

Long-acting Injectable Antipsychotics: Haloperidol and fluphenazine decanoate, aripiprazole (Abilify Maintena), risperidone (Risperdal Consta), and paliperidone (Invega Sustenna and Trinza)
Criteria for Use & Evidence Summary
April 2015; updated October 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <http://vaww.pbm.va.gov> for further information.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive a long-acting injectable antipsychotic (LAIA).*

- The patient has never taken the long-acting injectable antipsychotic ordered in any formulation (e.g., oral), with the exception of prior exposure to risperidone being an acceptable substitute for 1-month paliperidone (Sustenna).
- The patient has a hypersensitivity to the antipsychotic ordered. Note: Consider risperidone and paliperidone cross-sensitive.
- Aripiprazole only: the patient is taking a cytochrome 3A4 inducer.
- Paliperidone palmitate 3-month injection (Trinza) only: the patient has received fewer than 4 monthly injections of the 1-month paliperidone formulation.

Inclusion Criteria

The patient must meet ALL of the following:

- Have a diagnosis of schizophrenia or schizoaffective disorder, or bipolar I disorder by DSM-IV or 5
 - The prescriber is a Mental Health Provider
 - The patient has taken and tolerated the antipsychotic ordered prior to receiving it as a LAI (see Issues for Consideration)
- OR**
- The patient is currently receiving the LAIA ordered

PLUS the patient meets one of the following:

- The patient has relapsed or been hospitalized for the intended indication or complications of the intended indication because of nonadherence when treated with oral antipsychotics **OR**
- The patient's care environment is such that a LAIA is a more reliable route of administration, e.g., homeless, lack of medication supervision, or the medication cannot be stored safely

PLUS

- All oral antipsychotics will be discontinued according to the schedule below

LAIA Discontinuation of oral antipsychotics

Aripiprazole	Patients must continue oral aripiprazole 10 mg to 20 mg daily or their existing oral antipsychotic for 14 days after their first dose of aripiprazole LAI, then oral antipsychotics are to be discontinued.
Paliperidone	After the first paliperidone LA injection
Risperidone	Within 6 weeks after the first risperidone LA injection
Haloperidol	No need for oral overlap if loading dose method is used. If no loading dose given, supplement with oral antipsychotic for up to 3 months.
Fluphenazine	Decrease oral dose by half after first injection, then consider discontinuation after the second injection

Dosage and Administration

Please refer to individual package inserts.

Monitoring

Recommended:

- Baseline and annual EKG (with all LAIAs)
- Baseline and annual metabolic parameters (i.e. weight, waist circumference, blood glucose, blood pressure, lipids)
- Abnormal Involuntary Movement Scale (AIMS) at least annually

Issues for Consideration

- Consider use of haloperidol or fluphenazine decanoate as a first-line option for consideration in the absence of significant extrapyramidal side effects or prolactin elevation from previous trials of oral or LA formulations.
- Required exposure prior to receiving LAIA ordered

Aripiprazole	Patients who are naïve to aripiprazole should establish tolerability with oral aripiprazole prior to receipt of the LAIA formulation. No duration specified. Due to the half-life of oral aripiprazole, it may take up to 2 weeks to assess tolerability.
Paliperidone	It is recommended that patients naïve to paliperidone or risperidone receive two oral daily doses of either paliperidone 3 mg or risperidone 1 mg. This is not required with the 3-month paliperidone formulation.
Risperidone	For patients who have never taken oral risperidone, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with risperidone LAI. No duration specified.
Haloperidol	Patients who are naïve to haloperidol should establish tolerability with oral haloperidol prior to receipt of the LAIA formulation. No duration specified.
Fluphenazine	Patients who are naïve to fluphenazine should establish tolerability with oral fluphenazine prior to receipt of the LAIA formulation. No duration specified.

- Switching from another LAIA to 1-month paliperidone LAI: Administer paliperidone LAI in place of the next scheduled injection. Continue monthly injections of 1-month paliperidone LAI thereafter. No loading doses are required

Renewal Criteria

- Documented tolerability, benefit, and improvement of adherence after at least 8 weeks of treatment.
- Consider re-evaluation of appropriateness if patient adherence not improved within 1 year of therapy initiation.

Prepared: March 2015; Updated October 2015. Contact: Todd Semla, MS, Pharm.D., BCPS, VA Pharmacy Benefits Management Services

Criteria for Use – Long-acting Injectable Antipsychotics

Evidence Summary

The purpose of this review was to address the following questions in order to determine a place in therapy for long-acting injectable antipsychotics:

- Is there evidence to choose one long-acting injectable antipsychotic (LAIA) over the others? Are they all the same regarding efficacy/safety?
- Is the place in therapy of LAIAs only for patients who are non-adherent? What is the evidence regarding adherence?
- What is the evidence for/against combining oral antipsychotics and LAIAs?

Research Method:

- As of January 16, 2015, A PubMed and Cochrane search conducted for articles written in English using the following search terms (in various combinations) was performed. All trials were reviewed for inclusion, with case reports and series excluded. All information prior to January 16, 2015 was included in the search.
 - Long-acting injectable antipsychotics, depot, adherence, relapse, risperidone, olanzapine pamoate, once-monthly aripiprazole, paliperidone palmitate, fluphenazine decanoate, haloperidol decanoate, oral antipsychotics, combination.
- References of published studies were reviewed to determine relevant articles for inclusion

Abbreviations

<p>ADR: Adverse Drug Reaction ALAI: Aripiprazole Long-Acting Injectable BMI: Body Mass Index ER: Emergency Room EPSE: Extra-Pyramidal Side Effects FD: Fluphenazine Decanoate FGA: First-Generation Antipsychotics HD: Haloperidol Decanoate LAIA(s): Long-Acting Injectable Antipsychotic(s) LAI: Long-Acting Injectable MPR: Medication Possession Ratio OAP: Oral Antipsychotic OH: Oral Haloperidol OLAI: Olanzapine Long-Acting Injectable PANSS: Positive And Negative Symptom Scale PP: Paliperidone Palmitate RCT: Randomized-Controlled Trial RLAI: Risperidone Long-Acting Injectable</p>
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1. Comparison of Long-acting Injectable Antipsychotics:

Of the six available long-acting injectable antipsychotics (LAIAs), paliperidone palmitate, haloperidol decanoate, fluphenazine decanoate, and risperidone LAI are the only LAIAs compared head-to-head in randomized-controlled clinical trials. The following six studies compared LAIAs through double-blind randomized controlled trials (RCTs), open-label, or via a retrospective design. All patients included in the studies had a diagnosis of schizophrenia or schizoaffective disorder, and were predominately in a stable-phase identifying maintenance outcomes. Safety and efficacy endpoints were analyzed across the studies.

A study by Pandina and colleagues (N=913) compared paliperidone palmitate to risperidone LAI in a non-inferiority, double-blind, double-dummy design. Patients with acute-phase schizophrenia were randomized and followed for 13-weeks. The study reached power, and paliperidone palmitate was observed to be non-inferior to risperidone LAI in regards to efficacy (determined by Positive and Negative Symptom Scale (PANSS) scores). Adverse events were similar between both LAIAs.¹ A study by Li and colleagues (N=413) used the same endpoints as the trial by Pandina and colleagues, except the trial was an open-label, non-inferiority design. Patients were also in the acute-phase of schizophrenia, and were of Chinese ethnicity. The study reached power, and paliperidone palmitate was observed to be non-inferior to risperidone LAI in regards to efficacy. Adverse events were similar between both LAIAs.² Similar to the studies by Pandina¹ and Li², Fleischhacker and colleagues also compared risperidone LAI to paliperidone palmitate. This study was a 53-week, non-inferiority trial, which included patients with acute-phase schizophrenia and used low-doses of paliperidone palmitate for both initial and maintenance treatments. Non-inferiority was observed between paliperidone palmitate and risperidone LAI efficacy outcomes (as depicted by PANSS scores), as well as both agents had similar safety endpoints.³ (Table 1)

Covell and colleagues conducted a 12-month, open-label RCT and compared fluphenazine decanoate and haloperidol decanoate to risperidone LAI. A total of 53 patients were included in the study and were in the stable-phase of schizophrenia or schizoaffective disorder. The authors observed patients on risperidone LAI to have a shorter time to all-cause discontinuation at 12 months and had greater rates of discontinuation. Risperidone LAI was observed to have fewer hospitalizations and greater reductions in PANSS scores compared to haloperidol decanoate and fluphenazine decanoate; however, these differences were not significant. Greater increases in body mass index (BMI) and prolactin were observed in the risperidone LAI group.⁴ McEvoy and colleagues, compared haloperidol decanoate to paliperidone palmitate in acute-phase patients with schizophrenia or schizoaffective disorder over 24 months. No difference in efficacy was observed; however, weight and prolactin were greater in the paliperidone palmitate group compared to haloperidol decanoate.⁵ A large retrospective cohort study conducted by Nielsen and colleagues compared risperidone LAI to first-generation LAIs in stable patients with schizophrenia of Danish ethnicity. The authors observed no difference in time to hospitalization, all-cause discontinuation, and duration of hospitalization after medication failure between patients prescribed risperidone LAI compared to first-generation LAIs.⁶ (Table 1)

Conclusion: Based upon the limited evidence, no specific LAIA has shown superiority over the other LAIAs. Paliperidone palmitate was observed to be non-inferior to risperidone LAI in efficacy. Due to conflicting results and the weak study design of available studies comparing first-generation LAIAs to risperidone LAI, it is unclear if the efficacy of haloperidol or fluphenazine decanoate differs from risperidone LAI. Patients receiving risperidone and

paliperidone LAI had greater increases in BMI or weight and prolactin concentrations than either decanoate LAIA.

Table 1: Comparison of Long-acting Injectable Antipsychotics (*Frequency of LAIA administration follows package insert, unless otherwise noted*)

Reference	Design	# of Patients Analyzed	Patient Population	Objective(s)	Dose(s) Used	Results	Study Critique
Pandina, et al. 2011 ¹	13-week Non-inferiority Double-Blind RCT	913	<ul style="list-style-type: none"> Randomized Males: 701 Females: 513 Patients with acute schizophrenia Average duration of illness: 12 years Mean baseline PANSS score: 84.1 paliperidone palmitate (PP) and 83.6 risperidone LAI (RLAI) 	<p>(1) Compare efficacy outcomes of PP to RLAI</p> <p>(2) Assess safety and tolerability</p>	<ul style="list-style-type: none"> Mean PP dose: 104.5mg Mean RLAI dose: 31.7mg Mean risperidone oral overlap dose: 3.3mg 	<ul style="list-style-type: none"> PP: 453 patients, RLAI: 460 patients (analyzed) Change in baseline PANSS score at 13 weeks: -18.6 points (PP) and -17.9 points (RLAI); Treatment difference of change = 0.4 [CI: -1.62-2.38] Response to treatment*: 53% (PP) and 48.5% (RLAI); Point difference of relative risk = 1.2 [CI: -0.78-3.16] ADRs: PP = 57.9% and RLAI=52.8% More insomnia, injection site pain, and anxiety occurred in PP group with a $\geq 2\%$ difference compared to RLAI and constipation occurred $\geq 2\%$ more in the RLAI than PP group 	<p>Strengths:</p> <ul style="list-style-type: none"> Blinded, RCT Multiple outcomes studied Large sample size <p>Limitations:</p> <ul style="list-style-type: none"> Mood-stabilizers and antidepressants were selectively limited in the study Short-term study
Li, et al. 2011 ²	13-week Non-inferiority Open-Label RCT	413	<ul style="list-style-type: none"> Randomized Males: 181 Females: 271 Patients with acute schizophrenia Chinese patients Mean baseline PANSS score: 82.5 PP and 83.9 RLAI 	<p>(1) Compare efficacy outcomes of PP RLAI</p> <p>(2) Assess safety and tolerability</p>	<ul style="list-style-type: none"> Mean PP dose: 115.8mg Mean RLAI dose: 29.8mg Mean risperidone oral overlap dose: 2mg 	<ul style="list-style-type: none"> PP: 205 patients, RLAI: 208 patients (analyzed) Change in baseline PANSS score at 13 weeks: -23.6 points (PP) and -26.9 points (RLAI) ; [CI: -5.20-0.63] Response to treatment*: 70.7% (PP) and 78.4% (RLAI); Point difference of relative risk = 0.9 [CI: 0.81-1.01] ADRs: PP=73.4% and RLAI=74.9% 	<p>Strengths:</p> <ul style="list-style-type: none"> Average doses Multiple outcomes studied Took design of Pandina et al¹ and re-studied in a real-world setting Large sample size <p>Limitations:</p> <ul style="list-style-type: none"> Open-label study design may lead to bias No p-values calculated

						<ul style="list-style-type: none"> • Akathisia, tremor, and prolactin elevation occurred more in RLAI • Injection site reactions and somnolence greater with PP 	<ul style="list-style-type: none"> • to show significance • External validity with patient race • Short-term study
Fleischhacker, et al. 2012 ³	53-week Non-inferiority Double-Blind RCT	747	<ul style="list-style-type: none"> • Analyzed Males: 441 Females: 306 • Patients with acute schizophrenia • Mean PANSS score: 81.9 (PP) and 81.2 (RLAI) • Primarily Caucasian 	(1) Compare efficacy outcomes of PP to RLAI	<ul style="list-style-type: none"> • RLAI dose: initial dose: 25mg and 25-50mg for maintenance • PP Dose: initial dose: 50mg and 39mg-156mg for maintenance 	<ul style="list-style-type: none"> • Change in PANSS score from baseline at 53-weeks: -11.6 (PP) and -14.4 (RLAI); [CI: -5.84-0.61] • Insomnia, psychotic disorder, worsening or relapse of schizophrenia, anxiety, and headache occurred in >10%; no significant differences between groups 	<p>Strengths:</p> <ul style="list-style-type: none"> • Length of study • Efficacy and safety outcomes • Large sample size <p>Limitations:</p> <ul style="list-style-type: none"> • Low initial and maintenance doses of PP used
Covell, et al. 2012 ⁴	12-month Open-Label RCT	53	<ul style="list-style-type: none"> • Analyzed Males: 44 Females: 9 • Stable patients with schizophrenia or schizoaffective disorder • Prescribed fluphenazine decanoate (FD) or haloperidol decanoate (HD), then switched to risperidone LAI (RLAI) • Mean baseline PANSS: 69.9 (HD/FD) and 	(1) Time to all-cause discontinuation comparing HD, FD, and RLAI after switching patients to RLAI from HD and/or FD	<ul style="list-style-type: none"> • Mean HD dose: 114.7mg • Mean FD dose: 37.5mg • Mean RLAI dose not directly reported 	<ul style="list-style-type: none"> • FD/HD: 29 patients, RLAI: 24 patients (analyzed) • No difference in all-cause discontinuation at 6 months (P=0.33) • Time to all cause discontinuation at 12 months was shorter for RLAI (P=0.01) • After switching to RLAI, 31% of patients discontinued treatment versus 10% in the HD/FD group (P=0.03) • No difference in hospitalizations (P=0.62) • No difference in change in PANSS scores (P=0.48) • No difference between groups regarding adverse effects, except for greater prolactin elevations (P=0.02) 	<p>Strengths:</p> <ul style="list-style-type: none"> • Multiple outcomes analyzed • Length of study • Real-world applicability of open-label design <p>Limitations:</p> <ul style="list-style-type: none"> • Open-label study design may lead to bias • No report of mean risperidone dosage • Small sample size • Did not calculate power

			65.4 (RLAI)			and increased BMI (P=0.00) in RLAI group	
McEvoy, et al. 2014 ⁵	24-month Double-Blind RCT	290	<ul style="list-style-type: none"> Analyzed Males: 216 Females: 74 Acute Schizophrenia or schizoaffective disorder Baseline PANSS score: 73 (PP) and 70 (HD) 	(1) Compare efficacy and safety of HD to PP	<ul style="list-style-type: none"> Mean PP dose: 129-169mg Mean HD dose: 67-83mg 	<ul style="list-style-type: none"> PP: 145 patients, HD: 145 patients (analyzed) Efficacy failure over 24 months**:33.8% (PP) and 32.4% (HD); P=0.90 Weight increased 2.17kg (PP) and decreased 0.96kg (HD); P<0.001 Prolactin elevations were greater in PP group; P<0.001 	<p>Strengths:</p> <ul style="list-style-type: none"> Length of study Large sample size Safety and efficacy outcomes analyzed <p>Limitations:</p> <ul style="list-style-type: none"> Did not reach power No evaluation of relapse or adherence differences
Nielsen, et al. 2014 ⁶	Retrospective Cohort	4,532	<ul style="list-style-type: none"> Analyzed Males: 2,603 Females: 1,929 Stable schizophrenia Average duration of illness: 2.5 years Danish patients 	(1) Compare hospitalization and all-cause discontinuation of RLAI to first-generation LAIs (FGA-LAI)	<ul style="list-style-type: none"> Not reported 	<ul style="list-style-type: none"> RLAI: 2,454 patients, FGA-LAI: 2,078 patients (analyzed) No difference in time to hospitalization (P=0.199) No difference in time to all-cause discontinuation (P=0.166) No difference in duration of hospitalization after failure (P=0.744) 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size Multiple outcomes analyzed <p>Limitations:</p> <ul style="list-style-type: none"> Uneven group numbers and unmatched for baseline characteristics No evaluation of safety endpoints All medications were given bi-weekly, including haloperidol decanoate Reasons for discontinuation were not included

*Response was determined as a 30% decrease in PANSS scores.

**Efficacy failure was determined to be a psychiatric hospitalization, need for crisis stabilization, increased frequency of outpatient visits, need for continued OAPs, and decision to discontinue a LAIA.

2. Comparison of Oral Antipsychotics to Long-acting Injectable Antipsychotics:

A number of trials have compared the use of oral antipsychotics (OAPs) to LAIAs. The importance of this comparison is to identify if there is a difference in safety, efficacy, relapse rates, and adherence that warrants the use of LAIAs and the potential increase in cost to patients and healthcare systems. Trials have split patients into two main groups: patients with a first-episode of schizophrenia and those who have established schizophrenia that are switched from maintenance OAPs to LAIAs.

First-Episode Schizophrenia:

Three studies have been conducted in patients with first-episode schizophrenia, schizoaffective, or schizophreniform disorders. All patients were stable at the time of medication initiation and the majority of patients analyzed in the trials were of Finnish ethnicity.

The first study by Kim and colleagues compared adherence and relapse rates of oral risperidone to risperidone LAI. This was a small study with only 50 patients who were followed for 2 years after randomization. To be included in the study, patients had to be treated with oral risperidone for at least four weeks prior to enrollment and documented to have poor adherence prior to randomization. The authors identified a significant increase in adherence with risperidone LAI at one- and two-year(s), compared to oral risperidone, as well as fewer patients relapsing at one- and two-year(s) in the risperidone LAI group.⁷ In a large retrospective review, Tiihonen and colleagues looked at four LAIAs, including: haloperidol decanoate, perphenazine LAI, risperidone LAI, and zuclopenthixol LAI. The authors observed all-cause discontinuation and re-hospitalization to be significantly less when comparing all studied LAIAs to oral antipsychotics. Individually, haloperidol decanoate and risperidone LAI had significantly less all-cause discontinuation compared to oral antipsychotics, but no difference was observed in risk of re-hospitalization for both agents when compared to oral antipsychotics. Dosages of medications were not reported.⁸ The last study by Weiden and colleagues evaluated the time to non-adherence comparing oral risperidone to risperidone LAI. This was a small open-label study that included 37 African American patients. Power was not calculated and the authors observed no difference between the two groups in regards to adherence.⁹ (Table 2)

Conclusion: Currently there are conflicting results in regards to improvement in adherence between oral antipsychotics and LAIAs in patients with first-episode schizophrenia. One large retrospective study found lower all-cause discontinuation and re-hospitalization risk with LAIA compared to oral antipsychotics. As a result, the available data are insufficient to support or reject the idea that LAIAs increase adherence in previously nonadherent patients compared to oral.

Table 2: Comparison of Oral Antipsychotics to Long-acting Injectable Antipsychotics in First-Episode Schizophrenia
(Frequency of LAIA administration follows package insert, unless otherwise noted)

Reference	Design	# of Patients Analyzed	Patient Population	Objective(s)	Dose(s) Used	Results	Study Critique
Kim, et al. 2008 ⁷	2-year Prospective Open-Label RCT	50	<ul style="list-style-type: none"> Analyzed Males: 18 Females: 31 Stable schizophrenia Poor adherence Average duration of illness: 1.5 years (RLAI) and 2.2 years (oral risperidone [oral]) Baseline PANSS: 63.6 (RLAI) and 60.3 (oral) 	(1) Compare adherence and relapse rates of RLAI vs. oral	<ul style="list-style-type: none"> Mean oral dose: 2.79mg Mean RLAI dose: 28.98mg 	<ul style="list-style-type: none"> Oral: 28 patients, RLAI: 21 patients (analyzed) Adherence at 1-year*: 85.7% (RLAI) and 54.3% (oral); P<0.01 Adherence at 2-years: 81.4% (RLAI) and 54.6% (oral); P<0.01 Relapse at 1 year*: RLAI (18%) and oral (50%); (P=0.03) Relapse at 2 years: RLAI (23%) and oral (75%); (P<0.01) 	<p>Strengths:</p> <ul style="list-style-type: none"> Length of study Unique population Multiple outcomes analyzed Real-world application with open-label study design <p>Limitations:</p> <ul style="list-style-type: none"> Open-label design may lead to bias Small study size Did not calculate power
Tiihonen, et al. 2011 ⁸	Retrospective Study	2,588	<ul style="list-style-type: none"> Analyzed Males: 1605 Females: 983 Stable schizophrenia Finnish patients 	(1) Assess risk of re-hospitalization and all-cause discontinuation between HD and oral haloperidol (OH), as well as RLAI and oral risperidone (OR)	<ul style="list-style-type: none"> Not reported 	<ul style="list-style-type: none"> All-cause discontinuation was less with RLAI and HD compared to their oral counterparts (P=0.03, HD [HR: 0.27]; P<0.0001, RLAI [HR: 0.75]) No difference was noted between the groups for re-hospitalization: P=0.06, HD[HR: 0.12]; P=0.09, RLAI [HR: 0.57] 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size Multiple outcomes analyzed Unique population <p>Limitations:</p> <ul style="list-style-type: none"> Study design No report of dosages to evaluate appropriateness Article also looked at depot formulations not used in US
Weiden, et al.	2-year Prospective	37	<ul style="list-style-type: none"> Analyzed 	(1) Time until initial non-	<ul style="list-style-type: none"> Majority of patients 	<ul style="list-style-type: none"> Oral: 11 patients, RLAI: 26 	<p>Strengths:</p>

2012 ⁹	Open-Label RCT		<p>Males: 28 Females: 9</p> <ul style="list-style-type: none"> Stable schizophrenia, schizophreniform, or schizoaffective disorder African Americans 	adherence	<p>were on the 25mg RLAI dose (57.9%)</p> <ul style="list-style-type: none"> Mean oral doses: 3mg (risperidone), 10mg (aripiprazole), 20mg (olanzapine), 200mg (quetiapine), and 160mg (ziprasidone) 	<p>patients (analyzed)</p> <ul style="list-style-type: none"> Time until non-adherence^{**}: 42 weeks (RLAI) and 12 weeks (oral); P=0.19 	<ul style="list-style-type: none"> Length of study Real-world application with open-label study design Unique population <p>Limitations:</p> <ul style="list-style-type: none"> Open-label design may lead to bias Small study size Few baseline characteristics provided Did not calculate power Low doses of study medications
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*Non-adherence was defined as the number of injection visits (or outpatient visits for OAPs) that patients attended divided by the number of actual visits scheduled with an absence of medication ≥ 1 week. Relapse was defined as an increase in positive PANSS score by >5 points.

**Non-adherence was defined as a gap in refills or injections of ≥ 14 days.

Established Schizophrenia:

A number of studies have compared oral antipsychotics in regards to safety, efficacy, and adherence in patients who have established schizophrenia. The following studies are categorized by the LAIA used in comparison with oral antipsychotics.

Olanzapine LAI, Aripiprazole LAI, and Risperidone LAI: Efficacy

A retrospective review by Lafeuille and colleagues compared olanzapine, aripiprazole, and risperidone LAIs to oral antipsychotics. This was a large study that included patients in the acute-phase of schizophrenia. Patients were originally prescribed an oral antipsychotic to treat a first-episode of schizophrenia and then included in the study if they had a relapse of symptoms. The authors then compared patients who were stabilized and continued on oral antipsychotics to patients who were switched to a LAI after their relapse. The authors observed all-cause hospitalizations (including mental-health and schizophrenia-specific) and emergency room (ER) visits to be greater in the oral antipsychotic group compared to the LAIA group. Dosages of medications, specific oral antipsychotics compared, and PANSS data were not reported¹⁰ (Table 3)

Conclusion: Due to the retrospective design of this study, it cannot be concluded that the LAIAs reviewed are better than oral-antipsychotics at reducing hospitalizations and ER visits.

Olanzapine LAI: Efficacy

Detke and colleagues compared olanzapine LAI to oral olanzapine for all-cause discontinuation in an open-label RCT with patients currently in a stable-phase of schizophrenia. There were a total of 524 patients included and no difference was observed in all-cause discontinuation or time to discontinuation between groups. Time to relapse was longer for patients on olanzapine LAI and subsequent length of hospital days following the relapse was shorter for patients prescribed olanzapine LAI. Relapse rates were also observed to be less in patients prescribed olanzapine LAI. The authors noted no differences in adverse effects between groups.¹¹ (Table 4)

Conclusion: This prospective trial showed positive results favoring olanzapine LAI in regards to longer time to relapse, reduced rates of relapse, and shorter hospital stays.

Table 3: Comparison of Oral Antipsychotics to Long-acting Injectable Antipsychotics in Established Schizophrenia: Efficacy of Olanzapine LAI, Aripiprazole LAI, and Risperidone LAI (*Frequency of LAIA administration follows package insert, unless otherwise noted*)

Reference	Design	# of Patients Analyzed	Patient Population	Objective(s)	Dose(s) Used	Results	Study Critique
Lafeuille, et al. 2013 ¹⁰	Retrospective Review	3,828	<ul style="list-style-type: none"> Analyzed Males: 2,132 Females: 1,696 Acute schizophrenia 	(1) Compare number of re-hospitalizations and ER visits between patients continued on oral antipsychotics (oral) vs. patients switched to atypical long-acting injectable antipsychotics (LAIA)	<ul style="list-style-type: none"> Not reported 	<ul style="list-style-type: none"> Patients: 1032 (LAIA) and 2796 (oral) analyzed Mean number of all-cause re-hospitalizations: 1.25 (LAIA) and 1.61 (oral); P<0.0001 Mean number of mental-health hospitalizations: 1.24 (LAIA) and 1.59 (oral); P<0.0001 Mean number of schizophrenia-related hospitalizations: 1.15 (LAIA) and 1.41 (oral); P=0.0005 Mean number of all-cause ER visits: 2.33 (LAIA) and 2.67 (oral); P=0.0158 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size Multiple outcomes analyzed <p>Limitations:</p> <ul style="list-style-type: none"> Study design Only included one hospital to examine ER visits and re-hospitalizations No PANSS data reported Oral antipsychotics were not reported Doses were not reported

Table 4: Comparison of Oral Antipsychotics to Long-acting Injectable Antipsychotics in Established Schizophrenia: Efficacy of Olanzapine LAI
(Frequency of LAIA administration follows package insert, unless otherwise noted)

Reference	Design	# of Patients Analyzed	Patient Population	Objective(s)	Dose(s) Used	Results	Study Critique
Detke, et al. 2014 ¹¹	2-year Prospective Open-Label RCT	524	<ul style="list-style-type: none"> Analyzed Males: 352 Females: 172 Stable schizophrenia Mean duration of illness: 14.7 years Baseline PANSS: 56.6 	<p>(1) Compare time to all-cause discontinuation between oral olanzapine (oral) and olanzapine LAI (OLAI)</p> <p>(2) Compare discontinuation rate, time to relapse, change in symptom severity, and safety/tolerability between groups</p>	<ul style="list-style-type: none"> Oral: 13.8mg OLAI: 386.6mg 	<ul style="list-style-type: none"> Patients: 264 (OLAI) and 260 (oral) analyzed All-cause discontinuation: 53.8% (OLAI) and 51.2% (oral); P=0.6 Time to discontinuation: 645 days (OLAI) and 678 days (oral); P=0.612 Hospitalization days after relapse: 0.43 (OLAI) and 1.8 (oral); P=0.02 Time to relapse*: 539 days (OLAI) and 281 days (oral); P<0.001 Relapse rate: 20.1% (OLAI) and 39.6% (oral); P<0.001 No differences in adverse effects between groups 	<p>Strengths:</p> <ul style="list-style-type: none"> Length of study Large sample size Multiple outcomes analyzed Drug dosages <p>Limitations:</p> <ul style="list-style-type: none"> Open-label study design may lead to bias

*Relapse was defined as hospitalization for symptoms related to schizophrenia, a 25% increase in PANSS score from baseline (if score >40) or an increase in PANSS score by 10 points (if score ≤40), deliberate injury to others/self-injury due to worsening psychosis, or discontinuation from the study for worsening psychosis.

Aripiprazole LAI: Efficacy

Two studies have compared aripiprazole LAI to oral antipsychotics. Both studies evaluated patients currently in the stable-phase of schizophrenia or schizoaffective disorder and included relatively large sample of patients.

The first study by Kane and colleagues used a mirror-image design to compare hospitalization rates for patients taking oral antipsychotics to hospitalization rates after those patients were switched to once-monthly aripiprazole LAI. Six months of retrospective OAP data was compared to six months of prospective LAIA data. The authors observed a significant decrease in hospitalization rates with the switch to aripiprazole LAI.¹² Fleischhacker and colleagues conducted a non-inferiority study comparing standard-dose (400 mg/month) aripiprazole LAI to oral aripiprazole and low-dose (50 mg/month) aripiprazole LAI. Non-inferiority with regards to relapse rates was observed from the comparison of standard-dose aripiprazole LAI and oral aripiprazole; however, superiority was observed with standard-dose aripiprazole LAI compared to low-dose aripiprazole LAI. Reduction in PANSS scores were significant in the standard-dose aripiprazole LAI group compared to both comparator groups.¹³ (Table 5)

Conclusion: In the current studies evaluating standard-dose aripiprazole LAI, PANSS scores, relapse rates, and hospitalization rates were decreased in patients receiving standard-dose aripiprazole LAI compared to oral aripiprazole.

Table 5: Comparison of Oral Antipsychotics to Long-acting Injectable Antipsychotics in Established Schizophrenia: Efficacy of Aripiprazole LAI
(Frequency of LAIA administration follows package insert, unless otherwise noted)

Reference	Design	# of Patients Analyzed	Patient Population	Objective(s)	Dose(s) Used	Results	Study Critique
Kane, et al. 2013 ¹²	6-month Open-Label Mirror-Image Trial	181	<ul style="list-style-type: none"> Analyzed Males: 127 Females: 54 Stable schizophrenia Mean duration of illness: 15.7 years Baseline PANSS: 76.7 	(1) Total psychiatric hospitalization rates between retrospective oral antipsychotic (OAP) use vs. prospective aripiprazole LAI (ALAI) use at 6 months	<ul style="list-style-type: none"> Oral aripiprazole for titration: 10-30mg Aripiprazole 400mg once-monthly (7.2% of patients used 300mg once-monthly) 	<ul style="list-style-type: none"> Hospitalization rates: 14.2% (ALAI) and 41.5% (OAP); P<0.0001 	<p>Strengths:</p> <ul style="list-style-type: none"> Sample size Duration of study Real-world applicability with open-label study design <p>Limitations:</p> <ul style="list-style-type: none"> Open-label study design Historical control
Fleischhacker, et al. 2014 ¹³	38-week Non-Inferiority Double-Blind RCT	662	<ul style="list-style-type: none"> Analyzed Males: 406 Females: 256 Stable schizophrenia Primarily Caucasian and African American Baseline PANSS: 58 (standard-dose LAI), 56.6 (oral aripiprazole [oral]), and 56.1 (low-dose 	(1) Evaluate relapse rates of aripiprazole LAI (standard-dose LAI) 400mg compared to oral and aripiprazole LAI 50mg (low-dose LAI)	<ul style="list-style-type: none"> Oral: 10-30mg Standard-dose aripiprazole: 400mg/month Low-dose once-monthly aripiprazole: 50mg 	<ul style="list-style-type: none"> Standard-dose LAI: 265 patients, oral: 266 patients, low-dose LAI: 131 patients analyzed Relapse rates at week 26*: 7.12% (standard-dose LAI), 7.76% (oral), and 21.8% (low-dose LAI); standard-dose LAI was non-inferior to oral (P=0.7871) and superior (P=0.0006) to low-dose LAI Similar outcomes found at 38 weeks: standard-dose LAI vs. oral (P=0.992) and standard dose LAI vs. low-dose LAI (P<0.0001) Decreases observed in PANSS: standard-dose LAI vs. oral; -2.24 points (P<0.05) and standard-dose 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size Duration of study Double-blind RCT Multiple outcomes analyzed <p>Limitations:</p> <ul style="list-style-type: none"> Did not reach power in low-dose LAI arm

			LAI)			<p>LAI vs. low-dose LAI; -4.74 points (P<0.05)</p> <ul style="list-style-type: none"> • Standard-dose LAI had a 1.0kg increase in weight and low-dose LAI had a -1.6kg decrease in weight at 38 weeks (P<0.05) 	
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*Relapse was defined as a Clinical Global Impression – Improvement (CGI-I) score ≥ 5 and an increase in PANSS score >4 or ≥ 2 on a specific item, admission to the hospital for psychotic symptoms, CGI-SS score of 4 or 5 in part 1, CGI-SS score of 6 or 7 on part 2, or violent behavior resulting in self-injury, injury to another person, or property damage.

First-Generation LAIs: Efficacy and Adherence

Three studies have evaluated a comparison between first-generation LAIs (haloperidol decanoate and fluphenazine decanoate) to oral antipsychotics. Two of the three studies included patients in stable-phase schizophrenia or schizoaffective disorder, and the last study did not define which phase the patients were in.

The first study by Glick and colleagues aimed to identify efficacy differences in patients prescribed oral quetiapine vs. haloperidol decanoate. This was a small, 48-week, prospective, open-label study that included patients with schizophrenia or schizoaffective disorder. The authors observed no difference in patients remaining exacerbation-free throughout the study period between the two groups. PANSS negative scores and adverse events (rigidity and akathisia) were reported to be lower in the quetiapine group compared to patients on haloperidol decanoate. Baseline PANSS scores, power calculation, and acute vs. stable-phase were not provided.¹⁴ Olfson and colleagues conducted a large retrospective chart review in patients with stable-phase schizophrenia, schizoaffective, or schizophreniform disorder. The authors aimed to evaluate the continuity of use comparing fluphenazine decanoate, haloperidol decanoate, and risperidone LAI. The review identified adherence (defined as Medication Possession Ratio [MPR]) to be significantly less with fluphenazine decanoate (0.40) and risperidone LAI (0.40), compared to haloperidol decanoate (0.49). This difference was not observed to be clinically significant. The authors concluded that the increase in adherence could be due to the less frequent injections required by haloperidol decanoate (28 days) compared to fluphenazine decanoate (21 days) and risperidone LAI (14 days).¹⁵ The last study by Zhu and colleagues compared oral haloperidol and fluphenazine to their respective depot injections in an effort to identify time to discontinuation. A total of 299 patients with stable-phase schizophrenia or schizoaffective disorder were included. Both LAIA groups were observed to have significant decreases in time to discontinuation compared to oral antipsychotics.¹⁶ (Table 6)

Conclusion: Based upon the trials listed, there were conflicting results identified when comparing haloperidol decanoate to oral antipsychotics; however, fluphenazine decanoate had positive results in reducing time to discontinuation. Haloperidol decanoate was also observed to have greater adverse events, but these results were not reproducible in other studies.

Table 6: Comparison of Oral Antipsychotics to Long-acting Injectable Antipsychotics in Established Schizophrenia: Efficacy and Adherence of First-Generation LAIs
(Frequency of LAIA administration follows package insert, unless otherwise noted)

Reference	Design	# of Patients Analyzed	Patient Population	Objective(s)	Dose(s) Used	Results	Study Critique
Glick, et al. 2005 ¹⁴	48-week Prospective Open-Label RCT	22	<ul style="list-style-type: none"> Randomized Males: 20 Females: 5 Schizophrenia or schizoaffective disorder; <i>Unknown if stable or unstable</i> Mean duration of illness: 15 years (oral quetiapine [oral]) and 20 years (HD) 	(1) Compare long-term efficacy and tolerability of quetiapine (oral) and HD	<ul style="list-style-type: none"> Oral: 493mg HD: 170mg 	<ul style="list-style-type: none"> Oral: 15 patients, HD: 7 patients (analyzed) No difference in patients remaining exacerbation-free; P=0.77 Total change in baseline PANSS scores at 48-weeks: -2.0 (oral) and 0.6 (HD); <i>No p-value reported</i> Change in baseline PANSS Negative scores at 48 weeks: -3.2 (oral) and -0.5 (HD); P<0.05 Rigidity and akathisia greater in HD group vs. oral group; P<0.05 	<p>Strengths:</p> <ul style="list-style-type: none"> Length of study Real-world application of open-label design Multiple outcomes analyzed <p>Limitations:</p> <ul style="list-style-type: none"> Small sample size No power calculation No baseline PANSS score reported Uneven group sizes Open-label study design may lead to bias
Olfson, et al. 2007 ¹⁵	Retrospective Review	2,695	<ul style="list-style-type: none"> Analyzed Males: 1,578 Females: 1,117 Stable schizophrenia, schizophreniform, or schizoaffective disorder 	(1) Assess adherence of antipsychotic treatment of patients on FD, HD, and RLAI	<ul style="list-style-type: none"> Not provided 	<ul style="list-style-type: none"> HD: 1,631 patients, FD: 948 patients, RLAI: 116 patients (analyzed) Adherence* at 90 days: 0.40 (FD), 0.49 (HD), and 0.40 (RLAI); P<0.0001 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size <p>Limitations:</p> <ul style="list-style-type: none"> No power evaluation Study design Uneven group sizes Used refills to identify adherence No doses reported Adherence differences not clinically significant
Zhu, et al. 2008 ¹⁶	1-year Prospective Observational	299	<ul style="list-style-type: none"> Stable schizophrenia or schizoaffective 	(1) Comparison of time to medication discontinuation	<ul style="list-style-type: none"> Fluphenazine decanoate: 25mg Fluphenazine 	<ul style="list-style-type: none"> Depot: 97 patients, Oral: 202 patients Fluphenazine time to 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size Prospective design

	Trial		disorder	between oral and depot first-generation antipsychotics	<p>oral: 12mg</p> <ul style="list-style-type: none"> • Haloperidol oral: 10.7mg • Haloperidol decanoate: 100mg 	<p>discontinuation: 292 days (depot) and 272 days (oral); P<0.01</p> <ul style="list-style-type: none"> • Haloperidol time to discontinuation: 316 days (depot) and 257 days (oral); P<0.01 	<p>Limitations:</p> <ul style="list-style-type: none"> • Medication fills were analyzed electronically • Uneven group sizes
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*Adherence was defined as a medication possession ratio (MPR) >0.80.

Risperidone LAI: Adherence

Three large studies and one post-hoc analysis have evaluated adherence between risperidone LAI and oral antipsychotics. The majority of patients were in the stable-phase of schizophrenia or schizoaffective disorder, and many patients included were Veterans.

A retrospective review of Veterans conducted by Mohamed and colleagues identified significantly better adherence to oral clozapine, olanzapine, risperidone, and quetiapine compared to risperidone LAI. It was observed that aripiprazole had significantly lower adherence rates compared to risperidone LAI and ziprasidone had no significant difference in adherence. Of note, dosages of medications were not reported and adherence was evaluated by looking at refill history and anticipated coverage of medications.¹⁷ Olivares and colleagues conducted a 2-year prospective observational study with patients in the stable-phase of schizophrenia or schizoaffective disorder. The authors compared long-term treatment outcomes between OAPs and risperidone LAI. The study found a significant improvement in treatment retention for patients prescribed risperidone LAI (see risperidone LAI: adherence and table 8 for efficacy analysis).¹⁸ Rosenheck and colleagues aimed to identify adherence, efficacy, and hospitalization rates comparing OAPs and risperidone LAI in an open-label RCT with Veteran patients in acute-phase schizophrenia or schizoaffective disorder. No differences were observed in PANSS scores, adherence rates, or psychiatric hospitalizations at six months after randomization. This study did not reach power and physicians were unblinded, possibly leading to bias.¹⁹ A post-hoc analysis of the Rosenheck study¹⁹ found no significant difference in any endpoint of PANSS scores, re-hospitalization, or quality of life when separating Veterans into clinical subgroups; however, the analysis did observe a significant decrease in substance use in white Veterans prescribed risperidone LAI versus OAPs.²⁰ (Table 7)

Conclusion: Currently the studies evaluating adherence and retention rates between risperidone LAIs and oral antipsychotics have had conflicting results. A number of factors, including study designs, unpowered studies, and use of medical records to identify adherence may contribute to these findings.

Table 7: Comparison of Oral Antipsychotics to Long-acting Injectable Antipsychotics in Established Schizophrenia: Adherence of Risperidone LAI
(Frequency of LAIA administration follows package insert, unless otherwise noted)

Reference	Design	# of Patients Analyzed	Patient Population	Objective(s)	Dose(s) Used	Results	Study Critique
Mohamed, et al. 2009 ¹⁷	Retrospective Review	11,821	<ul style="list-style-type: none"> Analyzed Males: 11,040 Females: 781 Stable schizophrenia or schizoaffective disorder Veterans 	(1) Identify if RLAI versus OAPs improves adherence; measured by time to treatment discontinuation	<ul style="list-style-type: none"> Not reported 	<ul style="list-style-type: none"> RLAI: 280 patients, OAPs: 11,541 (analyzed) Patients were more likely initiated on RLAI if they were >65 years old, had a history of alcohol abuse, had an inpatient psychiatric hospitalization in <12 months, or had >12 outpatient visits (P<0.05) Patients were less likely to discontinue oral risperidone, olanzapine, clozapine, or quetiapine vs. RLAI within 2 years (P<0.01) No difference was observed in discontinuation of ziprasidone vs. RLAI (P=0.55) Patients were more likely to discontinue aripiprazole vs. RLAI (P=0.0001) 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size Multiple outcomes analyzed Veteran population <p>Limitations:</p> <ul style="list-style-type: none"> Study design Uneven group sizes No report of doses Used medical record for evaluation of drug discontinuation, as identified by first and last days of prescription coverage, not taking into account the length of effectiveness due to differences in half-lives
Olivares, et al. 2009 ¹⁸	2-year Prospective Observational Trial	1622	<ul style="list-style-type: none"> Analyzed Males: 1,030 Females: 592 Stable schizophrenia or schizoaffective disorder Duration of illness: 12.6 years (RLAI) and 10.9 years 	(1) Compare long-term treatment outcomes of OAPs to RLAI at 24 months	<ul style="list-style-type: none"> RLAI: 42.9mg OAP doses not specified 	<ul style="list-style-type: none"> OAP: 277 patients, RLAI: 1345 patients (analyzed) OAPs most commonly used: risperidone and olanzapine Adherence*: 81.8% (RLAI) and 63.4% (OAP); P<0.001 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size Prospective design Length of study <p>Limitations:</p> <ul style="list-style-type: none"> Doses of oral antipsychotics not provided

			(oral)				
Rosenheck, et al. 2011 ¹⁹	Open-Label RCT (VA Cooperative Study)	369	<ul style="list-style-type: none"> Acute schizophrenia or schizoaffective disorder Veterans 	<p>(1) Assess hospitalization rates within two years comparing OAPs to RLAI in unstable patients</p> <p>(2) Assess differences in adherence between groups</p>	<ul style="list-style-type: none"> RLAI: 25mg (17%), 37.5mg (31%), and 50mg (50%) Oral dose not reported 	<ul style="list-style-type: none"> OAP: 182 patients and RLAI: 187 patients (analyzed) No difference in time to hospitalization (P=0.39) No difference in PANSS scores (P=0.72) No difference in adherence** (P=0.19) 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size Veteran population Real-world applicability with open-label study design <p>Limitations:</p> <ul style="list-style-type: none"> Did not reach power Open-label study design may lead to bias
Leatherman, et al. 2014 ²⁰	Post-Hoc Analysis	369	<ul style="list-style-type: none"> Acute schizophrenia or schizoaffective disorder Veterans 	<p>(1) Identify if clinical subgroups in the Rosenheck⁹ trial observed a benefit in RLAI vs. OAPs</p>	<ul style="list-style-type: none"> RLAI: 25mg (17%), 37.5mg (31%), and 50mg (50%) Oral dose not reported 	<ul style="list-style-type: none"> OAP: 182 patients and RLAI: 187 patients (analyzed) Drug use (P=0.0127) and non-adherence (P=0.422) were more prevalent in the RLAI group vs. the OAP group White patients had greater improvement in substance abuse on RLAI vs. OAPs (P=0.001) No differences observed in PANSS scores between the two groups in any subgroup of patients No differences in re-hospitalization between the two groups in any subgroup No differences in quality of life observed between the two groups in any subgroup 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size Veteran population <p>Limitations:</p> <ul style="list-style-type: none"> Study design Did not reach power

* Adherence was defined as treatment retention at 24 months.

** Adherence was defined as the number of days until discontinuation or cross-over from oral to LAIA, as well as total number of injections, and personal report through patient interviews.

Risperidone LAI: Efficacy

Efficacy outcomes in patients prescribed risperidone LAI compared to oral antipsychotics was evaluated in nine studies. Many of the patients were diagnosed with schizophrenia or schizoaffective disorder and were stable at the time of inclusion. All studies were prospective, and designed to be open-label, single-blind, or double-blind. Most of the dosages used in the studies were moderate-high; however, two studies did not report doses for evaluation of applicability.

The first study by Keks and colleagues assessed a safety and efficacy comparison between oral olanzapine and risperidone LAI in patients with acute schizophrenia or schizoaffective disorder. This was a 53-week, open-label trial that included 347 patients. The authors observed greater improvement from baseline total PANSS scores in the RLAI group compared to oral olanzapine at 12 months. Significantly more weight was gained in the oral olanzapine group and more extra-pyramidal side effects (EPSEs) occurred in the risperidone LAI group.²¹ Chue and colleagues evaluated safety and efficacy outcomes in patients prescribed risperidone LAI compared to oral risperidone. This study was a 12-week, double-blind, RCT that included patients with stable schizophrenia. The majority of patients were on 4mg of oral risperidone and 50mg of risperidone LAI. The authors did not observe a difference in PANSS scores between the two groups, but did observe a significant decrease in prolactin levels in the risperidone LAI group.²² A 48-week single-blind RCT conducted by Bai and colleagues evaluated safety and efficacy outcomes in patients prescribed oral risperidone compared to risperidone LAI. Patients with stable schizophrenia were included and were primarily Caucasian. At the conclusion of the study, no difference in PANSS scores was noted; however, similar to Chue and colleagues a significant decrease in prolactin was observed in the risperidone LAI group compared to the oral risperidone group. Of note, mean dosages of study drugs were not provided for external validity.²³

Olivares and colleagues conducted a 2-years prospective observational study with patients in the stable-phase of schizophrenia or schizoaffective disorder. Long-term treatment outcomes between OAPs and risperidone LAI were evaluated. The study found a significant reduction in mean length of hospital stay, and reduction in mean hospital stays. No difference in reduction of patients hospitalized was observed between groups.¹⁸ A 2-year, open-label study by Macfadden and colleagues compared time to relapse and remission in patients taking oral aripiprazole compared to risperidone LAI. Patients were in the stable-phase of schizophrenia and were primarily of Asian ethnicity. No differences were observed for relapse and remission outcomes, as well as change in baseline total PANSS scores and adverse effects.²⁴

In the ConstaTRE trial conducted by Gaebel and colleagues a comparison between quetiapine and risperidone LAI was studied in regards to time to relapse. A total of 666 patients with stable schizophrenia were included in this 2-year, open-label, RCT. A decrease in time to relapse was observed between the two groups favoring the LAIA. The authors also identified improvement in PANSS scores in the LAIA group, but did not have the same finding in the quetiapine group from baseline.²⁵ A follow-up study looking at the aripiprazole arm of the ConstaTRE trial by Cordon and colleagues also observed a greater increase in the time to relapse and maintenance of remission, as well as a decrease in time to remission and PANSS scores in the risperidone LAI group compared to the aripiprazole group.²⁶

Bitter and colleagues conducted a comparative prospective study between risperidone LAI and oral antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone) to determine a difference in all-cause medication discontinuation, as well as time to all-cause discontinuation. Patients included were in the stable-phase of schizophrenia. All-cause medication discontinuation was observed to be less in the risperidone LAI group compared to all oral antipsychotics studied. Risperidone LAI also had significantly longer to all-cause discontinuation compared to oral antipsychotics. Of note, doses were not reported for external validity evaluations.²⁷ Lastly, a 30-month prospective study by Buckley and colleagues compared oral antipsychotics (olanzapine, aripiprazole, ziprasidone, paliperidone, quetiapine, and iloperidone) to risperidone LAI. Patients included were reported to be stable and have a diagnosis of schizophrenia or schizoaffective disorder. The authors did not observe a significant difference in time to relapse or time to hospitalization between risperidone LAI and oral antipsychotics. Anorexia was reported to be more common in patients in the risperidone LAI group. Of note, a power calculation was not provided.²⁸ (Table 8)

Conclusion: Trials evaluating differences in safety and efficacy between risperidone LAI and oral antipsychotics in patients with stable-phase schizophrenia have conflicting results. Some studies showed decreases in PANSS scores from baseline in the risperidone LAI group compared to oral antipsychotics, while others did not find the same difference. Similar conflicts were observed in adverse effect differences, as well as improvement in relapse and remission rates. Conversely, the one study that looked at acute-phase schizophrenia observed a decrease in PANSS scores from baseline in the risperidone LAI group compared to oral olanzapine, as well as greater weight gain in the olanzapine group and more EPSE in the risperidone LAI group. More studies need to be conducted to confirm these findings.

Table 8: Comparison of Oral Antipsychotics to Long-acting Injectable Antipsychotics in Established Schizophrenia: Efficacy of Risperidone LAI
(Frequency of LAIA administration follows package insert, unless otherwise noted)

Reference	Design	# of Patients Analyzed	Patient Population	Objective(s)	Dose(s) Used	Results	Study Critique
Keeks, et al. 2007 ²¹	53-week Prospective Open-Label RCT	362	<ul style="list-style-type: none"> Randomized Males: 312 Females: 235 Acute schizophrenia or schizoaffective disorder Mean duration of illness: 9 years 	<p>(1) Assess efficacy of oral olanzapine (oral) to RLAI</p> <p>(2) Assess safety</p>	<ul style="list-style-type: none"> RLAI: 40.7mg Risperidone oral overlap: 2.2mg Olanzapine: 14.6mg 	<ul style="list-style-type: none"> Olanzapine: 207 patients, RLAI: 155 patients (analyzed) Improvement from baseline in PANSS total scores at 12 months was greater in RLAI group (-25.8) vs. oral group (-23.7); P<0.0001 EPS: 25% (RLAI) and 15% (oral); P<0.05 Weight: +1.7kg (RLAI) and +4kg (oral); P<0.05 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size Length of study Multiple outcomes analyzed Real-world applicability with open-label study design <p>Limitations:</p> <ul style="list-style-type: none"> Open-label study design may lead to bias
Chue, et al. 2005 ²²	12-week Prospective Double-Blind RCT	541	<ul style="list-style-type: none"> Analyzed Males: 414 Females: 226 Stable schizophrenia Primarily Caucasian +Mean duration of illness: ~11 years 	<p>(1) Evaluate safety and efficacy of oral risperidone (oral) compared to RLAI</p>	<ul style="list-style-type: none"> Oral: 2mg (86 patients), 4mg (126 patients), 6mg (109 patients) RLAI: 25mg (88 patients), 50mg (126 patients), 75mg (105 patients) 	<ul style="list-style-type: none"> Oral: 275 patients, RLAI: 266 patients (analyzed) Improvement in PANSS for oral and RLAI was greater than baseline (P<0.001); no between-group difference was observed A significant decrease in prolactin was noted for each group; RLAI: P<0.001 (-4.8) and Oral: P=0.012 (-0.9); greater decrease in the RLAI group (P=0.025) No other differences in adverse effects were noted 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size Double-blind RCT Multiple outcomes analyzed <p>Limitations:</p> <ul style="list-style-type: none"> Short study duration Patients were not randomized for dose
Bai, et al. 2007 ²³	48-week Prospective Single-Blind RCT	45	<ul style="list-style-type: none"> Randomized Males: 25 Females: 25 	<p>(1) Evaluation of differences in safety and efficacy between</p>	<ul style="list-style-type: none"> Not reported 	<ul style="list-style-type: none"> Oral: 25 patients, RLAI: 20 patients (analyzed) No significant difference in PANSS total scores 	<p>Strengths:</p> <ul style="list-style-type: none"> Length of study RCT design

			<ul style="list-style-type: none"> Stable schizophrenia Baseline PANSS: 65.2 (RLAI) and 70.2 (oral risperidone) 	oral and RLAI		<ul style="list-style-type: none"> A significant difference in prolactin levels was observed: 8.8 points (oral) and -17.3 points (RLAI) 	<p>Limitations:</p> <ul style="list-style-type: none"> No power calculation No report of mean dosages Single-blind Small sample size
Olivares, et al. 2009 ¹⁸	2-year Prospective Observational Trial	1622	<ul style="list-style-type: none"> Analyzed Males: 1,030 Females: 592 Stable schizophrenia or schizoaffective disorder Duration of illness: 12.6 years (RLAI) and 10.9 years (oral) 	(1) Compare long-term treatment outcomes of OAPs to RLAI at 24 months	<ul style="list-style-type: none"> RLAI: 42.9mg OAP doses not specified 	<ul style="list-style-type: none"> OAP: 277 patients, RLAI: 1345 patients (analyzed) OAPs most commonly used: risperidone and olanzapine Reduction in patients hospitalized: 1.4% (OAP) and 6.2% (RLAI); P=0.4 Reduction in mean length of hospital stay: 0 days (OAP) and 1.5 days (RLAI); P<0.01 Reduction in mean number of hospital stays: -0.02 (OAP) and -0.09 (RLAI); P<0.05 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size Prospective design Length of study <p>Limitations:</p> <ul style="list-style-type: none"> Doses of oral antipsychotics not provided
Macfadden, et al. 2010 ²⁴	2-year Prospective Open-Label RCT	349	<ul style="list-style-type: none"> Analyzed Males: 210 Females: 139 Stable schizophrenia Primarily Asian patients Mean PANSS score: 68.6 (RLAI) and 69.1 (oral aripiprazole [oral]) Mean duration of illness: 9.9 years 	(1) Time to relapse comparing oral vs. RLAI (2) Time to remission comparing the two therapies	<ul style="list-style-type: none"> RLAI: 41.8mg Oral: 19.9mg 	<ul style="list-style-type: none"> Oral: 172 patients, RLAI: 177 patients (analyzed) No differences observed between time to relapse* (P=0.684) No differences observed between time to remission* (P=0.646) PANSS total scores decreased 11 points (RLAI) and 10.9 points (oral) (P=0.986) No differences in adverse effects noted with the exception of elevated prolactin levels in the 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size Real-world applicability of open-label design Length of study Multiple outcomes analyzed <p>Limitations:</p> <ul style="list-style-type: none"> Open-label study design may lead to bias

						RLAI group (No p-value reported)	
Gaebel, et al. 2010 ²⁵	2-year Prospective Open-Label RCT	666	<ul style="list-style-type: none"> Analyzed Males: 386 Females: 280 Stable schizophrenia or schizoaffective disorder Mean duration of illness: ~10 years Mean baseline PANSS scores: 72.7 (RLAI) and 73.2 (oral quetiapine [oral]) 	(1) Time to relapse comparing oral vs. RLAI	<ul style="list-style-type: none"> RLAI: 33.6mg Oral: 413.4mg 	<ul style="list-style-type: none"> Oral: 337 patients; RLAI: 329 patients (analyzed) 25% of oral patients relapsed** by day 248; the RLAI group never reached 25% of patients relapsing (study length=810 days); P<0.0001 Relapse occurred in 16.5% of patients (RLAI) and 31.3% (oral); <i>no p-value reported</i> PANSS total scores: -9.3 (RLAI); P<0.001. -1.1 (oral); P=0.1; Difference between groups: P<0.001 Adverse effects were similar between groups 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size Length of study Real-world applicability of open-label design Multiple outcomes analyzed <p>Limitations:</p> <ul style="list-style-type: none"> Open-label study design may lead to bias
Cordon, et al. 2012 ²⁶	2-year Prospective Open-Label RCT	370	<ul style="list-style-type: none"> Randomized Males: 220 Females: 154 Stable schizophrenia or schizoaffective disorder Mean duration of illness: 9.9 years (RLAI) and 8.1 years (oral) Mean PANSS score: 72.7 (RLAI) and 76.1 (oral aripiprazole [oral]) 	(1) Time to relapse comparing oral vs. RLAI	<ul style="list-style-type: none"> RLAI: 35.6mg Oral: 15.1mg 	<ul style="list-style-type: none"> Oral: 44 patients, RLAI: 326 patients (analyzed) Time to relapse[‡]: 244.9 days (RLAI) [CI: 188.1-301.7] and 147.7 days (oral) [CI: 73.8-221.6] Remission[‡] achieved in 51.1% of patients (RLAI) [CI: 45.5-56.6%] and 34.1% of patients (oral) [CI: 20.5-49.9%] Remission maintained until the end of the trial in 44% of patients (RLAI) [CI: 38.6-49.6%] and 29.6% of patients (oral) [CI: 16.8-45.2%] Total PANSS scores decreased 9.33 points 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size Length of study Real-world applicability of open-label design Multiple outcomes analyzed <p>Limitations:</p> <ul style="list-style-type: none"> Study did not reach power Uneven group sizes Open-label study design may lead to bias

						(RLAI); $P<0.0001$ and -7.66 points (oral); $P=0.0873$	
Bitter, et al. 2013 ²⁷	1-year Prospective Observational Trial	9,567	<ul style="list-style-type: none"> Analyzed Males: 3,805 Females: 5,762 Stable schizophrenia 	(1) Time to all-cause discontinuation between second-generation oral antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone) compared to risperidone LAI	<ul style="list-style-type: none"> Not reported 	<ul style="list-style-type: none"> RLAI: 1095 patients, Oral: 8472 patients (analyzed) All-cause medication discontinuation was less in the RLAI group vs. all oral antipsychotics ($P<0.01$) Time to all-cause discontinuation was significantly longer in the RLAI group (215 days) vs. olanzapine (136 days), aripiprazole (102 days), ziprasidone (93 days), quetiapine (89 days), clozapine (76 days), amisulpride (73 days), and risperidone (55 days) 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size <p>Limitations:</p> <ul style="list-style-type: none"> Uneven group sizes Doses not reported Study design Oral medications grouped together
Buckley, et al. 2014 ²⁸	30-month Prospective Open-Label RCT	305	<ul style="list-style-type: none"> Analyzed Males: 218 Females: 87 Stable schizophrenia or schizoaffective disorder Duration of illness: ~16 years 	(1) Comparison of relapse between patients prescribed OAPs vs. RLAI	<ul style="list-style-type: none"> RLAI: 50mg (38%), 37.5mg (22%), 25mg (22%), 12.5mg (6%), 62.5mg (5%), 75mg (5%) Oral: olanzapine 23mg, aripiprazole 23.4mg, ziprasidone 142.8mg, paliperidone 8.3mg, quetiapine 525mg, and iloperidone 12mg 	<ul style="list-style-type: none"> RLAI: 153 patients, OAPs: 152 patients (analyzed) No difference in time to relapse^e $P=0.13$ No difference in time to hospitalization ($P=0.305$) Anorexia was more common in the RLAI group vs. OAPs ($P=0.046$) 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size Length of study Real-world applicability with open-label design <p>Limitations:</p> <ul style="list-style-type: none"> Open-label study design may lead to bias No power calculation

*Relapse was defined as the time from the day the subject took the first dose of medication to day of relapse. Time in remission was defined as the simultaneous attainment of a score of ≤ 3 on PANSS items: delusions, concept disorganization, hallucinatory behavior, unusual thought content, mannerisms and posturing, blunted affect, passive/apathetic social withdrawal, and/or lack of spontaneity and flow of conversation.

** Relapse was defined as psychiatric hospitalization, increase in PANSS of $\geq 25\%$ or increase of 10 points if baseline PANSS was ≤ 40 , deliberate self-injury, emergence of suicidal/homicidal ideations, violent behavior resulting in injury to another person or property, CGI-Change score of 6, or exceeding dose of 50mg/2 weeks of risperidone LAI or 750mg of quetiapine.

‡ Relapse was defined as psychiatric hospitalization, increase in PANSS of $\geq 25\%$ or increase of 10 points if baseline PANSS was ≤ 40 , CGI-Change score of 6, deliberate self-injury, suicidal/homicidal ideations, violent behavior resulting in injury to another person or property, or exceeding dose of 50mg/2 weeks of risperidone LAI or 30mg of aripiprazole. Remission was defined as a score of ≤ 3 on PANSS items (blunted affect, passive/apathetic social withdrawal, lack of spontaneity and flow of conversation, disorganization, and psychoticism) maintained for ≥ 6 months.

€ Relapse was defined as psychiatric hospitalization for worsening symptoms, increase in psychiatric care, CGI-I score of 6 or 7, deliberate self-injury, suicidal/homicidal ideation, violent behavior resulting in injury to another person or property damage.

Meta-Analyses Comparing Oral Antipsychotics to LAIAs:

A number of meta-analyses have been completed on the available literature evaluating the difference in safety and efficacy endpoints between oral and long-acting injectable antipsychotics. A meta-analysis completed by Kishimoto and colleagues aimed to identify relapse differences comparing OAPs and LAIAs in 21 studies. Overall, the authors found no difference in relapse prevention between OAPs and LAIAs ($P=0.35$).²⁹ It was observed that studies included in the meta-analysis that were evaluating relapse rates comparing fluphenazine LAI to oral antipsychotics in prospective, double-blind, double-dummy trials prior to 1992, were superior to OAPs in preventing relapse ($P=0.02$).²⁹⁻³⁷ Another meta-analysis conducted by Kishimoto and colleagues pulled mirror-image studies comparing OAPs to LAIAs for evaluation of hospitalization risk, number of hospitalizations, and length of hospitalization stay. The studies ranged from publication year of 1971 through 2012 and included a variety of LAIAs. Fluphenazine decanoate and risperidone LAI were the most common LAIAs included in the analysis. Overall, the authors observed a statistically and clinically significant difference favoring LAIAs over OAPs for prevention of hospitalization with a 57% risk reduction ($P<0.001$; risk ratio of 0.43 [CI: 0.35-0.53]), as well as a 62% reduction in the number of hospitalizations ($P<0.001$; rate ratio of 0.38 [CI: 0.28-0.51]). Patients on LAIAs were also observed to spend significantly less time hospitalized compared to patients on OAPs (Hedge's $g=0.77$; $P=0.0063$ [CI: 0.22-1.33]).³⁸ Fusar-Poli and colleagues compared efficacy and safety outcomes in second-generation LAIAs compared to OAPs.³⁹ The authors observed no difference in PANSS scores ($P=0.326$), but greater treatment retention in the LAIA group ($P=0.017$). More EPS were observed in the LAIA group ($P=0.048$), but otherwise there were no differences in adverse effects.^{12, 19, 21-25, 39}

3. Use of Concurrent Oral Antipsychotics with Long-acting Injectable Antipsychotics:

There are two studies directly evaluating the use of concomitant OAPs with LAIAs. The retrospective review by Aggarwal and colleagues included patients in stable-phase schizophrenia or schizoaffective disorder, as well as a small portion of patients with bipolar disorder. The authors identified that concurrent use of OAPs may be common practice as evidenced by a large proportion of patients receiving both treatment modalities, which was also noted by Rosenheck and colleagues.¹⁹ The study did not identify efficacy and safety endpoints, nor a comparison of adherence outcomes.⁴⁰ Katona and colleagues conducted a non-interventional, retrospective-prospective study that also included patients in stable-phase schizophrenia or schizoaffective disorder. Monotherapy or a combination of oral and LAIAs were compared to identify differences in effectiveness. The authors observed time to all-cause discontinuation to be longer in the monotherapy group compared to the polypharmacy group for fluphenazine decanoate paired with ziprasidone, as well as risperidone LAI paired with all studied oral antipsychotics. Polypharmacy was observed to have longer time to all-cause discontinuation compared to the agents used as monotherapy for flupentixol LAI paired with clozapine, haloperidol, olanzapine, quetiapine, and zuclopenthixol, as well as fluphenazine decanoate paired with quetiapine and risperidone. This was also observed in patients prescribed polypharmacy with haloperidol decanoate and oral risperidone, as well as zuclopenthixol LAI with clozapine, haloperidol, risperidone and oral zuclopenthixol. The authors hypothesized that this may be a finding specific to first-generation depot antipsychotics due to the agents treating mainly positive

symptoms and combination with oral agents may target more symptoms on top of the positive symptoms. No specific safety and tolerability endpoints were studied.⁴¹ (Table 9)

Conclusion: Although the current literature suggests polypharmacy may have an advantage over monotherapy when using first-generation depot antipsychotics in efficacy outcomes, neither study looked specifically at adverse effects or safety outcomes. Currently, there is not enough evidence to say conclusively that the proposed benefits outweigh the risks.

Table 9: Use of Concurrent Oral Antipsychotics with Long-acting Injectable Antipsychotics (*Frequency of LAIA administration follows package insert, unless otherwise noted*)

Reference	Design	# of Patients Analyzed	Patient Population	Objective(s)	Dose(s) Used	Results	Study Critique	
Aggarwal, et al. 2012 ⁴⁰	Retrospective Review	124	<ul style="list-style-type: none"> Analyzed Males: 67 Females: 57 Majority of patients had stable schizophrenia or schizoaffective disorder (81.5%) Bipolar disorder (2.4%) Primarily African American (47%) and Caucasian (21%) males; 17% were Hispanic, and 14.5% were termed “other” 	<p>(1) Frequency of occurrence of concomitant use</p> <p>(2) Reasons for combination</p>	<p>Low dose LAI:</p> <ul style="list-style-type: none"> Haloperidol <75mg Fluphenazine <40mg Risperidone <50mg <p>Medium dose LAI:</p> <ul style="list-style-type: none"> Haloperidol 75-200mg Fluphenazine 40-75mg Risperidone 50mg <p>High dose LAI:</p> <ul style="list-style-type: none"> Haloperidol >200mg Fluphenazine >75mg Risperidone >50mg 	<ul style="list-style-type: none"> 46% of patients received concomitant oral APs Concomitant use was more common with high dose LAIAs (P=0.006) 60 patients were on low-dose LAIAs, 46 patients on medium-dose LAIAs, and 18 patients were on high-dose LAIAs Hispanic patients (P=0.01) and patients with a history of substance abuse (P=0.04) were more likely to be on concomitant OAPs LAIAs were most often combined with the oral counterpart 	<p>Strengths:</p> <ul style="list-style-type: none"> Multiple doses for comparison <p>Limitations:</p> <ul style="list-style-type: none"> Study design No evaluation of adherence No safety or efficacy endpoints Small sample size 	
Katona L, et al. 2014 ⁴¹	Non-Interventional Retrospective-Prospective Trial	13,381	<ul style="list-style-type: none"> Analyzed Males: 5,620 Females: 7761 Stable schizophrenia or schizoaffective disorder 	(1) Compare effectiveness of antipsychotic monotherapy vs. polypharmacy	Monotherapy/Polypharmacy Dose	<ul style="list-style-type: none"> Amisulpride: 341mg/416mg Aripiprazole: 20mg/23mg Clozapine: 96mg/125mg Haloperidol: 4.2mg/4.4mg Olanzapine: 10mg/11mg Quetiapine: 214mg/356mg Risperidone: 3.2mg/3.9mg 	<ul style="list-style-type: none"> Monotherapy: 5,480 patients, Polypharmacy: 7,901 patients Time to all-cause discontinuation: Flupentixol LAI: polypharmacy > monotherapy (all P<0.01) when paired 	<p>Strengths:</p> <ul style="list-style-type: none"> Large sample size <p>Limitations:</p> <ul style="list-style-type: none"> Study design Low clozapine, quetiapine (monotherapy), and haloperidol doses used

				<ul style="list-style-type: none"> • Ziprasidone: 100mg/112mg • Zuclopenthixol: 32mg/38mg • Flupentixol LAI*: 2.6mg/2.7mg • Fluphenazine LAI*: 2.2mg/1.8mg • Haloperidol LAI*: 4.1mg/4.0mg • Risperidone LAI*: 2.5mg/2.7mg • Zuclopenthixol LAI*: 10mg/11mg <p>*LAI doses are given in oral estimated equivalents</p>	<p>with clozapine, haloperidol, olanzapine, quetiapine, and zuclopenthixol; Fluphenazine decanoate: monotherapy > polypharmacy (P=0.000) when paired with ziprasidone, and polypharmacy > monotherapy (all P<0.01) when paired with quetiapine and risperidone; Haloperidol decanoate: polypharmacy > monotherapy (P=0.0011) when paired with risperidone; Risperidone LAI: monotherapy > polypharmacy (all P<0.01) when compared to all oral antipsychotics; Zuclopenthixol LAI: polypharmacy > monotherapy (all P<0.01) when paired with clozapine, haloperidol, risperidone, and zuclopenthixol</p>	<ul style="list-style-type: none"> • Combinations of 3+ medications were not included • No safety endpoints evaluated
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Summary:

1. Is there evidence to choose one long-acting injectable antipsychotic (LAIA) over the others? Are they all the same in regards efficacy/safety?
 - a. *Evidence does not support the use of any specific long-acting injectable antipsychotics over another.*

2. Is the place in therapy of LAIAs only for patients who are non-adherent? What is the evidence in regards to adherence?
 - a. *Due to the conflicting evidence and lack of reproducible studies with positive results, it cannot be concluded that safety, efficacy, and adherence are significantly better in patients prescribed LAIA; however, other factors for consideration may include: patient preference, decreased pill burden, patient environment, mental capacity, substance use disorder, etc. Systematic reviews by Zhornitsky and colleagues, Haddad and colleagues, Kane and colleagues, and Kirson and colleagues also concluded that results are inconclusive to say that LAIAs improve adherence, as well other endpoints in regards to relapse rates, time to discontinuation, and hospitalizations compared to oral antipsychotics.⁴²⁻⁴⁵ Similarly, a commentary paper by Stroup also concluded that adherence outcomes are variable across studies and it is unclear if adherence is enhanced.⁴⁶*

3. What is the evidence for/against combining oral antipsychotics and LAIAs?
 - a. *Evidence does not support or refute the combination of oral antipsychotics with LAIAs due to the absence of controlled and naturalistic studies evaluating the question. One would expect adherence to decrease with polypharmacy and adverse events would increase. Risk versus benefit still needs to be evaluated.*

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