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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

LONG ACTING INJECTABLE ANTIPSYCHOTICS

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Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

SPEAKER DISCLOSURES

- ✓ I have no actual or potential conflict of interest in relation to this program/presentation.

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OBJECTIVES

Review the history and utility of long acting injectable antipsychotics (LAI-AP)

Discuss the evidence and guidelines for use of LAI-AP in chronic psychotic disorders

Review the practical application of LAI-APs available in the US

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BRIEF TIMELINE

ECT

Chlorpromazine

Haloperidol
Fluphenazine
Thioridazine
Loxapine
Perphenazine

Fluphenazine enanthate (1966)
Fluphenazine decanoate (1967)

Haloperidol decanoate (1986)

Clozapine (1989)

Risperidone (1993)
Olanzapine (1996)
Quetiapine (1997)

Ziprasidone (2001)
Aripiprazole (2002)
LA Risperidone (2003)
Paliperidone (2006)
LA Paliperidone (2009)
Iloperidone & Asenapine (2009)
LA Olanzapine (2010)
Lurasidone (2010)

LA Aripiprazole Maintena (2013)
3 Month LA Paliperidone (2015)
LA Aripiprazole Aristada (2015)
Brexpiprazole (2015)
Cariprazine (2015)
LA Risperidone sub-Q (2018)
Lumateperone (2020)
LA Risperidone sub-Q (2018)
6 Month LA Paliperidone (2021)

LAI-APs noted in bold

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WHY?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 22, 2005 VOL. 353 NO. 12

Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia

Jeffrey A. Lieberman, M.D., T. Scott Stroup, M.D., M.P.H., Joseph P. McEvoy, M.D., Marvin S. Swartz, M.D., Robert A. Rosenheck, M.D., Diana O. Perkins, M.D., M.P.H., Richard S.E. Keefe, Ph.D., Sonia M. Davis, Dr.P.H., Clarence E. Davis, Ph.D., Barry D. Lebowitz, Ph.D., Joanne Severe, M.S., and John K. Hsiao, M.D., for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators*

- Non-adherence associated with relapse*, hospitalization, suicide and homelessness
- Relapse and duration untreated symptoms >>> more severe symptoms/course and functional impairment
- Estimates of non-adherence ~40% (20-80%)
- 74% Discontinued AP at 18 months CATIE

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THE DILEMMA OF ADHERENCE

- Overpredicted by client and prescribers
- Numerous factors promote non-adherence
  - Negative symptoms (lack of insight/cognitive impairment/avolition/disorganiztion)
  - Side effects of AP
  - Stigma
  - Psychosocial stressors (housing, lack of support, poverty, SUDs, medical comorbidity)
  - Lack of psychoeducation and behavioral treatment

LAI-AP VS ORAL AP

- Very few trials suggest oral more effective than LAIs
- MA 2011 of 10 controlled trials ≥ 12 months duration of LAI vs oral AP (Leucht et al, 2011) suggested **significant superiority of LAI's over oral** antipsychotics
- A meta-analysis of controlled trials done by Kishimoto et al in 2014 **failed to show superiority of LAIs** over oral medications
- A meta-analysis of **mirror-image studies** including Kishimoto et al in 2013 demonstrated **superiority of LAIs** in preventing hospitalizations
- Tiihonen et al reported two large-scale observational follow-up studies using a national, both of which showed that **LAIs** were **associated with significantly lower rates** of hospitalization

IDEAL TRIAL FOR LAI-AP

- RCTs tend to exclude patient with severe symptoms or comorbidity
- RCT design often increases adherence

- Mirror Image and reverse mirror image trials
- Pragmatic RCT
- Cohort Studies

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FEP DATA SUPPORT LAI-AP

- Naturalistic study of LAI vs. oral AP over 2 years: less relapse (23% vs 75%), improved symptoms, improved vocational and social functioning (Kane, 2008)
- RCT of LAI vs. oral risperidone: after 1 year higher relapse rate in oral med group (33%) compared to LAI group (5%) (Subotnik, 2015)
- May have neuroprotective effect by promoting intracortical myelination; At 6 mths white matter volume stable (on MRI) with LAI, decreased significantly with oral AP (Bartzokis, 2011)
- Prospective nationwide cohort in Finland (n=2,588) LAI-AP vs. oral AP associated with significantly decreased rate of hospitalization
- 3 years naturalistic study in Montreal FEP program found better outcomes and lower relapse rates for those on LAI despite poor prognostic factors of lower premorbid function, homelessness, substance abuse (Medrano, 2018; Abdel-Baki, 2019)

APA ON LAI-AP 2020 GUIDELINES

- **"APA suggests that patients receive treatment with a long-acting injectable antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence."**
  - **Any stage of illness**
  - **Non-adherence does not need to be confirmed**

GUIDELINE TRENDS

Canadian Psychiatric Association (2017)	National Institute of Clinical Excellence (2014)	Texas Medication Algorithm Project (2008)	French Association for Biological Psychiatry and Neuropsychopharmacology (2013)
Earlier use in the course of treatment has been advocated, as has the point that discussions regarding their use should **not be confined to only those for whom nonadherence** is a concern	Clinicians should consider offering LAI APs to patients **who would prefer such treatment** after an acute episode and where avoiding non-adherence is a clinical priority	Clinicians consider LAIs in patients who are **inadequately adherent at "any stage"**	LAI formulations should be systematically **proposed to any patients for whom maintenance antipsychotic treatment is indicated**. LAI antipsychotics can be used preferentially for non-compliant patients with frequent relapses or aggressive behaviors.

- 74% recommended LAI for non-adherence
- 63% cited patient preference as reason to consider LAI
- 68% recommended LAI as maintenance
- 26% recommended LAI at all phases of illness including FEP
- The Florida Medicaid Program recommended LAI as first step after stabilization on oral AP

LAI-AP GLOBALLY

Country	% Outpatients on LAIs
United Kingdom	30-40
Sweden	50
Austria	50
Germany	30
France	26
Italy	10
United States	10-15
Portugal	45
East Asia	36
Australia	27
Turkey	30.9

De Risio and Lang, 2014

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UNDERUSE IN UNITED STATES

- Lack of physician familiarity
- Inaccurate perception of efficacy and tolerability
- Drug cost
- Historical stigma/fear of coercion
- Predicting client aversion

COST OF LAI-AP

- Pharmacy cost often increased (SGA vs FG)
- Acute care cost reduced
- Overall cost similar to reduced
- Reduced cost confirmed in Sweden and Canada
- Large scale cost effectiveness data in US lacking
  - Claims data suggests greatest benefit most severe symptoms

WHICH LAI-AP?

- Similar efficacy for all SG LAI-AP and FG LAI-AP though head to head analysis lacking
- FG LAI-AP with more injection site reactions
- LAI vs oral generally equivalent AE
  - Exceptions:
    - FG LAI-AP vs FG oral AE
      - hyper-prolactinemia
      - EPS
    - SG LAI-AP vs SG oral AE
      - Akinesia
      - LDL elevation
      - Anxiety

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WHICH LAI-AP?

- Perceived safety of oral AP over LAI-AP may relate to non-adherence
- Choice based on:
  - Side effects
  - Ability to tolerate oral onboarding
  - Cost
  - Availability
  - Frequency

PROS/CONS OF LAI-AP

PROS

- No pills
- Adherence transparency
- Slower symptom rebound
- Clarifies treatment resistance
- Reduces overdose risk
- Avoids malabsorbtion difficulty
- More consistent blood level
- Regular visits

CONS

- Slower dose changes
- Longer time to steady state
- Delayed resolution side effects
- Pain/fear of needles
- Regular visits
- Perception of stigma
- May still need oral medications

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OPTIONS IN THE US

First generation long-acting antipsychotics (FGA's):

- Fluphenazine decanoate
- Haloperidol decanoate

Second generation long-acting antipsychotics (SGA's):

- Risperidone Consta
- Risperidone Perseris
- Paliperidone Sustenna
- Paliperidone Trinza
- Paliperidone Hafyera
- Olanzapine Relprevv
- Aripiprazole Maintena
- Aripiprazole Aristada

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FG LAI-AP

•AP attached to a fatty acid and dissolved in sesame oil

Forms a reservoir in the muscle

Gradual hydrolysis allows absorbtion of AP into the circulation

Prolonged duration of action

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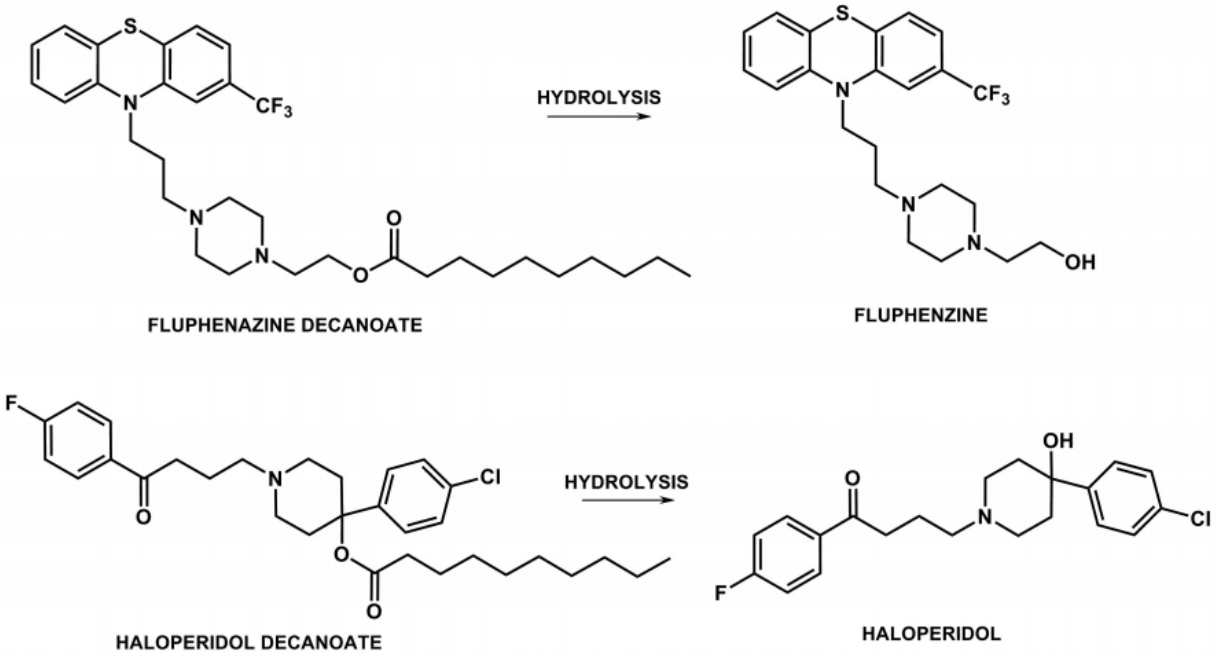
FG LAI-AP



Filho et al, 2010

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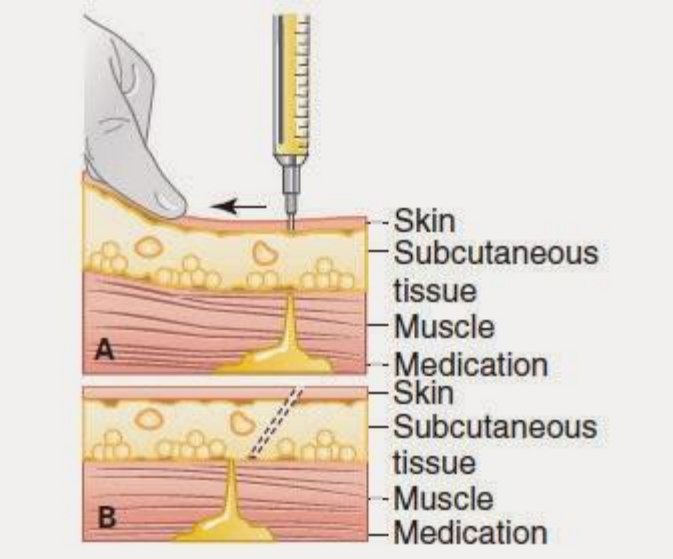
FG LAI-AP

- No clear data on in vivo processing of sesame oil
- Higher risk injection site reactions vs SG LAI-AP
- Some possible risk of calcification (which could affect drug release- not well studied)
- Gluteal or Deltoid site



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FIRST GENERATION LAIS

	Fluphenazine decanoate	Haloperidol decanoate
Dose Range	12.5-50mg	50-200mg (max initial dose = 100 mg)
Loading Dose	No	Yes
PO to IM Conversion	1.25 X PO dose	10-20 X PO dose
Frequency	q 2 to 3 weeks	q 4 weeks (can increase to q2-3 weeks if needed)
Half-life	14 days	21 days
Time to Peak	2-3 days	6 days
Oral Overlap	Yes: ~ one week	Yes: 1-2 weeks with loading doses vs. several months with conventional transition

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HALDOL DECANOATE LOADING

	Conventional Conversion	Loading Dose Strategy
Initial Dose	10 X PO Dose*	20 X PO Dose*
Monthly Dose	10 X PO Dose Q 4 Weeks	Option 1: 10 X PO Dose Q 4 Weeks Option 2: Decrease initial load by 25% Q 4 weeks eventually arriving at 10 x PO dose
PO Overlap	Several months-Could decrease oral by 25% at initiation and every month thereafter (goal to have off oral by month 3 or 4)	1-2 weeks

* first injection **not to exceed 100 mg** with the remainder to be given 3 to 7 days later

Ereshefsky et al, 1993

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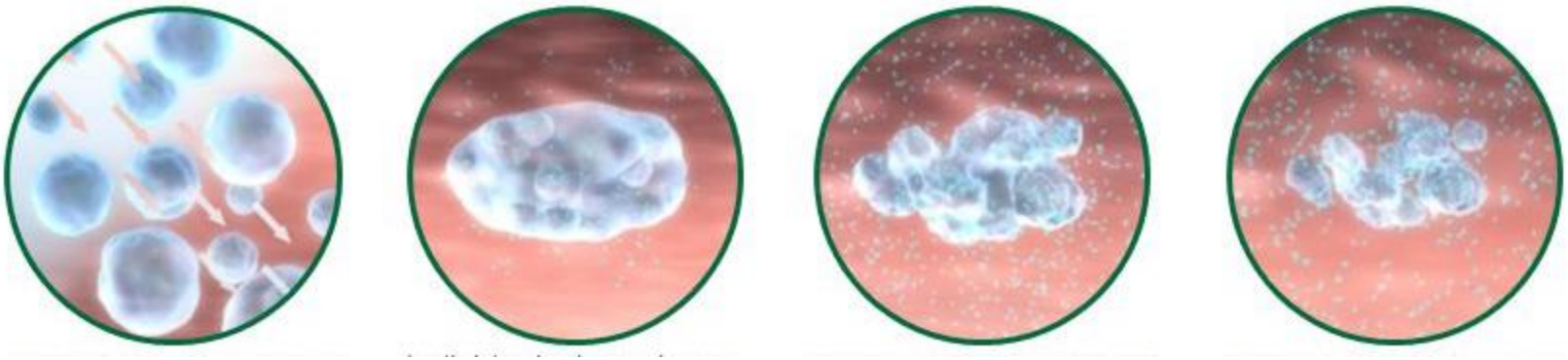
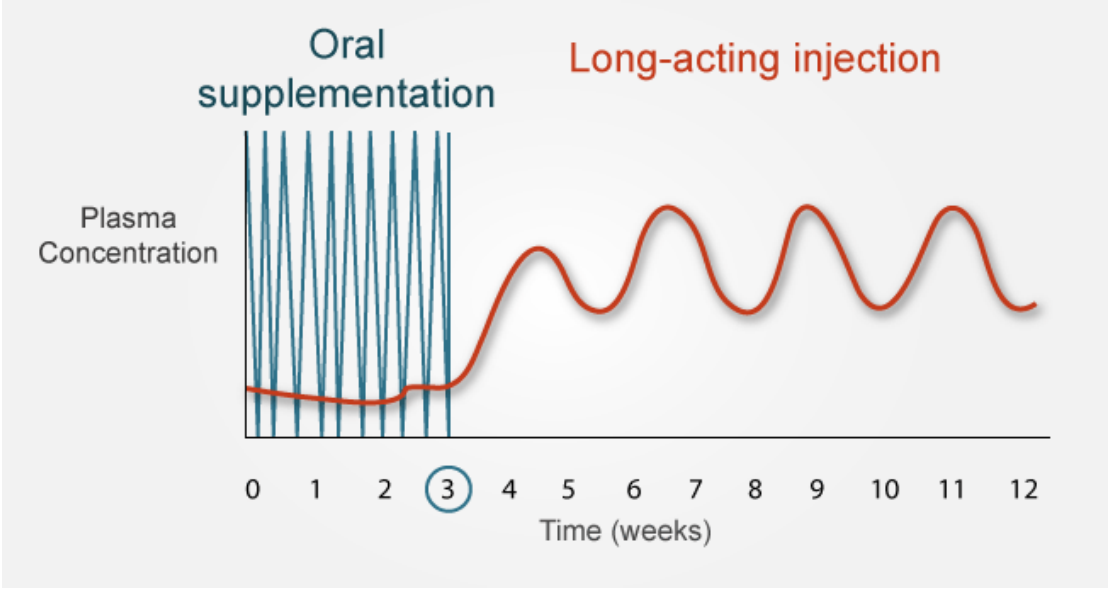
RISPERIDONE CONSTA





RISPERIDONE CONSTA

- Dosed q2weeks
- Oral overlap for 3 weeks
- Deltoid or gluteal sites
- Steady state after 8 weeks
- Complicated kinetics due to 2 week delay in release
- Reduced dose in renal impairment
- Metabolized by CYP2D6

1 mg po	12.5 mg IM
2 mg po	25 mg IM
3 mg po	37.5 mg IM
4 mg po	50 mg IM
6 mg po	75 mg IM (not FDA approved – 2 shots)

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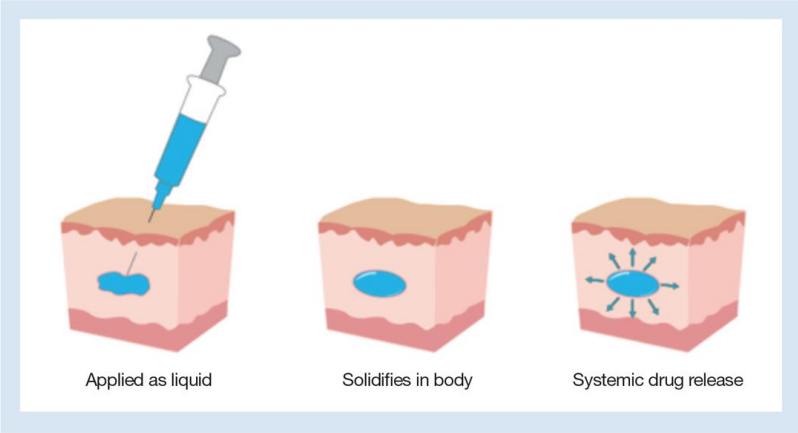
RISPERIDONE PERSERIS

PO Risperidone	SubQ Perseris
3 mg	90 mg
4 mg	120 mg

- SQ to the abdomen
- q4 weeks
- No oral overlap
- No loading



- First establish oral dose of at least 3mg daily
- Peak absorbtion 4-6 hours and 10-14 days
- Requires refrigeration and mixing between two syringes

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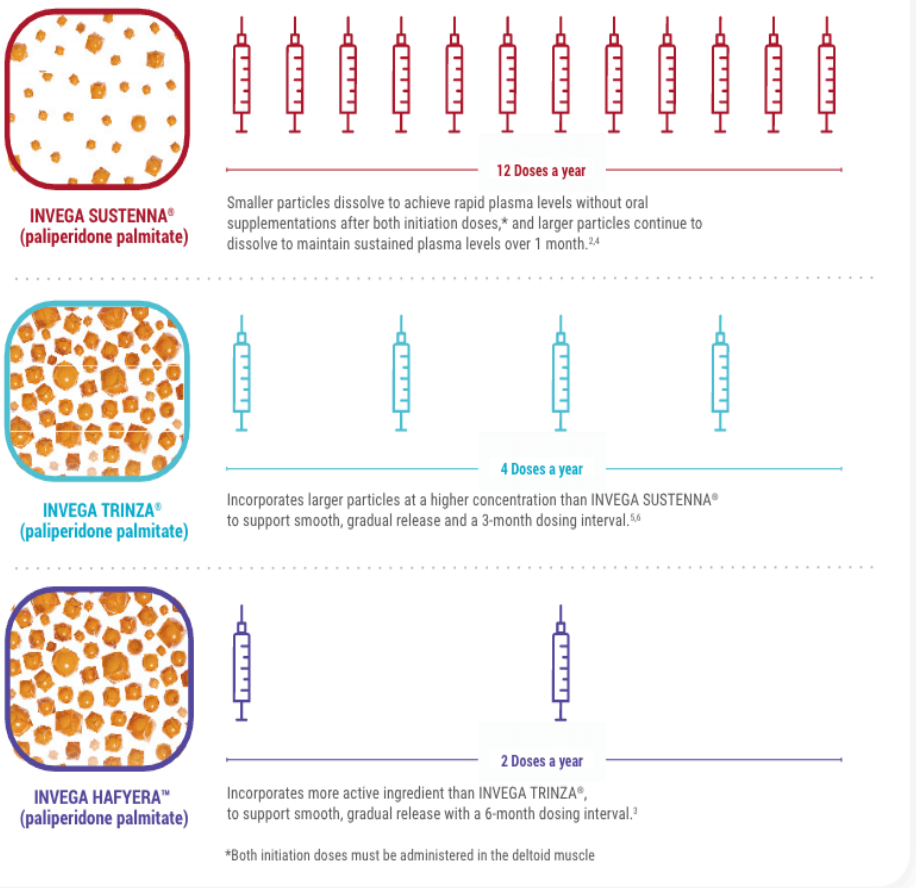
PALIPERIDONE IM



https://www.invegahafyerahcp.com/dosing/absorption-distribution

- Paliperidone palmitate is a prodrug that is hydrolyzed to paliperidone
- Major active metabolite of risperidone (9-hydroxyrisperidone)
- Aqueous extended release suspension of crystal salt
- Prefilled syringes
- Dose adjust for renal impairment
- Avoid CrCl <50 ml/min

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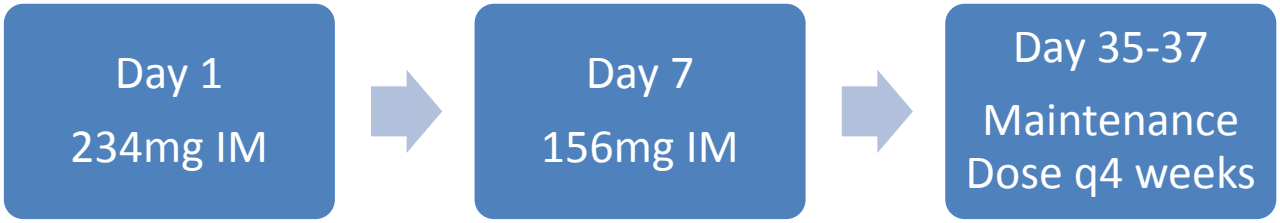
PALIPERIDONE INVEGA

IM Paliperidone	PO Paliperidone	PO Risperidone
234 mg	12 mg	5-6 mg
156 mg	9 mg	4 mg
117 mg	6 mg	3 mg
39-78	3	1-2

- No overlap per manufacturer
  - Recommend 7-14 day overlap
- Establish tolerability with risperidone or paliperidone
- Tmax (max plasma concentration) 13 days
- Deltoid or Gluteal



PALIPERIDONE TRINZA

- Q3 months IM
- Deltoid or Gluteal
- Only after 4 months of Sustenna with last two doses same strength

PALIPERIDONE HAFYERA

- Q6 months IM
- Gluteal only
- Only after 3 months Trinza or 4 months Sustenna

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OLANZAPINE RELPREVV

PO	IM Zyprexa Relprevv during the first 8 weeks	IM Zyprexa Relprevv after 8 weeks
10 mg	210 mg/**2 weeks** or 405 mg/**4 weeks**	150 mg/**2 weeks** or 300 mg/**4 weeks**
15 mg	300 mg/**2 weeks**	210 mg/**2 weeks** or 405 mg/**4 weeks**
20 mg	300 mg/**2 weeks**	300 mg/**2 weeks**

- Gluteal only
- Q2-4 weeks
- Aqueous crystalline salt
- Post-Injection Delirium/Sedation (Black Box Warning)
  - Facility, prescriber, patient and pharmacy require registration
  - 3 hour observation post IM
  - 0.07% risk per injection with cumulative risk over time
- Plasma concentrations within a week
- Half life 30 days
- No oral overlap

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LAI ARIPIPRAZOLE

	Abilify Maintena	Aripiprazole Aristada (lauroxil)
PO to IM Conversion	10mg PO daily ~ 300mg IM q4 weeks 15mg PO daily ~ 400mg IM q4 weeks 20mg PO daily ~ 600mg IM q4 weeks (x2 IM)	10mg PO daily = 441mg IM q4 weeks 15mg PO daily = 662mg IM q4 weeks = 882 IM q6 weeks = 1064 IM q8 weeks 20mg PO daily = 882mg IM q4 weeks
Loading Dose Available	No	Yes
Site	Deltoid or Gluteal	Gluteal for all other strengths but 441mg
Frequency of Injections	Every 4 weeks	Every 4-8 weeks
Oral Overlap Required	14 days	None- if loading dose 21 days - if no loading dose
T1/2	**29.9 days** for 300 mg **46.5 days** for 400 mg	Ranges from **29 to 35 days**
Elimination	CYP3A4 and CYP2D6	CYP3A4 and CYP2D6
Supplied As	Vials or Prefilled Syringes	Prefilled Syringes

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ARISTADA INITIO

- Give **1st Aristada IM dose + 675 mg IM Initio + 30 mg oral tablet of aripiprazole** (instead of 21 day oral overlap)
- First Aristada IM can on days 1-10
- Use different sites for multiple IM injections

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DIRECTIONS FOR MISSED ARISTADA DOSES

Dose of Patient's Last ARISTADA Injection	**Length of Time Since Last Injection**		
441 mg	≤6 weeks	>6 and ≤7 weeks	>7 weeks
662 mg	≤8 weeks	>8 and ≤12 weeks	>12 weeks
882 mg	≤8 weeks	>8 and ≤12 weeks	>12 weeks
1064 mg	≤10 weeks	>10 and ≤12 weeks	>12 weeks
Dosage and Administration for Re-initiation of ARISTADA	No Supplementation Required	Supplement with a Single Dose of ARISTADA INITIO	Re-initiate with a Single Dose of ARISTADA INITIO and a Single Dose of Oral Aripiprazole 30 mg

Aristada Initio Package Insert

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