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Assessment of oral overlap with antipsychotic long-acting injectables initiated in an inpatient setting

Jennifer T. Tran, PharmD[1]
Katie J. Binger, PharmD, BCPP[2]
Talia M. Miles, PharmD, BCPS, BCPP[3]

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Abstract

Introduction: Long-acting injectable (LAI) antipsychotics are a promising solution to combating issues related to nonadherence to oral antipsychotics. Oral overlap is utilized when an LAI is initiated to achieve therapeutic concentrations. The place in therapy in which additional overlap is warranted is often mistaken, and providers may prescribe additional overlap based on the presentation of the patient or misunderstanding of appropriate overlap.

Methods: This retrospective chart review assesses patients who were initiated on an LAI while admitted to the acute inpatient psychiatric unit from January 1, 2016, to December 31, 2019. The primary outcome assesses the appropriateness of oral overlap with LAIs. Secondary outcomes include adherence to oral overlap, discontinuation of an LAI within 4 months, and reason for discontinuation of LAI.

Results: A total of 62 patients were included: 40 (65%) had appropriate overlap, and 22 (35%) had inappropriate overlap. The most common LAI was paliperidone ($n = 50$, 81%). Patients were adherent to oral overlap in 67% ($n = 6$) of the appropriate overlap group and 85% ($n = 17$) of the inappropriate overlap group. Discontinuation of an LAI in 4 months occurred in 62.5% ($n = 25$) of the appropriate group and 40.9% ($n = 9$) of the inappropriate group. There were no significant differences in secondary outcomes when comparing adherence to oral overlap ($p = .26$), discontinuation of LAI within 4 months ($p = .62$), and reason for discontinuation ($p = .69$).

Discussion: This study identified that a majority of patients had appropriate prescribing of oral antipsychotic overlap.

Keywords: veterans, transitions of care, long-acting injectable, oral overlap

[1] (Corresponding author) PGY2 Psychiatric Pharmacy Resident, Richard L. Roudebush Veterans Affairs Medical Center, Indianapolis, Indiana; jtranpharmd@outlook.com, ORCID: https://orcid.org/0000-0001-7421-7219; [2] Clinical Pharmacy Specialist – Mental Health, Richard L. Roudebush Veterans Affairs Medical Center, Indianapolis, Indiana, ORCID: https://orcid.org/0000-0002-2031-5646; [3] Clinical Pharmacy Specialist – Mental Health, Richard L. Roudebush Veterans Affairs Medical Center, Indianapolis, Indiana, ORCID: https://orcid.org/0000-0003-0022-0591

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Introduction

Antipsychotics are used for the treatment of a number of psychiatric disorders, including schizophrenia, bipolar disorder, and schizoaffective disorder. They are shown to decrease psychotic symptoms, which include hallucinations and delusions.[1] A major barrier to achieving remission or periods of asymptomatic stability is nonadherence to medications. As many as 70% of patients with schizophrenia report partial adherence to their medication therapy.[2] For patients with bipolar disorder, treatment nonadherence can reach up to 40%.[3] The consequences of relapse include

TABLE 1: Manufacturer and literature recommendations for oral overlap

Medication	Manufacturer Recommendations
Aripiprazole monohydrate	Oral aripiprazole 10 to 20 mg/day or other oral antipsychotic already in use should be given after the first injection for 14 consecutive days[7]
Aripiprazole lauroxil	Administer oral aripiprazole for 21 days in conjunction with first dose of aripiprazole lauroxil based on the current oral aripiprazole dose or administer a single oral aripiprazole 30 mg dose with Aristada Initio plus the first dose of aripiprazole lauroxil based on current oral aripiprazole dose[8,9]
Olanzapine pamoate	Establishment of tolerance by prior oral administration is recommended, but no oral overlap is recommended[10]
Paliperidone palmitate	Establishment of tolerance by prior oral administration is recommended, but no oral overlap is recommended[11]
Risperidone long-acting injection	Given within first injection and continued for 21 days for intramuscular LAI or establishment of tolerance by prior oral administration is recommended[12]
Risperidone for extended-release injectable suspension	No oral overlap is recommended for subcutaneous LAI[13]
Medication	**Literature Recommendations**
Fluphenazine decanoate	Decrease dose by half after first injection and discontinue oral therapy after second injection[14]
Haloperidol decanoate	Continue oral for the first 2 to 3 injections if not using loading dose[14]

hospitalization and increased risk of suicide attempts, which are associated with a significant impact on the costs of the health care system.[2,3]

Long-acting injectable (LAI) antipsychotics are useful dosage forms that have the potential to address nonadherence. Guidelines published by the American Psychiatric Association recommend patients with schizophrenia who have a history of poor or uncertain adherence be prescribed an LAI.[4] Recent evidence supports the use of LAIs in treatment of schizophrenia as it shows benefits with "lower relapse rates, fewer hospitalizations, reduced illness-related complications, and cormobidities."[5(p374)] Rehospitalization rates among patients with schizophrenia can be 20%–30% lower compared with those receiving oral formulations.[6]

Prior to starting an LAI, tolerance must be established through prior administration of an oral equivalent. LAIs are pharmacokinetically designed to release slowly, which may delay onset of the therapeutic effect. Various LAIs require oral antipsychotic overlap or initiation doses to achieve therapeutic concentrations.[7-13] Recommendations for antipsychotic oral overlap based on the manufacturer and primary literature are listed in Table 1.

Providers may prescribe oral overlap that is not recommended by the manufacturer based on the presentation of the patient. Alternatively, they may not prescribe oral overlap even though it is recommended by the manufacturers, and this may lead to increased risk for polypharmacy, side effects, relapse, and nonadherence.[2]

There are studies reviewing prescribing patterns and frequency of oral overlap with LAIs. In an open-label, single-arm extension study by Ascher-Svanum and colleagues, 931 patients were given oral supplementation along with olanzapine LAI.[15] The study finds that supplementation appeared to be infrequent, of short duration, and reserved for more severely ill patients who were at higher risk of relapse.[15] To the authors' knowledge, there is currently one study in the veteran population, completed by Dimitropoulos and colleagues, that assesses LAIs and oral overlap. The researchers review prescribing patterns at their facility to evaluate the prevalence and rationale for prescribing both LAI antipsychotics and oral overlap. The researchers defined LAI and oral overlap polypharmacy as scheduled use of both agents outside of the manufacturer's recommendations for titration and overlap. Of those, half were as likely to be on a maximum-dose LAI compared with those on LAI monotherapy.[16] The results from studies completed by both Ascher-Svanum and colleagues and Dimitropoulos and colleagues address the prescribing patterns and frequency of oral overlap with an LAI; however, they do not report whether oral overlap was discontinued appropriately after discharge or the safety aspects of continuing oral overlap beyond manufacturer recommendations. Therefore, this current study aims to identify whether providers are appropriately overlapping patients with LAIs and identify additional gaps in care with LAIs to improve current practices at Veteran Health Indiana.

Methods

Study Design

This study is a retrospective electronic chart review conducted at a large Veterans Affairs medical center of

TABLE 2: Baseline characteristics of patients who met inclusion criteria

	Appropriate Overlap *N* (%)	Inappropriate Overlap *N* (%)	*P*-value
Sex			.69
Male	33 (83)	19 (86)	
Female	7 (17)	3 (14)	
Race			.29
White	30 (75)	15 (68)	.76
Black	10 (25)	5 (22)	.86
Other	0	1 (5)	.18
Not listed	0	1 (5)	-
Age, years	43	45	.69
DSM-5 diagnosis			.90
Bipolar disorder I	6 (15)	2 (9)	.54
Bipolar disorder II	1 (2)	0	.46
Schizophrenia	15 (38)	9 (41)	.84
Schizoaffective disorder	12 (30)	7 (32)	.90
Other	6 (15)	4 (18)	.77
LAI			.08
Aripiprazole	4 (10)	0	.14
Fluphenazine	1 (3)	1 (5)	.67
Haloperidol	4 (10)	0	.14
Paliperidone	31 (77)	19 (86)	.71
Risperidone	0	2 (9)	.06

patients who were admitted to the acute care psychiatric unit and initiated on an LAI antipsychotic at Veteran Health Indiana between January 1, 2016, and December 31, 2019. Appropriate oral overlap was defined using the manufacturer recommendation and primary literature. As oral overlap is not required for paliperidone per manufacturer recommendations, patients who were given paliperidone palmitate and prescribed oral overlap were counted as inappropriately orally overlapped. All prescribed LAIs were reviewed for use by a clinical pharmacist practitioner. Olanzapine pamoate was not included in this study due to limitations in the infrastructure of the facility that do not allow for use of olanzapine pamoate in concordance with the risk evaluation and mitigation strategy program. This project was deemed to be a quality improvement project by the institutional review board and did not require full review.

Study Population

Patients met inclusion criteria if they were initiated on an LAI antipsychotic from January 1, 2016, to December 31, 2019, at Veteran Health Indiana while admitted to the acute care psychiatric unit. Patients were excluded if they were prescribed dual antipsychotic therapy (including dual LAI antipsychotic therapy) or if psychiatric medications were not prescribed by a Veteran Health Indiana prescriber.

Study Outcomes

The primary outcome of this study was the appropriateness of oral antipsychotic overlap in patients prescribed LAI antipsychotics. Secondary outcomes included discontinuation of LAI within 4 months of discharge, reason for LAI discontinuation, and adherence to oral overlap. Adherence to oral overlap was measured through reviewing the refill history of oral overlap.

Statistical Analysis

Statistical analysis was conducted using the chi-square test for nominal variables and *t* test for continuous variables. Descriptive statistics were used to characterize patient demographics. A power calculation was not used given the relatively small sample size. Alpha level was set at .05.

Results

A total of 100 patients were excluded due to continuation of home dose ($n = 60$), dual antipsychotic therapy ($n = 34$), medication by a non-VA provider ($n = 3$), and inaccurate loading of an LAI ($n = 3$). A total of 62 patients met inclusion criteria. Baseline characteristics are shown in Table 2. The sex of patients in the study was 52 males (84%) and 10 females (16%). Paliperidone palmitate (82%) was the most predominantly used LAI followed by aripiprazole monohydrate and lauroxil (6%), haloperidol decanoate (6%), risperidone (3%), and fluphenazine decanoate (3%). For the primary outcome of assessing the appropriateness of oral antipsychotic overlap in patients who are prescribed LAIs, 40 patients had appropriate overlap (31 receiving paliperidone palmitate and not prescribed oral antipsychotics and 9 who were prescribed the appropriate oral overlap) and 22 patients had inappropriate overlap (20 prescribed oral incorrectly and 2 who should have been prescribed oral overlap but were not). The examples of inappropriate overlap included oral overlap that was not needed based on manufacturer recommendations and/or incorrect duration of oral overlap.

Regarding the secondary outcomes, 25 of 40 patients (62.5%) with appropriate overlap and 9 of 22 patients (40.9%) with inappropriate overlap discontinued their LAI within 4 months of discharge ($p = .62$). Reasons for discontinuation observed in both groups with LAI were lost to follow up ($n = 11$), adverse events ($n = 8$), other reasons ($n = 7$), no injection date scheduled ($n = 6$), and inefficacy ($n = 2$). Other reasons for discontinuation include patient transfer from our facility as shown in the figure.

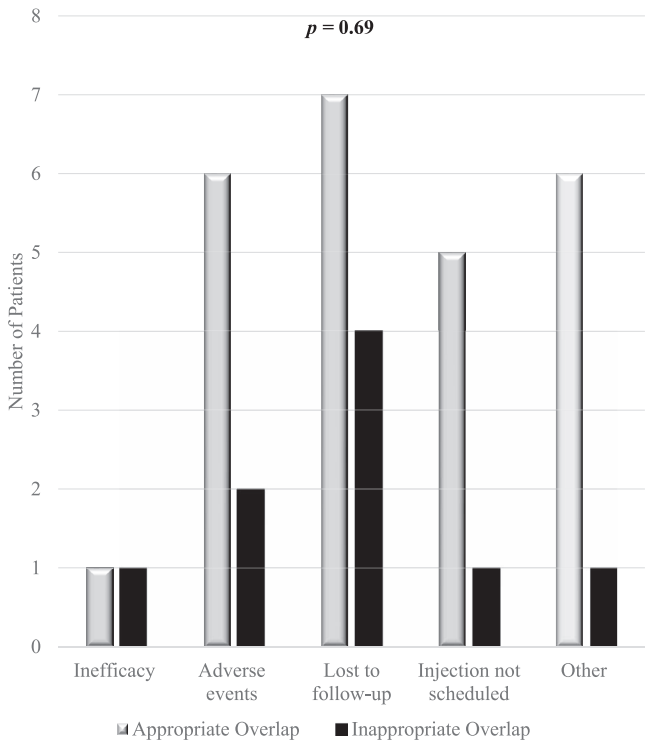

FIGURE: Reason for LAI discontinuation

As oral overlap is not required for paliperidone per manufacturer recommendations, all patients may not be prescribed oral overlap; if patients were administered on oral overlap and given paliperidone palmitate, then they were counted as inappropriately orally overlapped. For our secondary outcome, the study reviewed whether patients were adherent to oral overlap. There were 9 patients who were appropriately prescribed oral overlap, but only 6 patients (67%) were adherent. There were 20 patients who were prescribed inappropriate overlap, and 17 of those patients (85%) were adherent to oral overlap ($p = .26$).

Discussion

A majority of patients in our study had appropriate oral overlap. Results from this study show no statistically significant difference between patients who were appropriately prescribed oral overlap compared with those who were not in the secondary outcomes: discontinuation of LAI within 4 months, reasons for discontinuation of LAI, and adherence to oral overlap. This study examines gaps in the facility's transitions-of-care process by identifying instances of appropriate versus inappropriate prescribing of oral antipsychotic overlap to patients initiating LAI antipsychotics on an acute care psychiatric unit. This study further supports the impact a pharmacist can have in transitions of care. Most patients discontinued their LAI due to being lost to follow up and side effects. Pharmacists can play an important role in ensuring that injection visits are scheduled and educating patients about side effects. At the study facility, social workers are responsible for scheduling injection appointments. Currently, the clinical pharmacist practitioner notifies social work of the patient's next injection date to prevent any missed injections from occurring.

There are several limitations associated with this study. As power was not calculated, the probability of having a type II error is increased. Therefore, it is difficult to determine whether a statistically significant result reflects a true effect. The small sample size may be a contributing factor. A future direction for this study would be to include a larger patient population to minimize the risk of a type II error. The characteristics of the study population may limit the generalizability of the results due to the homogenous nature of the veteran population (i.e., predominantly male and white). This could limit the external validity of the study as the predominant ethnicity diagnosed in schizophrenia is African American.[17] Another limitation to the study is the unequal distribution of LAI usage as paliperidone palmitate is shown to be the predominant LAI used at the referenced facility. This could be due to provider preference or familiarity with the product. This is an area that needs to be further explored. It may be difficult to extrapolate these results to other LAIs due to the unequal availability and utilization of LAIs within this facility. In the study, the primary outcomes identified whether patients were on oral overlap appropriately. However, the study did not compare the length of time patients were on oral overlap. There is evidence to suggest that patients taking high doses of oral risperidone or paliperidone may require oral overlap with LAI loading doses.[18] This may contribute to a patient discontinuing the LAI and adherence to oral overlap.

The identification of areas for improvement in the LAI transitions-of-care process at this facility is a strength of this study. For instance, gaps in transitions of care may prevent patients from obtaining their medication after they are discharged from an inpatient hospitalization. Future directions based on the results of this study include development of an LAI order set to assist providers in appropriately determining whether oral overlap is indicated and identifying appropriate follow-up after discharge from the acute inpatient psychiatric unit. Currently, when patients are discharged from the acute inpatient psychiatric unit, they are scheduled for their next injection. The discharge team ensures that patients are scheduled for a medication management follow-up within 30 days of their discharge as recommended by the Strategic Analytics for Improvement and Learning model within Veterans Affairs. The issue that occurs is that patients are not engaging in these appointments or being lost to follow-up. To remedy this issue, it may be beneficial to develop a postdischarge team to follow up with patients that are missed. This interdisciplinary team may consist of psychiatrists, social workers, nursing, and pharmacists.

Conclusion

This study identifies that a majority of patients had appropriate prescribing of oral antipsychotic overlap. Larger prospective studies are needed to assess the impact of antipsychotic oral overlap.

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References

1. National Institute of Mental Health [Internet]. Mental health medications [revised 2016 Oct; 2021 Sep 27]. Available from: https://www.nimh.nih.gov/health/topics/mental-health-medications
2. Macfadden W, Ma Y-W, Thomas Haskins J, Bossie CA, Alphs L. A prospective study comparing the long-term effectiveness of injectable risperidone long-acting therapy and oral aripiprazole in patients with schizophrenia. Psychiatry (Edgmont). 2010;7(11):23-31. PubMed PMID: 21191530.
3. Devrımcı Özgüven H, Kir Y. Long acting injectable antipsychotics in the treatment of schizophrenia and bipolar disorder. Noro Psikiyatr Ars. 2021;58(Suppl 1):S47-52. DOI: 10.29399/npa.27480. PubMed PMID: 34658635.
4. Keepers GA, Fochtmann LJ, Anzia JM, Benjamin S, Lyness JM, Mojtabai R, et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. Focus (Am Psychiatr Publ). 2020;18(4):493-7. DOI: 10.1176/appi.focus.18402. PubMed PMID: 33343262.
5. Stevens GL, Dawson G, Zummo J. Clinical benefits and impact of early use of long-acting injectable antipsychotics for schizophrenia. Early Interv Psychiatry. 2016;10(5):365-77. DOI: 10.1111/eip.12278. PubMed PMID: 26403538.
6. Kane JM, Correll CU. Optimizing treatment choices to improve adherence and outcomes in schizophrenia. J Clin Psychiatry. 2019;80(5). DOI: 10.4088/JCP.IN18031AH1C. PubMed PMID: 31536686.
7. Otsuka America Pharmaceutical, Inc. ABILIFY MAINTENA (aripiprazole) extended-release injectable suspension. 2002 [rev. 2020 Jun; cited 2022 Oct 13]. In: DailyMed [Internet]. Tokyo, Japan: National Library of Medicine (US). Available from: https://dailymed.nlm.nih.gov/dailymed/medguide.cfm?setid=ee49f3b1-1650-47ff-9fb1-ea53fe0b92b6
8. Alkermes, Inc. ARISTADA INITIO (aripiprazole lauroxil) extended-release injectable suspension. 2018 [rev. 2022 Feb; cited 2022 Oct 13]. In: DailyMed [Internet]. Waltham (MA): National Library of Medicine (US). Available from: https://dailymed.nlm.nih.gov/dailymed/medguide.cfm?setid=b18fdfd9-31cd-4a2f-9f1c-ebc70d7a9403
9. Alkermes, Inc. ARISTADA (aripiprazole lauroxil) extended-release injectable suspension. 2018 [rev. 2022 Feb; cited 2022 Oct 13]. In: DailyMed [Internet]. Waltham (MA): National Library of Medicine (US). Available from: https://dailymed.nlm.nih.gov/dailymed/medguide.cfm?setid=b17a8d11b-73b0-4833-a0b4-cf1ef85edefb
10. Eli Lilly and Company. ZYPREXA RELPREVV (olanzapine pamoate) extended-release injectable suspension. 2009 [rev. 2021 Nov; cited 2022 Oct 13]. In: DailyMed [Internet]. Indianapolis (IN): National Library of Medicine (US). Available from: https://dailymed.nlm.nih.gov/dailymed/medguide.cfm?setid=f9a73185-88de-4d7b-b3c0-bbf231483241
11. Janssen Pharmaceuticals, Inc. INVEGA SUSTENNA (paliperidone palmitate) extended-release injectable suspension. 2006 [rev. 2022 Aug; cited 2022 Oct 13]. In. DailyMed [Internet]. Titusville (NJ): National Library of Medicine (US). Available from: https://dailymed.nlm.nih.gov/dailymed/medguide.cfm?setid
12. Janssen Pharmaceuticals, Inc. RISPERDAL CONSTA (risperidone) extended-release injectable suspension. 2003 [rev. 2021 Feb; cited 2022 Oct 13]. In. DailyMed [Internet]. Titusville (NJ): National Library of Medicine (US). Available from: https://dailymed.nlm.nih.gov/dailymed/medguide.cfm?setid
13. Indivior Inc. PERSERIS (risperidone) extended-release injectable suspension. 1993 [rev. 2022 Aug; cited 2022 Oct 13]. In. DailyMed [Internet]. North Chesterfield (VA): National Library of Medicine (US). Available from: https://dailymed.nlm.nih.gov/dailymed/medguide.cfm?setid
14. McEvoy JP. Risks versus benefits of different types of long-acting injectable antipsychotics. J Clin Psychiatry. 2006;67 Suppl 5:15-8. PubMed PMID: 16822092.
15. Ascher-Svanum H, Peng X, Montgomery W, Faries DE, Lawson AH, Witte MM, et al. Assessing the infrequent oral supplementation of olanzapine long-acting injection in the treatment of schizophrenia. Eur. Psychiatr. 2011;26(5):313-9. DOI: 10.1016/j.eurpsy.2010.03.015. PubMed PMID: 20621454.
16. Dimitropoulos E, Drogemuller L, Wong K. Evaluation of concurrent oral and long-acting injectable antipsychotic prescribing at the Minneapolis Veterans Affairs Health Care System. J Clin Psychopharmacol. 2017;37(5):605-8. DOI: 10.1097/JCP.0000000000000755. PubMed PMID: 28816923.
17. Morgan C, Charalambides M, Hutchinson G, Murray RM. Migration, ethnicity, and psychosis: toward a sociodevelopmental model. Schizophrenia Bulletin. 2010;36(4):655-64. DOI: 10.1093/schbul/sbq051. PubMed PMID: 20513653; PubMed Central PMCID: PMC2894585.
18. Vandenberg AM. An update on recently approved long-acting injectable second-generation antipsychotics: knowns and unknowns regarding their use. Ment Health Clin. 2022;12(5):270-81. DOI: 10.9740/mhc.2022.10.270. PubMed PMID: 36405505.