulations may exist.[10] For example, patients may experience difficulty with transportation or conflicting school or work schedules, making it challenging to adhere to office visits for LAI administration. Furthermore, some providers may have a lack of knowledge or limited experience with using LAI medications, or limited staffing availability for administering injections.[10] Providers should be knowledgeable on injection technique, as LAI antipsychotics have varying preparation and administration requirements, and deviations from the proper administration can influence the pharmacokinetics of the medication, thereby affecting patient outcomes.[1]

4.2.1 Overview of guideline-cited evidence

A systematic review and meta-analysis (SRMA) by Kishimoto et al (2021) cited by the VA/DoD guideline compared outcomes between LAI versus oral antipsychotic therapy in adults with schizophrenia or other related conditions among 32 RCTs, 65 cohort studies, and 40 pre-post studies; reported outcomes were various but included hospitalization, relapse, quality of life, among others.[8] For some included studies, adherence outcomes were also available, such as PDC, medication possession ratio (MPR), proportion of patients achieving good adherence (ie, "taking the medication ≥75% of the days in the treatment period" [page 37][40]), psychiatrist's opinion on adherence, and medication adherence scale scores.[8,40] Most treatment comparisons across included RCTs (56.3%; n=18) and cohort studies (30.8%; n=20) were SGA LAIs versus SGA oral antipsychotics. The specific generation of antipsychotics included was not reported for the majority of pre-post studies (50%; n=20).[8]

---

‡‡ While tolerability is generally established with the oral formulation of the same molecule antipsychotic as the LAI, oral risperidone or oral paliperidone may be used before starting the one-month injection LAI of paliperidone palmitate (Invega Sustenna). Patients switching between LAI formulations with the same active ingredient may be able to switch directly without oral medication use (refer to respective prescribing information).

For each reported MPR or PDC meta-analysis adherence outcome, fewer than 10 pre-post studies and cohort studies were included.[8] LAI antipsychotics were favored over oral therapy with respect to MPR and PDC overall, including MPR ≥80% or PDC ≥80%, with statistically significant differences found across both study types for most of these outcomes (except among the pooled results from the cohort studies for MPR ≥80%, which still trended toward favoring LAIs). Two RCTs and 2 cohort studies were included in the meta-analysis evaluations for the remaining adherence outcomes.[1,8,40] A statistically significant difference in favor of LAIs was reported for proportion of patients achieving good adherence, the psychiatrist's opinion on adherence, and medication adherence scale scores.[1,40] Meta-analysis adherence findings favoring LAIs to oral antipsychotics were consistent among both assessed RCTs and cohort studies. **Table 7** summarizes the pooled results for the adherence outcomes evaluated in Kishimoto et al (2021).

Table 7. Summary of Pooled Results for Adherence Outcomes from Kishimoto et al (2021)[8,40]

Adherence outcome	Number of studies included	Number of patients from included studies	RR or SMD (95% CI)[a]	P-value
MPR	Cohort: 2	8,889	SMD: −0.21 (−0.41 to −0.01)	0.039
	Pre-post: 2	5,230	SMD: −0.48 (−0.60 to −0.36)	<0.0001
MPR ≥80%	Cohort: 2	8,988	RR: 0.77 (0.59 to 1.01)	0.061
	Pre-post: 2	5,230	RR: 0.65 (0.45 to 0.95)	0.026
PDC	Cohort: 7	33,745	SMD: −0.20 (−0.29 to −0.12)	<0.0001
	Pre-post: 1	638	SMD: −0.67 (−0.83 to −0.51)	<0.0001
PDC ≥80%	Cohort: 8	74,075	RR: 0.75 (0.65 to 0.86)	<0.0001
	Pre-post: 1	638	RR: 0.26 (0.17 to 0.40)	<0.0001
Good adherence[b]	RCT: 1	95	RR: 0.69 (0.54 to 0.89)	0.005
	Cohort: 1	50	RR: 0.47 (0.26 to 0.87)	0.016
Psychiatrist's opinion on adherence	Cohort: 1	1,444	RR: 0.62 (0.53 to 0.73)	<0.0001
Medication adherence scale scores	RCT: 1	83	SMD: −1.19 (−1.66 to −0.72)	<0.0001

[a] *SMD is reported for continuous outcomes and RR is reported for dichotomous outcomes. For consistency, the RR and SMD outcomes were rescaled so that benefit of LAIs over orals was indicated by an RR lower than 1 or an SMD lower than 0.*

[b] *Defined as "taking medication ≥75% of the days in the treatment period"*

Abbreviations: CI, confidence interval; MPR, medication possession ratio; PDC, proportion of days covered; RR, risk ratio; SMD, standardized mean difference

Meta-analyses of RCTs cited by the 2020 APA guideline (publication dates ranging from 2014 to 2017) generally showed no efficacy benefit for LAI over oral antipsychotic formulations,[10,41-45] in contrast with cited observational evidence that found LAI antipsychotic usage to be associated with a decreased risk of mortality, hospitalization, and treatment discontinuation compared to oral usage.[10,46-51] Meta-analysis results from the newer 2021 SRMA by Kishimoto et al showed LAI antipsychotic therapy, compared to oral antipsychotics, was associated with a significantly lower risk of hospitalization or relapse (primary

outcome) regardless of study design (RCTs: 29 studies, 12% risk reduction; cohort studies: 44 studies, 8% risk reduction; pre-post studies: 28 studies, 56% risk reduction).[8] The difference in efficacy findings between older meta-analyses cited by the APA guideline and the newer SRMA by Kishimoto et al could be due to differences in a) the risk of non-adherence in patient populations among included RCTs, and/or b) LAI dosing characteristics. Kishimoto et al commented that potentially more high-risk groups for non-adherence (eg, first-episode schizophrenia) whom benefit from LAIs are being included in more recent RCTs; thus, a possible reason that older RCTs often did not find a difference in efficacy between LAIs and oral antipsychotics could be that they enrolled patients who were more likely to be adherent to their medication.[8] Notably, Kishimoto et al mentioned that an insufficient number of studies reported non-adherence data, preventing the ability to perform a meta-regression analysis to assess the extent to which non-adherence affected efficacy results.[8]

5.0 DESCRIPTIVE UTILIZATION AND ADHERENCE ANALYSES RESULTS

The following subsections outline the results for our analyses for 1) the utilization of LAIs among the Utah Medicaid population, according to their preference status on the PDL (as of August 2024), and 2) adherence (as measured by the PDC) to oral or LAI antipsychotics among Utah Medicaid adults with schizophrenia or schizoaffective disorder.

5.1 Utilization of LAI antipsychotics, by PDL preference status

During the 12-month observation period, from August 2023 through July 2024, 1,875 unique patients had at least 1 outpatient pharmacy claim for either a PDL-preferred or non-preferred LAI antipsychotic (the total LAI cohort), accounting for 12,997 total claims. Of these claims, approximately **97%** were for a preferred LAI product. Most of the total LAI cohort were male (58%) and nearly all were adults, with a mean age of 36.9 years. The few pediatric patients receiving LAI therapy (<11 total) were all at least 16 years of age. Of the total LAI cohort, about 25% had a diagnosis code for schizophrenia in their medical claims record during or up to 6 months before the observation period. **Table 8** summarizes the descriptive characteristics for the total LAI cohort during the observation period.

Table 8. Descriptive Characteristics for Utah Medicaid Patients with Pharmacy Claims for a PDL-listed LAI Antipsychotic from August 2023 Through July 2024[a]

Characteristic descriptive statistic	Total LAI cohort (N=1,875)	Preferred LAI subset (n=1,832)	Non-preferred LAI subset (n=59)
Age (years)			
Median (25th percentile, 75th percentile)	35 (28, 45)	35 (27, 45)	33 (28, 43)
Mean (SD)	36.9 (11.6)	36.9 (11.6)	36.3 (12.3)
Sex (n, %)			
Female	790 (42.1)	778 (42.5)	18 (30.5)
Male	1,085 (57.9)	1,054 (57.5)	41 (69.5)
Select diagnosis of interest[b] (n, %)			
Patients with schizophrenia diagnosis (**F20.XX**)	464 (24.7)	455 (24.9)	15 (25.4)
Patients with schizoaffective disorder (**F25.X**)	440 (23.5)	432 (23.6)	12 (20.3)
Patients with bipolar disorder (**F31.XX**)	354 (18.9)	348 (19.0)	<11 (<18.6)
Patients who filled a PDL-listed LAI *without* a claim for any of the above diagnoses	955 (50.9)	931 (50.8)	32 (54.2)

[a] *Classification of antipsychotic LAIs as preferred or non-preferred was based on the August 2024 PDL. Counts >0 and <11 are reported as <11 for patient privacy concerns, and the corresponding percentages were calculated using a numerator of 11.*

[b] *The proportion of patients with a diagnosis claim for schizophrenia, schizoaffective disorder, or bipolar disorder during or up to 6 months before the observation period (August 2023 through July 2024) among patients who had at least 1 outpatient pharmacy claim for a PDL-listed LAI antipsychotic are reported. Patients could have more than one ICD-10 code of interest and therefore, may be counted more than once between different rows.*

Abbreviations: ICD-10, International Classification of Diseases, 10th Revision; LAI, long-acting injectable; PDL, (Utah Medicaid) Preferred Drug List; SD, standard deviation

Refer to **Appendix C** for an overview of the FDA-approved indications for LAI antipsychotics and oral dosage forms with the same active ingredient (**Table C1**), along with drug compendia-recognized off-label uses for the active ingredient of LAI antipsychotics (ie, including for other dosage forms if available; **Table C2**).

Based on patient and claim counts, the most common PDL-preferred/non-preferred LAI antipsychotic filled was Invega Sustenna, followed by Abilify Maintena, and then Aristada (all PDL-preferred products). No claims were identified for the risperidone products, Risperdal Consta or Rykindo (both PDL-non-preferred products).

Table 9 shows the outpatient pharmacy utilization of PDL-listed LAIs, during the observation period, with the number of claims stratified by age (ie, <18 years of age or ≥18 years of age, according to the patient age at the time of the LAI claim).

Table 9. Pharmacy Utilization Data for PDL-listed LAI Antipsychotics, Stratified by Age[a]

LAI antipsychotic product (brand name, as applicable)		Number of claims, stratified by age (years)[b]		Number of patients[c]
		<18	≥18	
Preferred LAIs, as of August 2024 Utah Medicaid Preferred Drug List				
Aripiprazole	Abilify Asimtufii	0	157	60
	Abilify Maintena	<11	2,883	443
Aripiprazole lauroxil	Aristada	<11	2,284	403
Olanzapine	Zyprexa Relprevv	0	400	58
Paliperidone palmitate	**Invega Sustenna**	**12**	**6,113**	**884**
	Invega Trinza	<11	522	156
	Invega Hafyera	0	71	46
Risperidone	Perseris	0	126	24
Non-preferred LAIs, as of August 2024 Utah Medicaid Preferred Drug List				
Risperidone	Uzedy	<11	94	31
	Generic of Risperdal Consta	0	320	29
	Risperdal Consta	0	0	0
	Rykindo	0	0	0

[a] Classification of antipsychotic LAIs as preferred or non-preferred was based on the August 2024 PDL, and occurred during the observation period of August 2023 through July 2024.

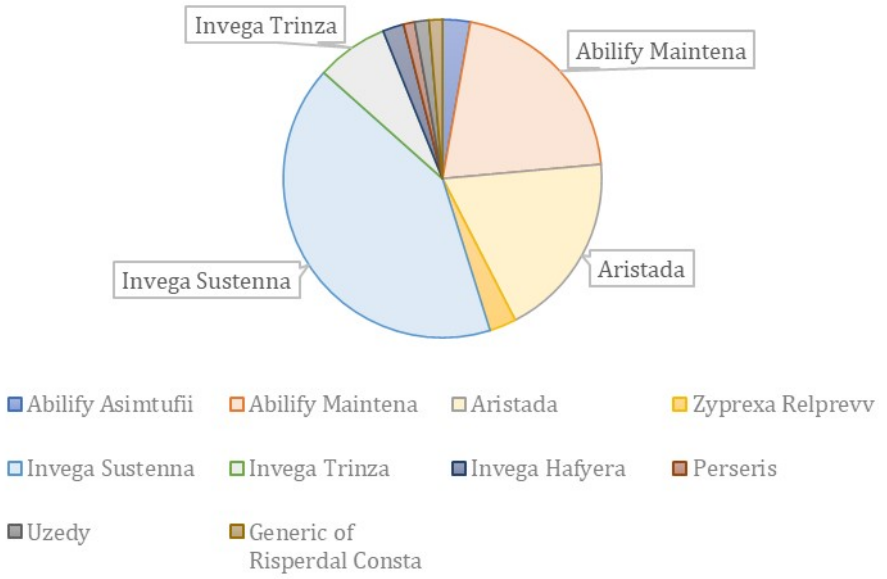
[b] Counts >0 and <11 are reported as <11 for patient privacy concerns. Patients may be counted more than once between columns depending on their age at the time of the claim.

[c] Patients may be counted more than once among different rows, as they could have claims for more than one product during the observation period.

Abbreviations: LAI(s), long-acting injectable(s); PDL, (Utah Medicaid) Preferred Drug List

Figure 1 shows a pie chart for the proportion of patients filling a PDL-listed LAI antipsychotic product.

Figure 1. Proportion of Patients with an Outpatient Pharmacy Claim for a PDL-listed LAI Antipsychotic[a]



[a] *Note that patients may be counted more than once if they had claims for more than one product during the observation period, from August 2023 through July 2024.*

Abbreviations: LAI, long-acting injectable; PDL, (Utah Medicaid) Preferred Drug List

5.2 Adherence to oral or LAI antipsychotics in adults with schizophrenia or schizoaffective disorder

Of the 4,352 Utah Medicaid-eligible adults identified with at least 1 claim of an antipsychotic of interest from August 2023 through July 2024 (ie, observation period) and who had an ICD-10 diagnosis code for schizophrenia or schizoaffective disorder in their medical record, **1,395** met our eligibility criteria (see **Appendix D** for the patient disposition diagram). In the total cohort of 1,395 patients, 701 (50%) were male and the median age was 37 years (25^{th}–75^{th} percentile, 30–47 years). The median duration of Utah Medicaid eligibility was 12 months (25^{th}–75^{th} percentile, 10–12 months).

5.2.1 LAI antipsychotics – GRMI results (Analysis 1)

The **population-level** PDCs with respect to the GRMI threshold were high (ie, PDC ≥0.8) for all LAI regimens, suggesting most patients adhered to their regimen without a late fill. PDCs remained unchanged or slightly decreased using a longer gap length of 60 or 90 days. The proportion of patients who were considered to have discontinued (ie, no fill for the particular antipsychotic regimen or a switch to a different regimen within 30, 60, or 90 days after the last day covered for that regimen) varied by antipsychotic regimen. Using a gap length of 30 days, the percentage of patients on a particular LAI regimen who discontinued ranged between 41% to <92% (among LAI regimens with claims from ≥11 total patients). Similar to the population-level PDC, the proportion of patients discontinuing a regimen

tended to slightly decrease as the assessed gap length increased. Generally, the percentage of total patients who received a particular LAI regimen who were considered to have switched therapies was lower than the percentage considered to have discontinued. **Table 10** summarizes the population-level PDC for each LAI antipsychotic regimen based on the GRMI, and reports the disposition of patients during the observation period by LAI regimen.

Table 10. Population-level PDCs Based on the GRMI for LAI Antipsychotic Regimens, by Gap Length

LAI antipsychotic regimen	Gap length (days)[a]	Number of patients[b]	Number of claims[b]	Number (%) of patients who discontinued the regimen[b]	Number (%) of patients who switched to a different regimen[b]	Number (%) of patients who lost Utah Medicaid eligibility[b]	Number (%) of patients lost to follow-up[b,c]	GRMI PDC
Abilify Asimtufii	30	<11	15	0 (0)	0 (0)	<11 (NC)	<11 (NC)	0.99
	60	<11	15	0 (0)	0 (0)	<11 (NC)	<11 (NC)	0.99
	90	<11	15	0 (0)	0 (0)	<11 (NC)	<11 (NC)	0.99
Abilify Maintena	30	55	316	28 (51)	<11 (<20)	<11 (<20)	18 (33)	0.91
	60	60	368	28 (47)	<11 (<18)	<11 (<18)	22 (37)	0.87
	90	62	390	27 (44)	<11 (<18)	<11 (<18)	24 (39)	0.85
Aristada (1064 mg)	30	23	89	12 (52)	<11 (<48)	0 (0)	<11 (<48)	0.98
	60	25	102	12 (48)	13 (52)			0.92
	90	26	104	12 (46)	14 (54)			0.92
Aristada (441 mg or 662 mg)	30	16	84	<11 (<69)	<11 (<69)	<11 (<69)	<11 (<69)	0.93
	60	16	89	<11 (<69)	<11 (<69)	<11 (<69)	<11 (<69)	0.90
	90	16	89	<11 (<69)	<11 (<69)	<11 (<69)	<11 (<69)	0.90
Aristada (882 mg)	30	29	182	12 (41)	<11 (<38)	<11 (<38)	14 (48)	0.95
	60	30	185	12 (40)	<11 (<37)	<11 (<37)	15 (50)	0.95
	90	30	186	11 (37)	<11 (<37)	<11 (<37)	16 (53)	0.94
Invega Sustenna	30	116	699	62 (53)	<11 (<10)	<11 (<10)	42 (36)	0.92
	60	122	761	63 (52)	<11 (<9)	<11 (<9)	47 (39)	0.90
	90	127	795	64 (50)	<11 (<9)	<11 (<9)	51 (40)	0.86

*For a description of how LAI antipsychotics were assigned into regimens, please refer to **Section 2.2** and/or **Appendix B**.*

[a] *Gap length is the threshold at which to classify a regimen as discontinued or switched; see **Table 5** for the definitions of a regimen discontinuation/switch.*

[b] *Counts >0 and <11 are reported as <11, and corresponding percentages were calculated using a count of 11 for patient privacy concerns.*

[c] *Patients were considered "lost to follow-up" if their ongoing regimen ran into the end of the observation period (ie, the regimen was not switched, discontinued, and the patient did not lose Utah Medicaid eligibility while on the regimen).*

Abbreviations: GRMI; general recommended maintenance interval; LAI, long-acting injectable; NC, not calculated; PDC, proportion of days covered

Table 10. Population-level PDCs Based on the GRMI for LAI Antipsychotic Regimens, by Gap Length

LAI antipsychotic regimen	Gap length (days)[a]	Number of patients[b]	Number of claims[b]	Number (%) of patients who discontinued the regimen[b]	Number (%) of patients who switched to a different regimen[b]	Number (%) of patients who lost Utah Medicaid eligibility[b]	Number (%) of patients lost to follow-up[b,c]	GRMI PDC
Invega Trinza	30	24	91	<11 (<46)	0 (0)	<11 (<46)	17 (71)	0.97
	60	26	98	<11 (<42)	0 (0)	<11 (<42)	18 (69)	0.96
	90	26	98	<11 (<42)	0 (0)	<11 (<42)	18 (69)	0.96
Invega Hafyera	30	12	17	<11 (<92)	0 (0)	0 (0)	<11 (<92)	0.98
	60	12	17	<11 (<92)	0 (0)	0 (0)	<11 (<92)	0.98
	90	12	17	<11 (<92)	0 (0)	0 (0)	<11 (<92)	0.98
Perseris	30	<11	15	0 (0)	0 (0)	<11 (NC)	<11 (NC)	0.86
	60	<11	15	0 (0)	0 (0)	<11 (NC)	<11 (NC)	0.86
	90	<11	15	0 (0)	0 (0)	<11 (NC)	<11 (NC)	0.86
Uzedy	30	<11	25	<11 (NC)	0 (0)	0 (0)	<11 (NC)	0.91
	60	<11	25	<11 (NC)	0 (0)	0 (0)	<11 (NC)	0.91
	90	<11	25	<11 (NC)	0 (0)	0 (0)	<11 (NC)	0.91
Risperdal Consta and its generic	30	<11	<11	0 (0)	0 (0)	0 (0)	<11 (NC)	0.88
	60	<11	<11	0 (0)	0 (0)	0 (0)	<11 (NC)	0.88
	90	<11	<11	0 (0)	0 (0)	0 (0)	<11 (NC)	0.88
Zyprexa Relprevv (300 mg or 405 mg)	30	<11	17	<11 (NC)	0 (0)	0 (0)	<11 (NC)	0.94
	60	<11	17	<11 (NC)	0 (0)	0 (0)	<11 (NC)	0.94
	90	<11	21	<11 (NC)	0 (0)	0 (0)	<11 (NC)	0.84

*For a description of how LAI antipsychotics were assigned into regimens, please refer to **Section 2.2** and/or **Appendix B**.*

[a] *Gap length is the threshold at which to classify a regimen as discontinued or switched; see **Table 5** for the definitions of a regimen discontinuation/switch.*

[b] *Counts >0 and <11 are reported as <11, and corresponding percentages were calculated using a count of 11 for patient privacy concerns.*

[c] *Patients were considered "lost to follow-up" if their ongoing regimen ran into the end of the observation period (ie, the regimen was not switched, discontinued, and the patient did not lose Utah Medicaid eligibility while on the regimen).*

Abbreviations: GRMI; general recommended maintenance interval; LAI, long-acting injectable; NC, not calculated; PDC, proportion of days covered

Based on **patient-level** PDCs with respect to the GRMI, the percent of patients with good adherence (PDC ≥0.8, right-most column of Table 11) was high for most LAI regimens (eg, proportion ≥85%) when using a gap length of 30 days (for the threshold at which to classify a regimen as discontinued or switched). Moreover, the proportion of patients with good adherence remained high regardless of gap length for several regimens with claims from ≥11 total patients: Aristada, Invega Trinza, and Invega Hafyera. However, when using longer gap lengths for the analysis, the proportion of patients with good adherence decreased below 85% for a couple regimens with claims from ≥11 total patients: Abilify Maintena and Invega Sustenna. Based on the PDC ≥0.6 threshold, we found there were very few patients with low adherence levels (ie, PDC <0.6). **Table 11** shows the number and proportion of patients with a PDC ≥0.6 or ≥0.8 for each LAI antipsychotic regimen based on the GRMI.

Table 11. Patients with a Patient-level PDC ≥0.6 or ≥0.8 for LAI Antipsychotic Regimens Based on GRMI

LAI antipsychotic regimen	Gap length (days)[a]	Number (%) of patients with an individual PDC ≥0.6[b] (%)	Number (%) of patients with an individual PDC ≥0.8[b] (%)
Abilify Asimtufii	30	<11 (100)	<11 (100)
	60	<11 (100)	<11 (100)
	90	<11 (100)	<11 (100)
Abilify Maintena	30	55 (100)	49 (89)
	60	59 (98)	47 (78)
	90	58 (94)	47 (76)
Aristada (1064 mg)	30	23 (100)	23 (100)
	60	25 (100)	22 (88)
	90	26 (100)	23 (88)
Aristada (441 mg or 662 mg)	30	16 (100)	15 (94)
	60	16 (100)	14 (88)
	90	16 (100)	14 (88)
Aristada (882 mg)	30	29 (100)	28 (97)
	60	30 (100)	29 (97)
	90	29 (97)	28 (93)
Invega Sustenna	30	116 (100)	108 (93)
	60	119 (98)	105 (86)
	90	117 (92)	104 (82)
Invega Trinza	30	24 (100)	24 (100)
	60	26 (100)	26 (100)
	90	26 (100)	26 (100)

[a] *Gap length is the threshold at which to classify a regimen as discontinued or switched; see* ***Table 5*** *for the definitions of a regimen discontinuation/switch.*

[b] *Counts >0 and <11 are reported as <11, and corresponding percentages were calculated using a count of 11 for patient privacy concerns.*

Abbreviations: GRMI, general recommended maintenance interval; LAI, long-acting injectable; NC, not calculated; PDC, proportion of days covered

Table 11. Patients with a Patient-level PDC ≥0.6 or ≥0.8 for LAI Antipsychotic Regimens Based on GRMI

LAI antipsychotic regimen	Gap length (days)[a]	Number (%) of patients with an individual PDC ≥0.6[b] (%)	Number (%) of patients with an individual PDC ≥0.8[b] (%)
Invega Hafyera	30	12 (100)	12 (100)
	60	12 (100)	12 (100)
	90	12 (100)	12 (100)
Perseris	30	<11 (100)	<11 (100)
	60	<11 (100)	<11 (100)
	90	<11 (100)	<11 (100)
Uzedy	30	<11 (100)	<11 (100)
	60	<11 (100)	<11 (100)
	90	<11 (100)	<11 (100)
Risperdal Consta and its generic	30	<11 (100)	<11 (100)
	60	<11 (100)	<11 (100)
	90	<11 (100)	<11 (100)
Zyprexa Relprevv (300 mg or 405 mg)	30	<11 (100)	<11 (100)
	60	<11 (100)	<11 (100)
	90	<11 (100)	<11 (NC)

5.2.2 LAI antipsychotics – TI results (Analysis 2)

Table 12 shows the population-level PDCs for each LAI antipsychotic regimen based on the TI threshold, which is the point at which product labeling recommends that the patient must receive supplementation with an oral product or LAI injections (in addition to the next dose) to restore therapeutic levels. Notably, this analysis includes only LAI antipsychotics with specified late-dose/supplementation information in their product labeling.

Using the TI, the population-level PDCs were very high (ie, PDC ≥0.9) for all LAI regimens. The proportion of patients who were considered to have discontinued varied by antipsychotic regimen. Among regimens with claims from ≥11 total patients, the percentage of patients who were considered to have discontinued ranged between 35% and <92%. Overall, the proportion of patients who were considered to have switched to a different regimen was relatively low across LAI antipsychotic regimens, ranging from 0% to <46%.

[a] *Gap length is the threshold at which to classify a regimen as discontinued or switched; see* ***Table 5*** *for the definitions of a regimen discontinuation/switch.*

[b] *Counts >0 and <11 are reported as <11, and corresponding percentages were calculated using a count of 11 for patient privacy concerns.*

Abbreviations: GRMI, general recommended maintenance interval; LAI, long-acting injectable; NC, not calculated; PDC, proportion of days covered

Table 12. Population-level PDCs Based on the TI for LAI Antipsychotic Regimens, Using a Gap Length of 30 Days

LAI antipsychotic regimen[a]	Number of patients[b]	Number of claims	Number (%) of patients who discontinued the regimen[b,c]	Number (%) of patients who switched to a different regimen[b,c]	Number (%) of patients who lost Utah Medicaid eligibility[b]	Number (%) of patients lost to follow-up[b,d]	TI PDC
Abilify Asimtufii	<11	15	0 (0)	0 (0)	<11 (NC)	<11 (NC)	1
Abilify Maintena	57	352	24 (42)	0 (0)	33 (58)		0.95
Aristada (1064 mg)	24	96	13 (54)	<11 (<46)	0 (0)	<11 (<46)	0.96
Aristada (441 mg)	<11	48	<11 (NC)	0 (0)	<11 (NC)	<11 (NC)	0.94
Aristada (662 mg or 882 mg)	37	226	13 (35)	0 (0)	24 (65)		0.98
Invega Sustenna	119	748	55 (46)	<11 (<9)	<11 (<9)	58 (49)	0.95
Invega Trinza	26	98	<11 (<42)	0 (0)	<11 (<42)	19 (73)	0.99
Invega Hafyera	12	17	<11 (<92)	0 (0)	0 (0)	<11 (<92)	0.99

*For a description of how LAI antipsychotics were assigned into regimens, please refer to **Section 2.2** and/or **Appendix B**.*

[a] *The TI-based PDC analysis only includes LAI products with specified late-dose/supplementation information in their product labeling.*

[b] *Counts >0 and <11 are reported as <11, and corresponding percentages were calculated using a count of 11 for patient privacy concerns.*

[c] *See **Table 5** for the definitions of a regimen discontinuation/switch.*

[d] *Patients were considered "lost to follow-up" if their ongoing regimen ran into the end of the observation period (ie, the regimen was not switched, discontinued, and the patient did not lose Utah Medicaid eligibility while on the regimen).*

Abbreviations: LAI, long-acting injectable; NC, not calculated; PDC, proportion of days covered; TI, therapeutic interval

5.2.3 Oral antipsychotics – results

The population-level PDC (based on the pharmacy-EDS) tended to be high (≥0.8) for most oral antipsychotic regimens. Generally, the population-level PDC tended to decrease as the gap length increased from 30 to 90 days, but with only a few exceptions, the PDCs still exceeded 0.8. The only regimens with a population-level PDC <0.8 were aripiprazole solution and prochlorperazine tablet (using the 90 day gap length only). Despite relatively high adherence according to the PDC for most oral antipsychotic regimens, the percentage of patients on a particular regimen who discontinued ranged between 35% and 58% (using a gap length of 30 days and among regimens with claims from ≥11 patients). Generally, the proportion of patients who were considered to have switched to a different regimen was lower than the proportion of patients who were considered to have discontinued. **Table 13** summarizes the population-level PDC for each oral antipsychotic regimen based on pharmacy-EDS, and reports the disposition of patients during the observation period by oral antipsychotic regimen.

Table 13. Population-level PDCs Based on the EDS for Oral Antipsychotic Regimens, by Gap Length

Oral antipsychotic regimen	Gap length (days)[a]	Number of patients[b]	Number of claims[b]	Number (%) of patients who discontinued the regimen[b]	Number (%) of patients who switched to a different regimen[b]	Number (%) of patients who lost Utah Medicaid eligibility[b]	Number (%) of patients lost to follow-up[b,c]	PDC
Aripiprazole solution	30	<11	<11	<11 (NC)	0 (0)	0 (0)	0 (0)	0.69
	60	<11	<11	<11 (NC)	0 (0)	0 (0)	0 (0)	0.69
	90	<11	<11	<11 (NC)	0 (0)	0 (0)	0 (0)	0.69
Aripiprazole tablet	30	332	1805	169 (51)	35 (11)	21 (6)	107 (32)	0.93
	60	356	2004	163 (46)	33 (9)	28 (8)	132 (37)	0.88
	90	368	2075	165 (45)	35 (10)	30 (8)	138 (38)	0.86
Asenapine sublingual tablet	30	33	174	17 (52)	<11 (<33)	<11 (<33)	<11 (<33)	0.91
	60	34	189	16 (47)	<11 (<32)	<11 (<32)	<11 (<32)	0.88
	90	35	192	17 (49)	<11 (<31)	<11 (<31)	<11 (<31)	0.87
Brexpiprazole tablet	30	22	128	11 (50)	<11 (<50)	0 (0)	<11 (<50)	0.90
	60	24	141	11 (46)	<11 (<46)	<11 (<46)	11 (46)	0.86
	90	24	147	<11 (<46)	<11 (<46)	<11 (<46)	12 (50)	0.85
Cariprazine capsule	30	171	935	65 (38)	13 (8)	19 (11)	74 (43)	0.93
	60	179	1036	64 (36)	<11 (<6)	19 (11)	87 (49)	0.89
	90	183	1059	62 (34)	<11 (<6)	20 (11)	92 (50)	0.88
Chlorpromazine tablet	30	<11	76	<11 (NC)	<11 (NC)	0 (0)	<11 (NC)	0.93
	60	11	81	<11 (NC)	<11 (NC)	0 (0)	<11 (NC)	0.89
	90	11	83	<11 (NC)	0 (0)	0 (0)	<11 (NC)	0.88

[a] *Gap length is the threshold at which to classify a regimen as discontinued or switched; see* ***Table 5*** *for the definitions of a regimen discontinuation/switch.*

[b] *Counts >0 and <11 are reported as <11, and corresponding percentages were calculated using a count of 11 for patient privacy concerns.*

[c] *Patients were considered "lost to follow-up" if their ongoing regimen ran into the end of the observation period (ie, the regimen was not switched, discontinued, and the patient did not lose Utah Medicaid eligibility while on the regimen).*

Abbreviations: EDS, entered days' supply; ER, extended-release; NC, not calculated; ODT, orally disintegrating tablet; PDC, proportion of days covered

Table 13. Population-level PDCs Based on the EDS for Oral Antipsychotic Regimens, by Gap Length

Oral antipsychotic regimen	Gap length (days)[a]	Number of patients[b]	Number of claims[b]	Number (%) of patients who discontinued the regimen[b]	Number (%) of patients who switched to a different regimen[b]	Number (%) of patients who lost Utah Medicaid eligibility[b]	Number (%) of patients lost to follow-up[b,c]	PDC
Clozapine tablet	30	43	449	18 (42)	<11 (<26)	<11 (<26)	21 (49)	0.96
	60	44	485	18 (41)	0 (0)	26 (59)		0.93
	90	44	486	17 (39)	0 (0)	27 (61)		0.92
Fluphenazine tablet	30	<11	20	<11 (NC)	0 (0)	0 (0)	<11 (NC)	0.99
	60	<11	20	<11 (NC)	0 (0)	0 (0)	<11 (NC)	0.99
	90	<11	20	<11 (NC)	0 (0)	0 (0)	<11 (NC)	0.99
Haloperidol tablet	30	38	241	20 (53)	<11 (<29)	<11 (<29)	14 (37)	0.95
	60	40	257	21 (53)	<11 (<28)	<11 (<28)	15 (38)	0.92
	90	41	267	20 (49)	<11 (<27)	<11 (<27)	17 (41)	0.89
Iloperidone tablet	30	<11	15	0 (0)	0 (0)	0 (0)	<11 (NC)	0.99
	60	<11	15	0 (0)	0 (0)	0 (0)	<11 (NC)	0.99
	90	<11	15	0 (0)	0 (0)	0 (0)	<11 (NC)	0.99
Lumateperone capsule	30	23	114	<11 (<48)	<11 (<48)	<11 (<48)	<11 (<48)	0.93
	60	23	123	11 (48)	<11 (<48)	<11 (<48)	<11 (<48)	0.91
	90	23	133	<11 (<48)	<11 (<48)	<11 (<48)	12 (52)	0.87
Lurasidone tablet	30	142	880	61 (43)	12 (8)	14 (10)	55 (39)	0.94
	60	148	960	63 (43)	85 (57)			0.91
	90	153	987	63 (41)	90 (59)			0.88

[a] *Gap length is the threshold at which to classify a regimen as discontinued or switched; see* ***Table 5*** *for the definitions of a regimen discontinuation/switch.*

[b] *Counts >0 and <11 are reported as <11, and corresponding percentages were calculated using a count of 11 for patient privacy concerns.*

[c] *Patients were considered "lost to follow-up" if their ongoing regimen ran into the end of the observation period (ie, the regimen was not switched, discontinued, and the patient did not lose Utah Medicaid eligibility while on the regimen).*

Abbreviations: EDS, entered days' supply; ER, extended-release; NC, not calculated; ODT, orally disintegrating tablet; PDC, proportion of days covered

Table 13. Population-level PDCs Based on the EDS for Oral Antipsychotic Regimens, by Gap Length

Oral antipsychotic regimen	Gap length (days)[a]	Number of patients[b]	Number of claims[b]	Number (%) of patients who discontinued the regimen[b]	Number (%) of patients who switched to a different regimen[b]	Number (%) of patients who lost Utah Medicaid eligibility[b]	Number (%) of patients lost to follow-up[b,c]	PDC
Olanzapine ODT	30	24	103	13 (54)	<11 (<46)	0 (0)	<11 (<46)	0.94
	60	26	110	15 (58)	<11 (<42)	0 (0)	<11 (<42)	0.87
	90	26	113	14 (54)	<11 (<42)	0 (0)	<11 (<42)	0.86
Olanzapine tablet	30	276	1659	120 (43)	29 (11)	28 (10)	99 (36)	0.93
	60	289	1842	125 (43)	17 (6)	30 (10)	117 (40)	0.89
	90	301	1929	132 (44)	15 (5)	29 (10)	125 (42)	0.86
Olanzapine + samidorphan tablet	30	22	216	<11 (<50)	0 (0)	<11 (<50)	15 (68)	0.96
	60	22	219	<11 (<50)	0 (0)	<11 (<50)	15 (68)	0.94
	90	22	224	22 (100)				0.94
Paliperidone ER tablet	30	53	243	31 (58)	<11 (<21)	<11 (<21)	13 (25)	0.95
	60	57	276	35 (61)	<11 (<19)	<11 (<19)	15 (26)	0.92
	90	62	296	36 (58)	<11 (<18)	<11 (<18)	19 (31)	0.86
Perphenazine tablet	30	<11	62	<11 (NC)	0 (0)	<11 (NC)	<11 (NC)	0.97
	60	<11	62	<11 (NC)	0 (0)	<11 (NC)	<11 (NC)	0.97
	90	<11	62	<11 (NC)	0 (0)	<11 (NC)	<11 (NC)	0.97
Prochlorperazine tablet	30	<11	15	<11 (NC)	0 (0)	<11 (NC)	0 (0)	0.95
	60	<11	16	<11 (NC)	0 (0)	<11 (NC)	0 (0)	0.89
	90	<11	20	<11 (NC)	0 (0)	<11 (NC)	0 (0)	0.71

[a] *Gap length is the threshold at which to classify a regimen as discontinued or switched; see* ***Table 5*** *for the definitions of a regimen discontinuation/switch.*

[b] *Counts >0 and <11 are reported as <11, and corresponding percentages were calculated using a count of 11 for patient privacy concerns.*

[c] *Patients were considered "lost to follow-up" if their ongoing regimen ran into the end of the observation period (ie, the regimen was not switched, discontinued, and the patient did not lose Utah Medicaid eligibility while on the regimen).*

Abbreviations: EDS, entered days' supply; ER, extended-release; NC, not calculated; ODT, orally disintegrating tablet; PDC, proportion of days covered

Table 13. Population-level PDCs Based on the EDS for Oral Antipsychotic Regimens, by Gap Length

Oral antipsychotic regimen	Gap length (days)[a]	Number of patients[b]	Number of claims[b]	Number (%) of patients who discontinued the regimen[b]	Number (%) of patients who switched to a different regimen[b]	Number (%) of patients who lost Utah Medicaid eligibility[b]	Number (%) of patients lost to follow-up[b,c]	PDC
Quetiapine ER tablet	30	37	251	13 (35)	<11 (<30)	<11 (<30)	15 (41)	0.95
	60	39	282	12 (31)	<11 (<28)	<11 (<28)	18 (46)	0.93
	90	39	286	14 (36)	<11 (<28)	<11 (<28)	18 (46)	0.91
Quetiapine tablet	30	364	2397	160 (44)	18 (5)	31 (9)	155 (43)	0.94
	60	390	2610	162 (42)	21 (5)	34 (9)	173 (44)	0.90
	90	405	2702	164 (40)	20 (5)	34 (8)	187 (46)	0.88
Risperidone ODT	30	<11	29	<11 (NC)	<11 (NC)	0 (0)	<11 (NC)	0.95
	60	<11	31	<11 (NC)	0 (0)	0 (0)	<11 (NC)	0.93
	90	<11	34	<11 (NC)	0 (0)	0 (0)	<11 (NC)	0.86
Risperidone solution	30	<11	<11	<11 (NC)	0 (0)	0 (0)	0 (0)	1
	60	<11	<11	<11 (NC)	0 (0)	0 (0)	0 (0)	1
	90	<11	<11	<11 (NC)	0 (0)	0 (0)	0 (0)	1
Risperidone tablet	30	131	850	61 (47)	12 (9)	12 (9)	46 (35)	0.94
	60	139	931	65 (48)	74 (53)			0.89
	90	147	991	68 (46)	79 (54)			0.86
Thioridazine tablet	30	<11	<11	<11 (NC)	0 (0)	0 (0)	0 (0)	1
	60	<11	<11	<11 (NC)	0 (0)	0 (0)	0 (0)	1
	90	<11	<11	<11 (NC)	0 (0)	0 (0)	0 (0)	1

[a] *Gap length is the threshold at which to classify a regimen as discontinued or switched; see* ***Table 5*** *for the definitions of a regimen discontinuation/switch.*

[b] *Counts >0 and <11 are reported as <11, and corresponding percentages were calculated using a count of 11 for patient privacy concerns.*

[c] *Patients were considered "lost to follow-up" if their ongoing regimen ran into the end of the observation period (ie, the regimen was not switched, discontinued, and the patient did not lose Utah Medicaid eligibility while on the regimen).*

Abbreviations: EDS, entered days' supply; ER, extended-release; NC, not calculated; ODT, orally disintegrating tablet; PDC, proportion of days covered

Table 13. Population-level PDCs Based on the EDS for Oral Antipsychotic Regimens, by Gap Length

Oral antipsychotic regimen	Gap length (days)[a]	Number of patients[b]	Number of claims[b]	Number (%) of patients who discontinued the regimen[b]	Number (%) of patients who switched to a different regimen[b]	Number (%) of patients who lost Utah Medicaid eligibility[b]	Number (%) of patients lost to follow-up[b,c]	PDC
Thiothixene capsule	30	<11	<11	0 (0)	<11 (NC)	0 (0)	0 (0)	0.97
	60	<11	<11	0 (0)	<11 (NC)	0 (0)	0 (0)	0.97
	90	<11	<11	0 (0)	<11 (NC)	0 (0)	0 (0)	0.97
Trifluoperazine tablet	30	<11	11	0 (0)	<11 (NC)	0 (0)	0 (0)	0.94
	60	<11	11	0 (0)	<11 (NC)	0 (0)	0 (0)	0.94
	90	<11	11	0 (0)	<11 (NC)	0 (0)	0 (0)	0.94
Ziprasidone capsule	30	51	326	20 (39)	<11 (<22)	<11 (<22)	21 (41)	0.95
	60	56	347	23 (41)	<11 (<20)	<11 (<20)	23 (41)	0.92
	90	58	365	26 (45)	<11 (<20)	<11 (<20)	24 (41)	0.88

[a] *Gap length is the threshold at which to classify a regimen as discontinued or switched; see* ***Table 5*** *for the definitions of a regimen discontinuation/switch.*

[b] *Counts >0 and <11 are reported as <11, and corresponding percentages were calculated using a count of 11 for patient privacy concerns.*

[c] *Patients were considered "lost to follow-up" if their ongoing regimen ran into the end of the observation period (ie, the regimen was not switched, discontinued, and the patient did not lose Utah Medicaid eligibility while on the regimen).*

Abbreviations: EDS, entered days' supply; ER, extended-release; NC, not calculated; ODT, orally disintegrating tablet; PDC, proportion of days covered

Across oral antipsychotic regimens, the proportion of patients with a patient-level PDC ≥0.8 tended to decrease as the gap length increased. Among oral antipsychotic regimens with claims from ≥11 total patients, regimens that had >80% of patients with a PDC ≥0.8 across all gap lengths were asenapine sublingual tablet, clozapine tablet, olanzapine + samidorphan tablet, and quetiapine ER tablet. Oral antipsychotic regimens with claims from ≥11 total patients and fewer than 70% of patients with a PDC ≥0.8 across any gap length were brexpiprazole tablet, olanzapine ODT, and risperidone tablet. **Table 14** shows the number and proportion of patients with a PDC ≥0.6 or ≥0.8 for each oral antipsychotic regimen based on the EDS.

Table 14. Patients with a Patient-level PDC ≥0.6 or ≥0.8 for Oral Antipsychotic Regimens Based on the EDS

Oral antipsychotic regimen	Gap length (days)[a]	Number (%) of patients with an individual PDC ≥0.6[b]	Number (%) of patients with an individual PDC ≥0.8[b]
Aripiprazole solution	30	<11 (100)	0 (0)
	60	<11 (100)	0 (0)
	90	<11 (100)	0 (0)
Aripiprazole tablet	30	331 (99)	301 (91)
	60	343 (96)	281 (79)
	90	338 (92)	272 (74)
Asenapine sublingual tablet	30	31 (94)	28 (85)
	60	32 (94)	28 (82)
	90	32 (91)	28 (80)
Brexpiprazole tablet	30	22 (100)	18 (82)
	60	22 (92)	15 (63)
	90	21 (88)	15 (63)
Cariprazine capsule	30	171 (100)	153 (89)
	60	173 (97)	145 (81)
	90	174 (95)	144 (79)
Chlorpromazine tablet	30	<11 (100)	<11 (NC)
	60	<11 (NC)	<11 (NC)
	90	<11 (NC)	<11 (NC)
Clozapine tablet	30	43 (100)	41 (95)
	60	44 (100)	38 (86)
	90	43 (98)	38 (86)

[a] *Gap length is the threshold at which to classify a regimen as discontinued or switched; see* ***Table 5*** *for the definitions of a regimen discontinuation/switch.*

[b] *Counts >0 and <11 are reported as <11 , and corresponding percentages were calculated using a count of 11 for patient privacy concerns.*

Abbreviations: EDS, entered days' supply; ER, extended-release; NC, not calculated; ODT, orally disintegrating tablet; PDC, proportion of days covered

Table 14. Patients with a Patient-level PDC ≥0.6 or ≥0.8 for Oral Antipsychotic Regimens Based on the EDS

Oral antipsychotic regimen	Gap length (days)[a]	Number (%) of patients with an individual PDC ≥0.6[b]	Number (%) of patients with an individual PDC ≥0.8[b]
Fluphenazine tablet	30	<11 (100)	<11 (100)
	60	<11 (100)	<11 (100)
	90	<11 (100)	<11 (100)
Haloperidol tablet	30	36 (95)	33 (87)
	60	37 (93)	32 (80)
	90	36 (88)	30 (73)
Iloperidone tablet	30	<11 (100)	<11 (100)
	60	<11 (100)	<11 (100)
	90	<11 (100)	<11 (100)
Lumateperone capsule	30	23 (100)	21 (91)
	60	23 (100)	20 (87)
	90	23 (100)	17 (74)
Lurasidone tablet	30	142 (100)	132 (93)
	60	144 (97)	123 (83)
	90	141 (92)	118 (77)
Olanzapine ODT	30	24 (100)	19 (79)
	60	25 (96)	17 (65)
	90	25 (96)	16 (62)
Olanzapine tablet	30	274 (99)	243 (88)
	60	279 (97)	229 (79)
	90	278 (92)	224 (74)
Olanzapine + samidorphan tablet	30	22 (100)	22 (100)
	60	22 (100)	21 (95)
	90	22 (100)	21 (95)
Paliperidone ER tablet	30	53 (100)	47 (89)
	60	56 (98)	47 (82)
	90	54 (87)	44 (71)
Perphenazine tablet	30	<11 (100)	<11 (100)
	60	<11 (100)	<11 (100)
	90	<11 (100)	<11 (100)

[a] *Gap length is the threshold at which to classify a regimen as discontinued or switched; see* ***Table 5*** *for the definitions of a regimen discontinuation/switch.*

[b] *Counts >0 and <11 are reported as <11 , and corresponding percentages were calculated using a count of 11 for patient privacy concerns.*

Abbreviations: EDS, entered days' supply; ER, extended-release; NC, not calculated; ODT, orally disintegrating tablet; PDC, proportion of days covered

Table 14. Patients with a Patient-level PDC ≥0.6 or ≥0.8 for Oral Antipsychotic Regimens Based on the EDS

Oral antipsychotic regimen	Gap length (days)[a]	Number (%) of patients with an individual PDC ≥0.6[b]	Number (%) of patients with an individual PDC ≥0.8[b]
Prochlorperazine tablet	30	<11 (100)	<11 (NC)
	60	<11 (NC)	<11 (NC)
	90	<11 (NC)	<11 (NC)
Quetiapine ER tablet	30	36 (97)	35 (95)
	60	38 (97)	35 (90)
	90	36 (92)	33 (85)
Quetiapine tablet	30	362 (99)	327 (90)
	60	369 (95)	312 (80)
	90	373 (92)	309 (76)
Risperidone ODT	30	<11 (100)	<11 (NC)
	60	<11 (100)	<11 (NC)
	90	<11 (100)	<11 (NC)
Risperidone solution	30	<11 (100)	<11 (100)
	60	<11 (100)	<11 (100)
	90	<11 (100)	<11 (100)
Risperidone tablet	30	131 (100)	114 (87)
	60	129 (93)	107 (77)
	90	129 (88)	102 (69)
Thioridazine tablet	30	<11 (100)	<11 (100)
	60	<11 (100)	<11 (100)
	90	<11 (100)	<11 (100)
Thiothixene capsule	30	<11 (100)	<11 (100)
	60	<11 (100)	<11 (100)
	90	<11 (100)	<11 (100)
Trifluoperazine tablet	30	<11 (100)	<11 (100)
	60	<11 (100)	<11 (100)
	90	<11 (100)	<11 (100)
Ziprasidone capsule	30	51 (100)	48 (94)
	60	54 (96)	49 (88)
	90	53 (91)	46 (79)

[a] *Gap length is the threshold at which to classify a regimen as discontinued or switched; see* ***Table 5*** *for the definitions of a regimen discontinuation/switch.*

[b] *Counts >0 and <11 are reported as <11 , and corresponding percentages were calculated using a count of 11 for patient privacy concerns.*

Abbreviations: EDS, entered days' supply; ER, extended-release; NC, not calculated; ODT, orally disintegrating tablet; PDC, proportion of days covered

5.2.4 Limitations to adherence analyses

There are several limitations of our data analyses that should be considered when interpreting the results. As is typical with claims-based data, we used prescription claims as a proxy for medication administration, but a prescription claim does not guarantee that the medication was actually taken (for oral products) or administered on the day of the fill (for LAIs).

Because of the complexity and feasibility purposes of our adherence analyses, we primarily captured each patient's first observed course for a particular regimen, in addition to regimen switches. However, we did not capture all subsequent courses (eg, a medication of the same regimen after a long gap in therapy for a given patient) for each antipsychotic regimen. Our sensitivity analysis using different gap lengths addresses this issue to some degree, catching subsequent courses within up to 90 days. **Appendix E** provides the number of subsequent courses that were excluded from the PDC calculation for each oral antipsychotic regimen[§§] after 90 days.

When analyzing claims data at a population level, the reasons behind a patient's failure to refill a prescription as expected are not always apparent, which may lead to misclassifications of their adherence and over- or under-estimation of the PDCs. For example, patients with continued Medicaid coverage without a refill of a given antipsychotic regimen or a switch to a new regimen within an assigned gap length were assumed to have discontinued the regimen, and any days after the end of the supply/coverage of the regimen **were not counted** as "non-adherent" in our PDC calculation. Thus, we could have overestimated the PDC if some patients that we defined as discontinuing therapy were actually intended to continue therapy by their provider, and the days without antipsychotic therapy should have been classified as "non-adherent". Conversely, the PDC may be underestimated for patients who intended to temporarily discontinue their medication according to their provider's instruction and did not meet the criteria for a regimen switch, as the days after the end of the supply/coverage of the regimen **were counted** as "non-adherent" in our PDC calculation. Moreover, for oral antipsychotics, the adherence analysis "assumes" patients should be on these oral formulations ongoing. Yet, this assumption may be a misclassification for some patients who are intended/prescribed oral therapy only for temporary use, such as for patients using oral therapy to supplement an LAI missed/late dose, as directed by labeling.

Although use of the GRMI for classifying non-adherent days to LAI antipsychotics is likely more restrictive than clinically necessary, as even 1 day past the GRMI is counted as a non-adherent day, using a PDC analysis allows flexibility in interpretation of results; for example, PDCs of ≥0.8 (ie, ≥80% of days covered) are considered/interpreted as adherent cases when using the GRMI. We also performed Analysis 2 using a longer allowance in the dosing interval (TI) corresponding to descriptions in labeling that suggest therapeutic levels are potentially maintained for some period past the GRMI. However, an additional buffer of 20% is likely inappropriate when interpreting adherence per PDCs calculated in Analysis 2, as it already accounts for late-dose allowances.

[§§] Due to time constraints, we were only able to acquire the number of subsequent courses excluded for **oral** antipsychotic regimens (not LAI antipsychotic regimens).

6.0 SUMMARY

Antipsychotics are the mainstay pharmacological treatment for schizophrenia,[2,3] and are an option for schizoaffective disorder.[5] Unfortunately, antipsychotic non-adherence is highly prevalent in patients with these conditions,[8,34] potentially leading to adverse outcomes (eg, relapse) and hindering treatment response.[1,10] Antipsychotics are available in a variety of dosage formulations, including oral and long-acting injectables (LAIs), with the choice of formulation potentially influencing medication adherence for some patients.[10]

Reviewed schizophrenia guidelines by the American Psychiatric Association (APA; 2020) and the Department of Veteran's Affairs/Department of Defense (VA/DoD; 2023) strongly recommend maintenance antipsychotic treatment in patients with schizophrenia who have responded to initial treatment, highlighting the benefits of continuous therapy for most patients, such as decreasing the risk of relapse, rehospitalization, and mortality.[1,10] The APA (2020) suggests continuing the *same* antipsychotic that led to symptom improvement, cautioning against switching medications due to potential risks (eg, clinical destabilization).[10] However, switching agents may be considered for various reasons, including but not limited to patient preference, intolerability or lack of efficacy. The VA/DoD (2023) weakly recommends an alternative antipsychotic in patients with schizophrenia who are unresponsive or intolerant to an initial antipsychotic.[1]

Both the VA/DoD (2023) and APA (2020) guidelines suggest *offering* LAI antipsychotics to patients with schizophrenia, either to improve medication adherence or based on patient preference.[1,10] LAI antipsychotics may be particularly beneficial for patients who struggle with adherence or are unresponsive to oral antipsychotics, or those transitioning between healthcare settings.[10] Additionally, early consideration of an LAI antipsychotic may be warranted in patients with limited treatment awareness or a comorbid substance use disorder, as they may be at an increased risk of poor adherence.[10] Compared to oral antipsychotics, LAI antipsychotics generally offer the advantage of no pill burden, less frequent dosing, and the benefit of regular provider interaction, as they must be administered by a healthcare provider.[10-21] Nonetheless, time constraints of patients and providers, along with transportation challenges may be barriers to receiving in-office administration of LAIs.[10]

Results from a 2021 systematic review and meta-analysis in adults with schizophrenia or other related conditions (Kishimoto et al; cited by the VA/DoD guideline), consisting of 32 randomized controlled trials (RCTs), 65 cohort studies, and 40 pre-post studies, showed that LAI antipsychotics were associated with a significantly lower risk of hospitalization or relapse (primary outcome) compared to oral antipsychotics.[8] Additionally, in the included studies for which adherence data were available, LAI antipsychotics were favored over oral antipsychotics for adherence outcomes, including proportion of days covered (PDC), medication possession ratio (MPR), proportion of patients achieving good adherence (ie, "taking the medication ≥75% of the days in the treatment period" [page 37][40]), psychiatrist's opinion on adherence, and medication adherence scale scores.[8,40]

Our data-driven utilization review descriptively 1) assessed the number of patients and claims for LAI antipsychotics, according to their preference status on the Utah Medicaid Preferred Drug List (PDL), and 2) measured adherence, using the PDC, to oral or LAI antipsychotics among Utah Medicaid adults with schizophrenia or schizoaffective disorder.

From the period of August 2023 through July 2024 (ie, observation period), 1,875 unique patients had at least 1 outpatient pharmacy claim for a PDL-listed LAI antipsychotic, with approximately 97% of the claims being for a PDL-preferred product. Based on patient and claim counts, Invega Sustenna was the most common LAI antipsychotic filled during the observation period, followed by Abilify Maintena, and then Aristada.

We included 1,395 Utah Medicaid adults with a presumed diagnosis of schizophrenia or schizoaffective disorder (per International Classification of Diseases, 10th Revision [ICD-10] codes) with ≥2 outpatient pharmacy fee-for-service (FFS) claims for the same oral or LAI regimen (except for Invega Hafyera, for which we required ≥1 claim) during the observation period (see **page 4** for full eligibility criteria) in our adherence analyses. PDC adherence was calculated 2 different ways: at the "population level" and "patient level"; calculated by dividing the total number of days covered by fills for an antipsychotic regimen (based on the entered days' supply [EDS] for oral antipsychotics, or an assumed dosing interval for LAI antipsychotics) by the total number of observation days. Observation days were defined as the total number of Medicaid-eligible days after the first fill in the medication regimen until meeting our definitions for a regimen discontinuation or switch, lost Utah Medicaid coverage, or the observation period ended during the assessed gap length (30, 60, or 90 days; see definitions in **Table 5**). Generally, a PDC ≥0.8 (ie, with ≥80% of days covered by the therapy) is considered "good" adherence.[30]

The population-level PDCs for LAI antipsychotic regimens, based on the general recommended maintenance interval (GRMI; Analysis 1)[***] and therapeutic interval (TI; Analysis 2),[†††] were high (≥0.8) for each assessed gap length, including for the least restrictive gap length of 90 days. Based on patient-level PDCs with respect to the GRMI, the percentage of patients with a PDC ≥0.8 was >85% for nearly all LAI regimens except for Abilify Maintena and Invega Sustenna.

The population-level PDCs with respect to the EDS tended to be high (≥0.8) across all gap lengths for most oral antipsychotic regimens, but had more outliers and more variability depending on the gap length than LAIs. The only oral antipsychotic regimens with a population-level PDC <0.8 were aripiprazole solution and prochlorperazine tablet (using the 90 day gap length only). According to patient-level PDCs, oral antipsychotic regimens with claims from ≥11 total patients and fewer than 70% of patients with a PDC ≥0.8 across any gap length were brexpiprazole tablet, olanzapine ODT, and risperidone tablet.

[***] The GRMI is the dosing interval recommended by the package insert (product labeling), which does not account for early- or late-dose allowances that may also be outlined in the package inserts.

[†††] The TI represents the longest duration that the injection may be therapeutically effective as inferred based on the point at which the product labeling recommends that the patient must receive supplementation with an oral product or LAI injections (in addition to the next dose) to restore therapeutic levels. Only LAI antipsychotics with this late-dose/supplementation information specified in their product labeling were included in Analysis 2.

There are several limitations of our data analyses that should be considered when interpreting the results.

- Prescription claims were used as a proxy for medication administration, but a prescription claim does not guarantee that the medication was actually taken (for oral products) or administered on the day of the fill (for LAIs).
- Regarding our adherence analysis, we primarily captured each patient's first observed course for a particular regimen, in addition to regimen switches. However, we did not capture all subsequent courses for each regimen. Our sensitivity analysis using different gap lengths addresses this issue to some degree, catching subsequent courses within up to 90 days.
- Population- or patient-level PDCs could have been overestimated or underestimated based on misclassification of adherence.
- The use of GRMI for classifying non-adherence to LAI antipsychotics (Analysis 1), while restrictive, allowed flexibility in interpretation of PDC results, with PDCs of ≥0.8 considered adherent.

The high population-level adherence (ie, PDC ≥0.8) for most antipsychotic regimens was contrasted with many potential therapy discontinuations for some regimens (discontinuation percentages per regimen at a gap length of 30 days ranged from 41% to <92% for LAI regimens using the GRMI threshold, and 35% to 58% for oral regimens; among those regimens with claims from ≥11 total patients). At the population level, we cannot be certain the reason patients discontinued therapy; it is possible that some patients discontinuing therapy were non-adherent to treatment. While non-adherent days among patients with a gap between fills of the same antipsychotic regimen of up to 90 days would have been caught by our PDC calculation, our calculations would not have caught patients with more than 90 days between fills of the same regimen (such patients could be classified as discontinuing therapy if they met our definition). Particularly because our descriptive analysis is cross-sectional (ie, potentially including both new initiators and long-term users of the same regimen), it is possible that some discontinuations were due to legitimate reasons (eg, temporarily paused due to intolerability, or planned discontinuation).

REFERENCES

1. Department of Veterans Affairs and Department of Defense. *Clinical Practice Guideline for Management of First-Episode Psychosis and Schizophrenia*. Department of Veterans Affairs and Department of Defense; 2023: 232 pages. Accessed August 7, 2024. Available at https://www.healthquality.va.gov/guidelines/MH/scz/VA-DoD-CPG-Schizophrenia-CPG_Finalv231924.pdf

2. Guo J, Lv X, Liu Y, Kong L, Qu H, Yue W. Influencing factors of medication adherence in schizophrenic patients: a meta-analysis. *Schizophrenia (Heidelb)*. 2023;9(1):31. doi:10.1038/s41537-023-00356-x

3. Crismon ML, Smith TL, Buckley PF. Schizophrenia. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey LM, eds. McGraw Hill; 2023. Accessed 2024/08/13. Available at accesspharmacy.mhmedical.com/content.aspx?aid=1201554450

4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders Text Revision (DSM-5-TR).* 5th ed. American Psychiatric Association; 2022. doi:10.1176/appi.books.9780890425763 Last Updated 2022. Accessed August 13, 2024. Available at https://www.appi.org/Products/DSM-Library/Diagnostic-and-Statistical-Manual-of-Mental-Di-(1)

5. Wy TJP, Saadabadi A. Schizoaffective Disorder. StatPearls Publishing Copyright 2024, StatPearls Publishing LLC.; 2024.

6. Paliperidone (Lexi-Drugs). online.lexi.com; 2024. Last Updated August 7, 2024. Accessed August 13, 2024. Available at http://online.lexi.com

7. CloZAPine (Lexi-Drugs). online.lexi.com; 2024. Last Updated August 2, 2024. Accessed August 13, 2024. Available at http://online.lexi.com

8. Kishimoto T, Hagi K, Kurokawa S, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. *Lancet Psychiatry*. 2021;8(5):387-404. doi:10.1016/s2215-0366(21)00039-0

9. Kikkert MJ, Dekker J. Medication Adherence Decisions in Patients With Schizophrenia. *Prim Care Companion CNS Disord*. 2017;19(6)doi:10.4088/PCC.17n02182

10. American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Schizophrenia*. Third Edition. American Psychiatric Association; 2020: 312 pages. Accessed August 7, 2024. Available at https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890424841

11. Aristada (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use. Package insert. Alkermes Inc.; 2023. Accessed August 12, 2024. Available at https://www.aristada.com/downloadables/ARISTADA-PI.pdf

12. Zyprexa Relprevv (olanzapine) for extended release injectable suspension. Package insert. CHEPLAPHARM Registration GmbH; 2023. Accessed August 12, 2024. Available at

https://www.zyprexarelprevvprogram.com/PDF/CHEPLAPHARM%20Prescribing%20Information.pdf

13. Perseris (risperidone) for extended-release injectable suspension, for subcutaneous use. Package insert. Indivior Inc.; 2022. Accessed August 12, 2024. Available at https://www.perseris.com/Downloads/USPI.pdf

14. Invega Hafyera (paliperidone palmitate) extended-release injectable suspension, for gluteal intramuscular use. Package insert. Janssen Pharmaceuticals Inc.; 2021. Accessed August 12, 2024. Available at https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVEGA+HAFYERA-pi.pdf

15. Invega Trinza (paliperidone palmitate) extended-release injectable suspension, for intramuscular use. Package insert. Janssen Pharmaceuticals Inc.; 2021. Accessed August 12, 2024. Available at https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVEGA+TRINZA-pi.pdf

16. Risperdal Consta (risperidone) long-acting injection. Package insert. Janssen Pharmaceuticals Inc.; 2021. Accessed August 12, 2024. Available at https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/RISPERDAL+CONSTA-pi.pdf

17. Invega Sustenna (paliperidone palmitate) extended-release injectable suspension, for intramuscular use. Package insert. Janssen Pharmaceuticals Inc.; 2022. Accessed August 12, 2024. Available at https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVEGA+SUSTENNA-pi.pdf

18. Abilify Maintena (aripiprazole) for extended-release injectable suspension, for intramuscular use. Package insert. Otsuka America Pharmaceutical Inc.; 2020. Accessed August 12, 2024. Available at https://www.otsuka-us.com/sites/g/files/qhldwo9046/files/media/static/Abilify-M-PI.pdf

19. Abilify Asimtufii (aripiprazole) extended-release injectable suspension, for intramuscular use. Package insert. Otsuka America Pharmaceutical Inc.; 2023. Accessed August 12, 2024. Available at https://otsuka-us.com/sites/g/files/qhldwo9046/files/media/static/Abilify-Asimtufii-PI.pdf

20. Rykindo (risperidone) for extended-release injectable suspension, for intramuscular use. Package insert. Shandong Luye Pharmaceutical Co. Ltd.; 2023. Accessed August 12, 2024. Available at https://www.luye.cn/lvye_en/rykindo.pdf

21. Uzedy (risperidone) extended-release injectable suspension, for subcutaneous use. Package insert. Teva Neuroscience Inc.; 2024. Accessed August 12, 2024. Available at https://www.uzedy.com/globalassets/uzedy/prescribing-information.pdf

22. FluPHENAZine (Lexi-Drugs). online.lexi.com; 2024. Last Updated September 3, 2024. Accessed September 17, 2024. Available at http://online.lexi.com

23. Haloperidol (Lexi-Drugs). online.lexi.com; 2024. Last Updated July 17, 2024. Accessed August 13, 2024. Available at http://online.lexi.com

24. Lauriello J, Campbell AR. Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication. UpToDate.com; 2024. Last Updated January 22, 2024. Accessed

August 16, 2024. Available at https://www.uptodate.com/contents/schizophrenia-in-adults-pharmacotherapy-with-long-acting-injectable-antipsychotic-medication

25. Drug Regimen Review Center. *High-dose Therapy and Multiple Antipsychotics in Adults: Guideline Summary and Retrospective Utilization Review*. Utah Department of Health & Human Services Medicaid Drug Utilization Review Board; 2024: 85 pages. Accessed August 22, 2024. Available at https://medicaid.utah.gov/pharmacy/drug-utilization-review-board/

26. Utah Department of Health & Human Services. *Preferred Drug List & Pharmacy Coverage Resources*. Utah Department of Health & Human Services; 2024: 115 pages. Last Updated August 1, 2024. Accessed August 12, 2024. Available at https://medicaid.utah.gov/pharmacy/preferred-drug-list/

27. Strohecker J. *Long-Acting Injectable Typical and Atypical Antipsychotic Payment*. Utah Department of Health and Human Services; 2023: 8 pages. Last Updated November 2023. Accessed September 13, 2024. Available at https://le.utah.gov/interim/2023/pdf/00004493.pdf

28. Loxapine (Lexi-Drugs). online.lexi.com; 2024. Last Updated August 7, 2024. Accessed August 13, 2024. Available at http://online.lexi.com

29. Pharmacy Quality Alliance (PQA). PQA Adherence Measures. pqaalliance.org. Accessed August 23, 2024. Available at https://www.pqaalliance.org/adherence-measures

30. Health Services Advisory Group (HSAG) with the Centers for Medicare & Medicaid Services. *Adherence to Antipsychotic Medications For Individuals with Schizophrenia*. Quality ID #383 (NQF 1879). Health Services Advisory Group (HSAG) with the Centers for Medicare & Medicaid Services; 2021: 12 pages. Accessed August 16, 2024. Available at https://qpp.cms.gov/docs/QPP_quality_measure_specifications/CQM-Measures/2021_Measure_383_MIPSCQM.pdf

31. Fluphenazine decanoate injection, solution. Package insert. Eugia Pharma Specialities Limited; 2023. Accessed August 22, 2024. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1f532edc-1a2c-4221-80dd-1ac158dd3a72

32. Haloperidol decanoate injection. Package insert. Janssen Pharmaceuticals Inc.; 2020. Accessed August 22, 2024. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=af0159a8-dff5-449a-aa2b-a0c430081e21

33. Aristada Initio (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use. Package insert. Alkermes Inc.; 2023. Accessed August 12, 2024. Available at https://www.aristada.com/downloadables/ARISTADA-INITIO-PI.pdf

34. Goff DC, Hill M, Freudenreich O. Treatment adherence in schizophrenia and schizoaffective disorder. *J Clin Psychiatry*. 2011;72(4):e13. doi:10.4088/JCP.9096tx6cc

35. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209-1223. doi:10.1056/NEJMoa051688

36. Kessler T, Lev-Ran S. The association between comorbid psychiatric diagnoses and hospitalization-related factors among individuals with schizophrenia. *Compr Psychiatry*. 2019;89:7-15. doi:10.1016/j.comppsych.2018.12.004

37. Campagna EJ, Muser E, Parks J, Morrato EH. Methodological considerations in estimating adherence and persistence for a long-acting injectable medication. *J Manag Care Spec Pharm*. 2014;20(7):756-766. doi:10.18553/jmcp.2014.20.7.756

38. Correll CU, Kim E, Sliwa JK, et al. Pharmacokinetic Characteristics of Long-Acting Injectable Antipsychotics for Schizophrenia: An Overview. *CNS Drugs*. 2021;35(1):39-59. doi:10.1007/s40263-020-00779-5

39. Dyrmishi E, De Pieri M, Ferrari M, et al. Case Report: Long-Acting Oral Cariprazine. *Front Psychiatry*. 2022;13:876003. doi:10.3389/fpsyt.2022.876003

40. Kishimoto T, Hagi K, Kurokawa S, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies [Supplementary Appendix 8]. *Lancet Psychiatry*. 2021;8(5):387-404. doi:10.1016/s2215-0366(21)00039-0

41. McDonagh MS, Dana T, Selph S, et al. AHRQ Comparative Effectiveness Reviews - Treatments for Schizophrenia in Adults: A Systematic Review. Agency for Healthcare Research and Quality (US); 2017.

42. Kishi T, Matsunaga S, Iwata N. Mortality Risk Associated With Long-acting Injectable Antipsychotics: A Systematic Review and Meta-analyses of Randomized Controlled Trials. *Schizophr Bull*. 2016;42(6):1438-1445. doi:10.1093/schbul/sbw043

43. Kishi T, Oya K, Iwata N. Long-acting injectable antipsychotics for the prevention of relapse in patients with recent-onset psychotic disorders: A systematic review and meta-analysis of randomized controlled trials. *Psychiatry Res*. 2016;246:750-755. doi:10.1016/j.psychres.2016.10.053

44. Kishimoto T, Robenzadeh A, Leucht C, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. *Schizophr Bull*. 2014;40(1):192-213. doi:10.1093/schbul/sbs150

45. Ostuzzi G, Bighelli I, So R, Furukawa TA, Barbui C. Does formulation matter? A systematic review and meta-analysis of oral versus long-acting antipsychotic studies. *Schizophr Res*. 2017;183:10-21. doi:10.1016/j.schres.2016.11.010

46. Taipale H, Mehtälä J, Tanskanen A, Tiihonen J. Comparative Effectiveness of Antipsychotic Drugs for Rehospitalization in Schizophrenia-A Nationwide Study With 20-Year Follow-up. *Schizophr Bull*. 2018;44(6):1381-1387. doi:10.1093/schbul/sbx176

47. Taipale H, Mittendorfer-Rutz E, Alexanderson K, et al. Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. *Schizophr Res*. 2018;197:274-280. doi:10.1016/j.schres.2017.12.010

48. Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. *Am J Psychiatry*. 2011;168(6):603-609. doi:10.1176/appi.ajp.2011.10081224

49. Tiihonen J, Mittendorfer-Rutz E, Majak M, et al. Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29 823 Patients With Schizophrenia. *JAMA Psychiatry*. 2017;74(7):686-693. doi:10.1001/jamapsychiatry.2017.1322

50. Kishimoto T, Hagi K, Nitta M, et al. Effectiveness of Long-Acting Injectable vs Oral Antipsychotics in Patients With Schizophrenia: A Meta-analysis of Prospective and Retrospective Cohort Studies. *Schizophr Bull*. 2018;44(3):603-619. doi:10.1093/schbul/sbx090

51. Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. *J Clin Psychiatry*. 2013;74(10):957-965. doi:10.4088/JCP.13r08440

52. ARIPiprazole (Lexi-Drugs). online.lexi.com; 2024. Last Updated August 13, 2024. Accessed August 13, 2024. Available at http://online.lexi.com

53. OLANZapine (Lexi-Drugs). online.lexi.com; 2024. Last Updated September 3, 2024. Accessed September 16, 2024. Available at http://online.lexi.com

54. RisperiDONE (Lexi-Drugs). online.lexi.com; 2024. Last Updated September 4, 2024. Accessed September 16, 2024. Available at http://online.lexi.com

55. Aripiprazole. micromedexsolutions.com; 2024. Last Updated Septmeber 11, 2024. Accessed September 16, 2024. Available at https://www.micromedexsolutions.com/home/dispatch

56. ARIPiprazole Lauroxil (Lexi-Drugs). online.lexi.com; 2024. Last Updated September 6, 2024. Accessed September 16, 2024. Available at http://online.lexi.com

57. Aripiprazole Lauroxil. micromedexsolutions.com; 2024. Last Updated Septmeber 11, 2024. Accessed September 16, 2024. Available at https://www.micromedexsolutions.com/home/dispatch

58. Fluphenazine. micromedexsolutions.com; 2024. Last Updated Septmeber 17, 2024. Accessed September 18, 2024. Available at https://www.micromedexsolutions.com/home/dispatch

59. Haloperidol. micromedexsolutions.com; 2024. Last Updated Septmeber 17, 2024. Accessed September 18, 2024. Available at https://www.micromedexsolutions.com/home/dispatch

60. Olanzapine. micromedexsolutions.com; 2024. Last Updated Septmeber 11, 2024. Accessed September 16, 2024. Available at https://www.micromedexsolutions.com/home/dispatch

61. Olanzapine Pamoate. micromedexsolutions.com; 2024. Last Updated Septmeber 11, 2024. Accessed September 16, 2024. Available at https://www.micromedexsolutions.com/home/dispatch

62. Paliperidone Palmitate. micromedexsolutions.com; 2024. Last Updated Septmeber 11, 2024. Accessed September 16, 2024. Available at https://www.micromedexsolutions.com/home/dispatch

63. Risperidone. micromedexsolutions.com; 2024. Last Updated Septmeber 13, 2024. Accessed September 16, 2024. Available at https://www.micromedexsolutions.com/home/dispatch

APPENDIX A: DOSAGE FORMS FOR ORAL ANTIPSYCHOTICS

Table A1 provides an overview of the oral dosage forms that were included for each active ingredient in our adherence data analysis for the oral products, each indicated for at least schizophrenia or schizoaffective disorder. Notably, some active ingredients may also be available in dosage forms not addressed by this report (eg, short-acting injectable, transdermal patch).

Table A1. Oral Dosage Formulations Included for Each Active Ingredient in Our Adherence Analysis for Oral Products

First generation antipsychotics		Second generation antipsychotics	
Active ingredient	**Oral dosage formulation(s)**	**Active ingredient**	**Oral dosage formulation(s)**
Chlorpromazine	tablet; concentrate; syrup; CR capsule	Aripiprazole	tablet (with sensor); ODT; solution
Fluphenazine	tablet; elixir; concentrate	Asenapine	sublingual tablet
Haloperidol[b]	tablet; concentrate; solution	Brexpiprazole	tablet
Loxapine[c]	capsule; concentrate	Cariprazine	capsule
Molindone	tablet; solution	Clozapine	tablet; ODT; suspension
Perphenazine	tablet; concentrate	Iloperidone	tablet
Perphenazine and amitriptyline	tablet	Lumateperone	capsule
Prochlorperazine	tablet; syrup; CR capsule	Lurasidone	tablet
Thioridazine	tablet; concentrate; suspension	Olanzapine	tablet; ODT
Thiothixene	capsule; concentrate	Olanzapine and samidorphan	tablet
Trifluoperazine	tablet; concentrate	Paliperidone	ER tablet
		Quetiapine	tablet; ER tablet
		Risperidone	tablet; ODT; solution
		Ziprasidone	capsule

[a] *Some products are available in dosage forms not addressed by this report (eg, short-acting injectable, transdermal patch). Consequently, this table is not comprehensive of all available dosage forms for some listed antipsychotics, but rather focuses exclusively on oral forms.*

[b] *Haloperidol is available as a concentrate and solution, but for the purposes of our adherence analysis we classified the concentrate as a solution to represent the same regimen.*

[c] *Loxapine is also available as an oral inhalation powder, but this formulation was excluded from our analysis as it is used for acute treatment only.*[28]

Abbreviations: CR, controlled-release; ER, extended-release; ODT, orally disintegrating tablet

APPENDIX B: ASSIGNED REGIMENS FOR LAI ANTIPSYCHOTICS FOR ADHERENCE ANALYSES

LAI antipsychotics were grouped into the same regimen if they had the same brand name (or generic equivalent) for second-generation antipsychotics (SGAs) or generic name for first-generation antipsychotics (FGAs), and respective to their dosing intervals. **Table B1** shows the assigned regimens for the LAI antipsychotics for the adherence analyses.

Table B1. Regimen Groupings for LAI Antipsychotics

LAI antipsychotic product (brand name, as applicable)		Dose (mg)	Dosing interval		LAI antipsychotic regimen	
			GRMI (days)	TI (days)	GRMI analysis	TI analysis
Aripiprazole	Abilify Asimtufii	720; 960	60	98	Abilify Asimtufii	
	Abilify Maintena	300; 400	30	42	Abilify Maintena	
Aripiprazole lauroxil	Aristada	1064	60	70	Aristada 1064 mg	
		441	30	42	Aristada 441 mg or 662 mg	Aristada 441 mg
		662	30	56		Aristada 662 mg or 882 mg
		882	42	56	Aristada 882 mg	
Fluphenazine decanoate	Generic	25/mL	28	42	Fluphenazine decanoate	
Haloperidol decanoate	Generic	50/ mL; 100/mL; 500/5 mL	30	NA	Haloperidol decanoate	
Olanzapine pamoate	Zyprexa Relprevv	210	14	NA	Zyprexa Relprevv 150 mg or 210 mg	
		300; 405	28	NA	Zyprexa Relprevv 300 mg or 405 mg	
Paliperidone palmitate	Invega Sustenna	39/0.25 mL; 78/0.5 mL; 117/0.75 mL; 156/mL; 234/1.5 mL	30	42	Invega Sustenna	
	Invega Trinza	273/0.88 mL; 410/1.32 mL; 546/1.75 mL; 819/2.63 mL	90	120	Invega Trinza	
	Invega Hafyera	1092/3.5 mL; 1560/5 mL	180	201	Invega Hafyera	
Risperidone	Perseris	90; 120	30	NA	Perseris	
	Uzedy	50/0.14 mL; 75/0.21 mL; 100/0.28 mL; 125/0.25 mL; 150/0.42 mL; 200/0.56 mL; 250/0.7 mL	60	NA	Uzedy	

Abbreviations: LAI, long-acting injectable; NA, not applicable

Table B1. Regimen Groupings for LAI Antipsychotics

LAI antipsychotic product (brand name, as applicable)		Dose (mg)	Dosing interval		LAI antipsychotic regimen	
			GRMI (days)	TI (days)	GRMI analysis	TI analysis
	Risperdal Consta and its generic	12.5; 25; 37.5; 50	14	NA	Risperdal Consta and its generic	

Abbreviations: LAI, long-acting injectable; NA, not applicable

APPENDIX C: USES (ON-AND OFF-LABEL) FOR THE ACTIVE INGREDIENT OF LAI ANTIPSYCHOTICS

Table C1 provides the FDA-approved indications for LAI antipsychotics and oral dosage forms with the same active ingredient. **Table C2** summarizes compendia-recognized off-label uses for the active ingredient of LAI antipsychotics (including for different formulations).

Table C1. FDA-approved Indications for LAI Antipsychotics, and for the Same Oral Molecule

Active ingredient	FDA-approved indication(s) for the corresponding LAI product (brand name, as applicable) per prescribing information[11-15,17-19,31,32]	FDA-approved indication(s) for at least 1 oral dosage form per Lexidrug monographs[6,22,23,52-54]
Aripiprazole	Abilify Asimtufii* and Abilify Maintena*: Treatment of schizophrenia in adults; and maintenance monotherapy for bipolar I in adults	Monotherapy or adjunctive therapy to lithium or valproate for acute mania or mixed episodes with features associated with bipolar disorder and maintenance treatment; treatment of irritability associated with autistic disorder in pediatric patients; adjunctive treatment for resistant major depressive disorder in patients unresponsive to prior antidepressant use; treatment of schizophrenia; treatment of Tourette disorder in pediatric patients
Aripiprazole lauroxil	Aristada*: Treatment of schizophrenia in adults	NA
Fluphenazine	Fluphenazine decanoate: "Management of patients requiring prolonged parenteral neuroleptic therapy" (page 2)[31]	For the management of psychotic disorders *Limitation of use:* not effective for managing behavioral complications in patients with intellectual disabilities
Haloperidol	Haloperidol decanoate: Treatment of schizophrenia in patients requiring prolonged parenteral antipsychotic therapy	Treatment of several nonpsychotic behavioral disorders in children unresponsive to psychotherapy or non-antipsychotic medications; short-term treatment of hyperactivity in children unresponsive to psychotherapy or non-antipsychotic medications; treatment of psychotic disorders; treatment of adults and children with tics and vocal utterances related to Tourette syndrome
Olanzapine	Zyprexa Relprevv*: Treatment of schizophrenia[a]	Monotherapy or as combination therapy with lithium or valproate for acute mania, acute episodes with mixed features associated with bipolar I disorder, and maintenance treatment (bipolar depression in combination with fluoxetine); treatment resistant major depressive disorder (unipolar; in combination with fluoxetine); treatment of schizophrenia

**** Denotes the LAI products with a preferred status on the Utah Medicaid Preferred Drug List, as of August 2024.***

***** Denotes the LAI products with a non-preferred status on the Utah Medicaid Preferred Drug List, as of August 2024.***

[a] According to Zyprexa Relprevv prescribing information, efficacy was established in 2 clinical trials among adults with schizophrenia, and safety and efficacy has not been studied in pediatric patients.

[b] According to Risperdal Consta prescribing information, efficacy and safety has not been established in pediatric patients.

Abbreviations: FDA, US Food and Drug Administration; LAI, long-acting injectable; NA, not applicable; US, United States

Table C1. FDA-approved Indications for LAI Antipsychotics, and for the Same Oral Molecule

Active ingredient	FDA-approved indication(s) for the corresponding LAI product (brand name, as applicable) per prescribing information[11-15,17-19,31,32]	FDA-approved indication(s) for at least 1 oral dosage form per Lexidrug monographs[6,22,23,52-54]
Paliperidone	Invega Sustenna*: Treatment of schizophrenia in adults; and as monotherapy and as an adjunct to mood stabilizers or antidepressants for the treatment of schizoaffective disorder in adults	Treatment of schizophrenia; and as monotherapy and as an adjunct to mood stabilizers or antidepressants for the treatment of schizoaffective disorder
	Invega Trinza*: Treatment of schizophrenia, as a follow on option to at least 4 months of treatment with Invega Sustenna	
	Invega Hafyera*: Treatment of schizophrenia in adults, as a follow on option to at least 4 months of Invega Sustenna or at least one three-month cycle of Invega Trinza	
Risperidone	Perseris*: Treatment of schizophrenia in adults	Treatment of acute mania or acute episodes with mixed features of bipolar disorder as monotherapy or as an adjunct to lithium or valproate in adults, or as monotherapy for acute mania or acute mixed episodes associated with bipolar disorder in pediatric patients aged 10–17 years of age; treatment of irritability associated with autistic disorder in pediatric patients aged 5–17 years; treatment of schizophrenia in adolescents (13–17 years of age) and adults
	Rykindo**: Treatment of schizophrenia in adults; and as monotherapy or as adjunctive therapy to lithium or valproate for bipolar I in adults	
	Uzedy**: Treatment of schizophrenia in adults	
	Risperdal Consta**: Treatment of schizophrenia; and as monotherapy or as adjunctive therapy to lithium or valproate for bipolar I[b]	

**** Denotes the LAI products with a preferred status on the Utah Medicaid Preferred Drug List, as of August 2024.***

***** Denotes the LAI products with a non-preferred status on the Utah Medicaid Preferred Drug List, as of August 2024.***

[a] According to Zyprexa Relprevv prescribing information, efficacy was established in 2 clinical trials among adults with schizophrenia, and safety and efficacy has not been studied in pediatric patients.

[b] According to Risperdal Consta prescribing information, efficacy and safety has not been established in pediatric patients.

Abbreviations: FDA, US Food and Drug Administration; LAI, long-acting injectable; NA, not applicable; US, United States

Table C2. Off-label Indications for Active Ingredients of LAI Antipsychotics[a]

Off-label indication(s) per drug compendia			
Micromedex[b]		**Lexidrug[c]**	
Pediatric off-label indications	**Adult off-label indications**	**Pediatric off-label indications**	**Adult off-label indications**
Aripiprazole[52,55]			
Evidence favors efficacy (Category B): • Anorexia nervosa	*Evidence favors efficacy (Category B):* • Borderline personality disorder • Dementia-related psychosis • Antipsychotic-induced hyperprolactinemia • Obsessive-compulsive disorder; adjunct • Postoperative delirium; prophylaxis • Schizoaffective disorder	None reported	*LOE B, G:* • Acute, severe agitation/aggression associated with psychiatric disorders, substance intoxication, or other organic causes • Severe or refractory dementia-related agitation/aggression and psychosis *LOE C, G:* • Delusion infestation (delusional parasitosis) • Treatment resistant obsessive-compulsive disorder • Tourette syndrome *LOE C:* • Delusional disorder • Huntington disease-associated chorea
Aripiprazole lauroxil[56,57]			
None reported	None reported	None reported	None reported

[a] *Reported off-label uses are according to the active ingredient, potentially comprising of several different formulations.*

[b] *Only off-label indications indexed as "effective" or "evidence favors efficacy" were extracted; some off-label uses are displayed in the "In-depth Answers" view of the database only.*

Micromedex categories for the strength of evidence: Category A, based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B, based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies.

[c] *Lexidrug level of evidence (LOE): A, based on well-conducted RCTs or overwhelming evidence of some other form. Estimate of effect is unlikely to change with future research. B, based on RCTs with critical limitations (eg, flawed methods, inconsistent results), or very strong evidence from an alternative study design. Estimate of effect may change with future research; C, based on evidence from observational studies, unsystematic clinical experience, or potentially flawed RCTs. Estimate of effect is uncertain. G, supported by inclusion in at least one evidence- or consensus-based clinical practice guideline.*

[d] *The adult off-label indications indexed in Micromedex for fluphenazine decanoate (ie, dementia-related agitation, Huntington's disease, self-injurious behavior) were all classified as evidence is inconclusive, and therefore were not extracted.*

Abbreviations: ICU, intensive care unit; LAI, long-acting injectable; LOE, level of evidence; N/V, nausea and vomiting; RCT(s), randomized controlled trial(s)

Table C2. Off-label Indications for Active Ingredients of LAI Antipsychotics[a]

Off-label indication(s) per drug compendia			
Micromedex[b]		**Lexidrug[c]**	
Pediatric off-label indications	**Adult off-label indications**	**Pediatric off-label indications**	**Adult off-label indications**
Fluphenazine decanoate[58]		**Fluphenazine[22]**	
None reported	None reported[d]	None reported	*LOE C, G:* • Tics
Haloperidol decanoate[59]		**Haloperidol[23]**	
None reported	None reported	None reported	*LOE B, G:* • Acute, severe agitation/aggression associated with psychiatric disorders, substance intoxication, or other organic causes • Bipolar disorder (acute mania, episodes with acute hypomania or mixed features) • Delirium, hyperactive; treatment • Postoperative N/V, prevention, moderate-to-high risk patients *LOE C, G:* • Chemotherapy-induced breakthrough N/V • N/V in advanced or terminal illness (palliative care) • Postpartum psychosis

[a] *Reported off-label uses are according to the active ingredient, potentially comprising of several different formulations.*

[b] *Only off-label indications indexed as "effective" or "evidence favors efficacy" were extracted; some off-label uses are displayed in the "In-depth Answers" view of the database only.*

Micromedex categories for the strength of evidence: Category A, based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B, based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies.

[c] *Lexidrug level of evidence (LOE): A, based on well-conducted RCTs or overwhelming evidence of some other form. Estimate of effect is unlikely to change with future research. B, based on RCTs with critical limitations (eg, flawed methods, inconsistent results), or very strong evidence from an alternative study design. Estimate of effect may change with future research; C, based on evidence from observational studies, unsystematic clinical experience, or potentially flawed RCTs. Estimate of effect is uncertain. G, supported by inclusion in at least one evidence- or consensus-based clinical practice guideline.*

[d] *The adult off-label indications indexed in Micromedex for fluphenazine decanoate (ie, dementia-related agitation, Huntington's disease, self-injurious behavior) were all classified as evidence is inconclusive, and therefore were not extracted.*

Abbreviations: ICU, intensive care unit; LAI, long-acting injectable; LOE, level of evidence; N/V, nausea and vomiting; RCT(s), randomized controlled trial(s)

Table C2. Off-label Indications for Active Ingredients of LAI Antipsychotics[a]

Off-label indication(s) per drug compendia			
Micromedex[b]		**Lexidrug**[c]	
Pediatric off-label indications	**Adult off-label indications**	**Pediatric off-label indications**	**Adult off-label indications**
Olanzapine (pamoate)[53,60,61]			
Evidence favors efficacy (Category B): • Chemotherapy-induced N/V, moderately or highly emetogenic chemotherapy; treatment and prophylaxis	*Evidence favors efficacy (Category B):* • Acute dementia-related agitation • Anorexia nervosa • Cancer cachexia • Delirium • Schizoaffective disorder • Refractory schizophrenia • Severe major depression with psychotic features; adjunct *Effective (Category B):* • Acute agitation • Chemotherapy-induced N/V, moderately or highly emetogenic chemotherapy; treatment and prophylaxis	None reported	*LOE A, G:* • Chemotherapy-induced acute and delayed N/V (high emetic risk [90%]); prophylaxis • Chemotherapy-induced breakthrough N/V; treatment *LOE B,G:* • Dementia-related agitation/aggression and psychosis • Cancer-related anorexia and cachexia • Major depressive disorder (unipolar) with psychotic features • N/V associated with advanced cancer *LOE C, G:* • Anorexia nervosa • Bipolar disorder, hypomania • Delirium, hyperactive (ICU and non-ICU treatment) • Delusional infestation (delusional parasitosis) • Postpartum psychosis

[a] *Reported off-label uses are according to the active ingredient, potentially comprising of several different formulations.*

[b] *Only off-label indications indexed as "effective" or "evidence favors efficacy" were extracted; some off-label uses are displayed in the "In-depth Answers" view of the database only.*

Micromedex categories for the strength of evidence: Category A, based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B, based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies.

[c] *Lexidrug level of evidence (LOE): A, based on well-conducted RCTs or overwhelming evidence of some other form. Estimate of effect is unlikely to change with future research. B, based on RCTs with critical limitations (eg, flawed methods, inconsistent results), or very strong evidence from an alternative study design. Estimate of effect may change with future research; C, based on evidence from observational studies, unsystematic clinical experience, or potentially flawed RCTs. Estimate of effect is uncertain. G, supported by inclusion in at least one evidence- or consensus-based clinical practice guideline.*

[d] *The adult off-label indications indexed in Micromedex for fluphenazine decanoate (ie, dementia-related agitation, Huntington's disease, self-injurious behavior) were all classified as evidence is inconclusive, and therefore were not extracted.*

Abbreviations: ICU, intensive care unit; LAI, long-acting injectable; LOE, level of evidence; N/V, nausea and vomiting; RCT(s), randomized controlled trial(s)

Table C2. Off-label Indications for Active Ingredients of LAI Antipsychotics[a]

Off-label indication(s) per drug compendia			
Micromedex[b]		**Lexidrug[c]**	
Pediatric off-label indications	**Adult off-label indications**	**Pediatric off-label indications**	**Adult off-label indications**
			LOE C: • Huntington disease-associated chorea
Paliperidone palmitate[6,62]			
None reported	*Evidence favors efficacy (Category B):* • Acute manic and mixed episodes of bipolar I disorder	None reported	None reported
Risperidone[54,63]			
Evidence favors efficacy (Category B): • Autism spectrum disorder • Intellectual disability behavioral syndrome • Gilles de la Tourette's syndrome	*Evidence favors efficacy (Category A):* • Dementia-related psychosis *Evidence favors efficacy (Category B):* • Dementia-related behavioral syndrome • Intellectual disability behavioral syndrome • Delirium, patients undergoing cardiac surgery; prophylaxis • Gilles de la Tourette's syndrome • Neuroleptic-induced tardive dyskinesia • Schizoaffective disorder	None reported	*LOE B, G:* • Severe or refractory dementia-related agitation/aggression and psychosis • Treatment resistant major depressive disorder (unipolar) • Tourette syndrome *LOE C, G:* • Acute, severe agitation/aggression associated with psychiatric disorders, substance intoxication, or other organic causes • Bipolar disorder, hypomania • Delusional infestation (delusional parasitosis) • Treatment resistant obsessive-compulsive disorder

[a] *Reported off-label uses are according to the active ingredient, potentially comprising of several different formulations.*

[b] *Only off-label indications indexed as "effective" or "evidence favors efficacy" were extracted; some off-label uses are displayed in the "In-depth Answers" view of the database only.*

Micromedex categories for the strength of evidence: Category A, based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B, based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies.

[c] *Lexidrug level of evidence (LOE): A, based on well-conducted RCTs or overwhelming evidence of some other form. Estimate of effect is unlikely to change with future research. B, based on RCTs with critical limitations (eg, flawed methods, inconsistent results), or very strong evidence from an alternative study design. Estimate of effect may change with future research; C, based on evidence from observational studies, unsystematic clinical experience, or potentially flawed RCTs. Estimate of effect is uncertain. G, supported by inclusion in at least one evidence- or consensus-based clinical practice guideline.*

[d] *The adult off-label indications indexed in Micromedex for fluphenazine decanoate (ie, dementia-related agitation, Huntington's disease, self-injurious behavior) were all classified as evidence is inconclusive, and therefore were not extracted.*

Abbreviations: ICU, intensive care unit; LAI, long-acting injectable; LOE, level of evidence; N/V, nausea and vomiting; RCT(s), randomized controlled trial(s)

Table C2. Off-label Indications for Active Ingredients of LAI Antipsychotics[a]

Off-label indication(s) per drug compendia			
Micromedex[b]		**Lexidrug**[c]	
Pediatric off-label indications	**Adult off-label indications**	**Pediatric off-label indications**	**Adult off-label indications**
			LOE C: • Delusional disorder • Huntington disease-associated chorea

[a] *Reported off-label uses are according to the active ingredient, potentially comprising of several different formulations.*

[b] *Only off-label indications indexed as "effective" or "evidence favors efficacy" were extracted; some off-label uses are displayed in the "In-depth Answers" view of the database only.*

Micromedex categories for the strength of evidence: Category A, based on consistent results from meta-analyses of RCTs or several well-conducted, large RCTs; Category B, based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies.

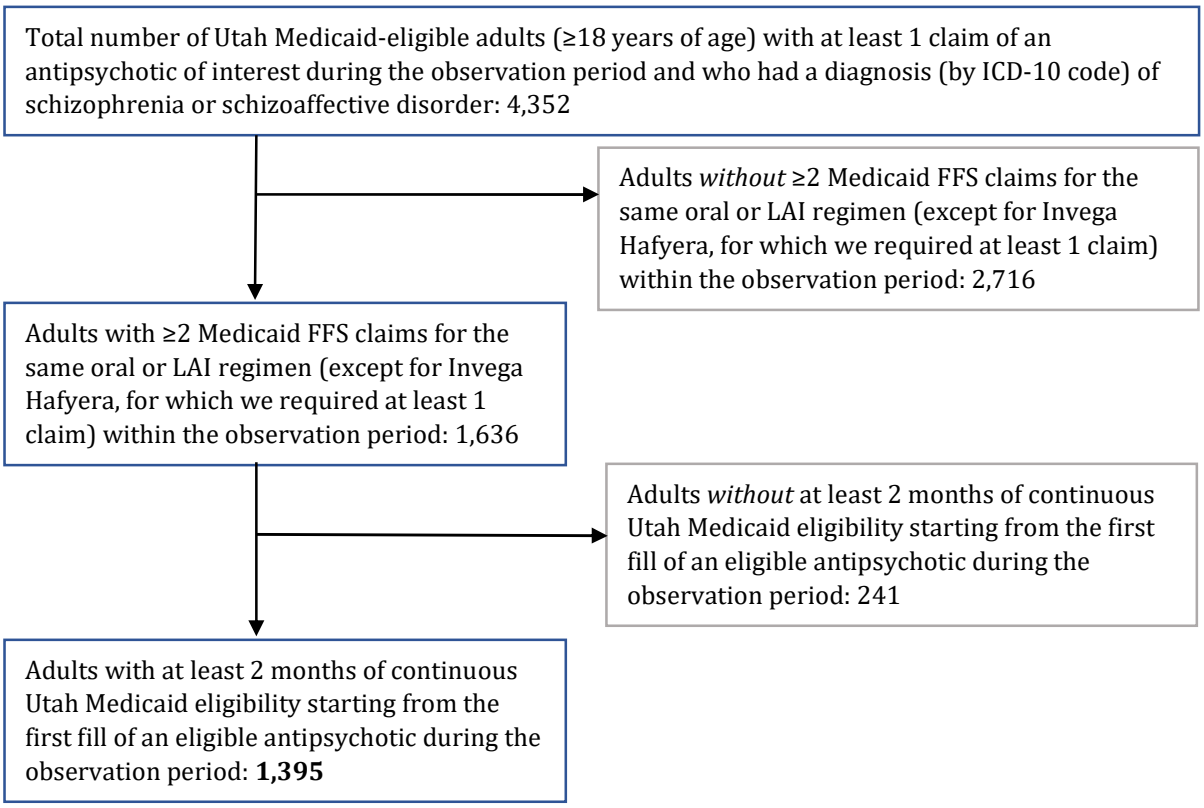
[c] *Lexidrug level of evidence (LOE): A, based on well-conducted RCTs or overwhelming evidence of some other form. Estimate of effect is unlikely to change with future research. B, based on RCTs with critical limitations (eg, flawed methods, inconsistent results), or very strong evidence from an alternative study design. Estimate of effect may change with future research; C, based on evidence from observational studies, unsystematic clinical experience, or potentially flawed RCTs. Estimate of effect is uncertain. G, supported by inclusion in at least one evidence- or consensus-based clinical practice guideline.*

[d] *The adult off-label indications indexed in Micromedex for fluphenazine decanoate (ie, dementia-related agitation, Huntington's disease, self-injurious behavior) were all classified as evidence is inconclusive, and therefore were not extracted.*

Abbreviations: ICU, intensive care unit; LAI, long-acting injectable; LOE, level of evidence; N/V, nausea and vomiting; RCT(s), randomized controlled trial(s)

APPENDIX D: COHORT DISPOSITION DIAGRAM FOR THE ADHERENCE ANALYSES

Figure D1. Adherence Descriptive Analyses Cohort Disposition Diagram, by Unique Patients[a]



[a] *The observation period occurred from August 1, 2023 to July 31, 2024.*

Abbreviations: FFS, fee-for-service; ICD-10, International Classification of Diseases, 10th Revision; LAI, long-acting injectable

APPENDIX E: SUBSEQUENT COURSES EXCLUDED FROM ORAL ANTIPSYCHOTIC PDC CALCULATIONS

Table E1 shows the number of subsequent courses that were excluded from the PDC calculation after the 90-day gap for each oral antipsychotic regimen. Due to time constraints, we were unable to acquire the number of subsequent courses that were excluded from the PDC calculation for LAI antipsychotic regimens.

Table E1. Number of Subsequent Courses Excluded from the PDC Calculation for Oral Antipsychotic Regimens, Using the 90-Day Gap Length

Oral antipsychotic regimen	Number of subsequent courses excluded
Aripiprazole solution	<11
Aripiprazole tablet	15
Asenapine sublingual tablet	<11
Brexpiprazole tablet	<11
Cariprazine capsule	<11
Chlorpromazine tablet	0
Clozapine tablet	0
Fluphenazine tablet	0
Haloperidol tablet	<11
Iloperidone tablet	0
Lumateperone capsule	0
Lurasidone tablet	<11
Olanzapine ODT	0
Olanzapine tablet	11
Olanzapine + samidorphan tablet	0
Paliperidone ER tablet	<11
Perphenazine tablet	<11
Prochlorperazine tablet	<11
Quetiapine ER tablet	<11
Quetiapine tablet	11
Risperidone ODT	0
Risperidone solution	0
Risperidone tablet	<11
Thioridazine tablet	0
Thiothixene capsule	<11
Trifluoperazine tablet	0
Ziprasidone capsule	<11

Counts >0 and <11 are reported as <11 for patient privacy concerns.

Abbreviations: ER, extended-release; ODT, orally disintegrating tablet; PDC, proportion of days covered