Neuropsychotropic Drug Therapy 2020

When Psychiatry Breaks Skin: An Update on Long Acting Injectable Antipsychotics

Chelsea Markle, PharmD

Objectives for Learning Outcomes:

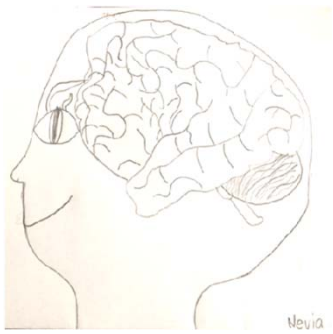
1. Discuss history and utility of long acting injectable antipsychotics.
2. Review Pharmacokinetic Considerations with regard to long acting injectable antipsychotics.
3. Discuss practical application of each long acting injection.

When Psychiatry Breaks Skin:

An Update On Long Acting Injectable Antipsychotics

Chelsea Markle, PharmD, BCPP

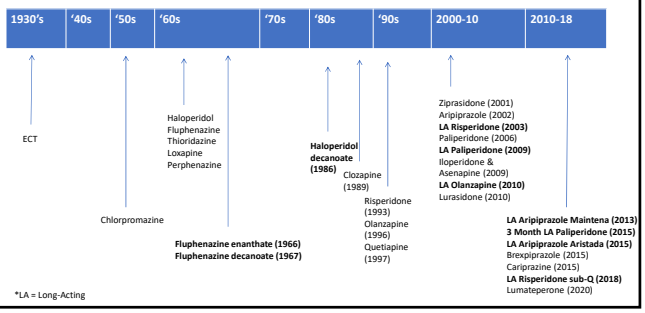
June 4, 2020



Objectives

- Discuss history and utility of long acting injectable antipsychotics
- Review pharmacokinetic considerations with regard to long acting injectable antipsychotics
- Discuss practical application of each long acting injection

Chronology of Antipsychotic Approval



*LA = Long-Acting

The Dilemma

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*

74% Discontinued at 18 months

Barriers to Adherence

- ❑ Forget to take meds
- ❑ Don't like side effects
- ❑ Makes me feel spacey, flat or have difficulty feeling emotions
- ❑ Don't like taking pills
- ❑ Lost or stolen meds
- ❑ I have trouble managing all the medications I have to take
- ❑ Forget to refill
- ❑ My medication schedule is inconvenient
- ❑ Don't have a daily schedule or habits to remind me
- ❑ Can't afford them
- ❑ Have transportation problems-can't get to pharmacy
- ❑ Felt good, stopped taking
- ❑ Felt worse, stopped taking
- ❑ Pills are too big-can't swallow
- ❑ Pill bottles are hard to open
- ❑ Makes me feel like a mentally ill person
- ❑ Conflicts with my substance use
- ❑ I have trouble talking with my doctor
- ❑ Homeless, no place to keep meds
- ❑ I'm careless at times about taking meds
- ❑ Get criticism from family, friends for taking meds
- ❑ Voices tell me not take meds
- ❑ Not educated about them & want to know more

The Debate

- Rates of relapse have not been found to differ between oral and LAI antipsychotics… or have they?
- RCTs are the gold standard -- Is this the most appropriate way to assess efficacy when comparing LAIs and oral therapies??

The Debate

A meta-analysis published in 2011 reviewed 10 studies lasting at least 12 months comparing outpatients randomly assigned to LAI or oral medication (Leucht et al, 2011) suggested **significant superiority of LAI's over oral** antipsychotics (Due to methodological differences, the evidence was not conclusive)

A meta-analysis of controlled trials done by Kishimoto et al in 2014 **failed to show superiority of LAIs** over oral medications

Two large-scale, government-funded studies **did not demonstrate** the **superiority of LAI's** over oral medication (Rosenheck et al, 2011 and Schooler et al, 2011)

Another meta-analysis of **mirror-image studies** done by 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 registry of patients with schizophrenia, both of which showed that **LAIs** were **associated with significantly lower rates** of hospitalization than oral meds

The Debate

"When a study has a particular focus on non-adherence and its consequences, it may well be that the RCT by its very nature has too much impact on the primary outcome measure."

…Kane et al, 2013

Pragmatic vs Explanatory Study Designs

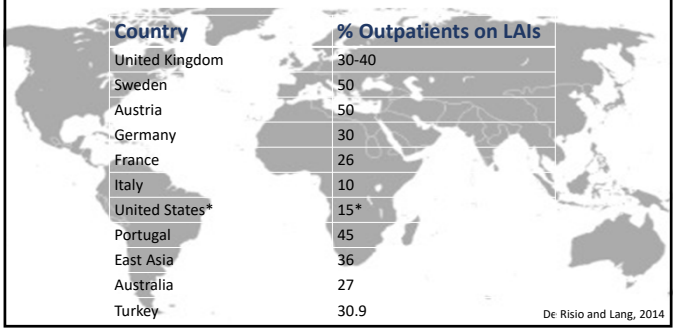
PRAGMATIC TRIALS

High external validity	High internal validity
Large sample size	Smaller sample size
Simple design	Sophisticated design
Diverse settings	
Mostly phase IV	Mostly phase II-III

EXPLANATORY TRIALS

Adapted from Patsopoulos, 2011

Prevalence of LAIs



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

De Risio and Lang, 2014

American Psychiatric Association

- Treatment of patients with schizophrenia (undergoing copyediting)
- Final version anticipated release → summer of 2020.
- Preliminary practice guideline available electronically (Dec 2019)

UPDATED: Patients should **receive** treatment with a LAI antipsychotic medication if they **prefer** such treatment **or** if they have a history of poor or **uncertain adherence**

Place for Long Acting Injectables

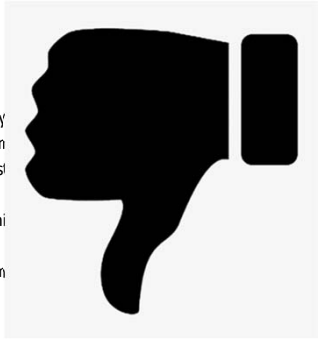
Canadian Psychiatric Association (2017)	National Institute of Clinical Excellence (2014)	Texas Medication Algorithm Project (2008)	French Association for Biological Psychiatry and Neuropsychopharmacology (2013)
Earlier use in the course of treatment has been advocated, as has the point that discussions 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 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.

Pros

- **No** need for **daily** administration
- **Guaranteed administration**/transp
- Allow caregivers to **intervene early**
- **Less** probability for rebound sympt
- **Overcome** partial adherence or ov
- If relapse occurs, it is due to reason
- Reduced risk of **unintentional over**
- **Minimize GI** absorption problems
- More **consistent bioavailability**
- **Reduced peak-trough** plasma level
- **Regular contact** between the patie
- Potential to give patient more **auto**

Cons

- **Slow** dose titration
- **Longer time** to achieve steady
- **Less flexibility** of dose adjustn
- **Delayed disappearance** of dis
- **Pain** at injection site
- Must frequent outpatient clini
- Perception of **stigma**
- May **still require oral** supplem
- $$



The Options

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

- Fluphenazine decanoate
- Haloperidol decanoate

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

- Risperidone Consta
- Risperidone Perseris
- Invega Sustenna
- Invega Trinza
- ~~Zyprexa Relprevv~~
- Aripiprazole Maintena
- Aripiprazole Aristada

More Options... Just Not Here

- Zuclopenthixol Decanoate
- Bromperidol Decanoate
- Perphenazine Decanoate
- Pipothiazine Palmitate
- Oxyprothepin Decanoate
- Flupenthixol Decanoate

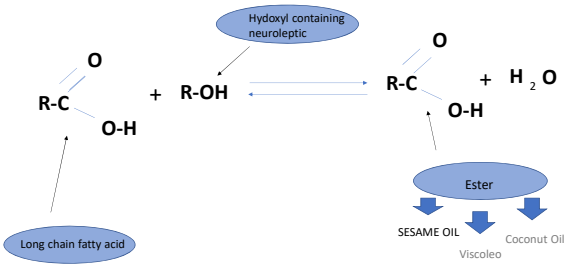
De Risio and Lang, 2014

The Options

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

- Fluphenazine decanoate
- Haloperidol decanoate

Breaking It Down-FGA LAIs



Breaking It Down-FGA LAIs

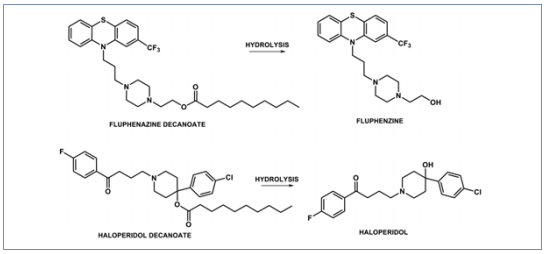
•Available in sesame oil

Forms a reservoir in the muscle

Allows drug to be slowly absorbed into the systemic circulation

Prolonged duration of action

Breaking It Down- FGA LAIs



Filho et al, 2010

Leftovers

- **No concrete evidence** to explain what happens to sesame seed oil **in vivo**
- Don't know **potential** effects of sesame oil **accumulation**
- Repeated administration could result in **calcification** (potentially effect release of the drug from the site—research is lacking)

Flip Flop Kinetics

- Abs
- A d bed
- Ha n is
  taki

First Generation LAIs

	Fluphenazine	Haloperidol
Typical Dose Range	12.5-50 mg	50-200 mg (max initial dose = 100 mg)
Loading Dose Used	No	Yes
PO to IM Conversion	1.25 X po dose Or 12.5 mg Q 3 weeks = 10 mg po daily	10-20 X po dose (see slide on loading strategies)
Frequency of Injections	Every 2 to 3 weeks	Every 4 weeks (can increase to 2 to 3 if clinically indicated)
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 dose vs. several months with conventional transition

Case

A **53 year old homeles** your service for the past 5 weeks a apine 30 mg po daily for 2.5 weeks weeks. Her chart reveals that she **fluphenazine** 20 mg d led to go back to that since it may ha case manager would like to see her o has been in and out of jail multiple tting in **aggressive behavior** i olerates **fluphenazine 20 mg**, h her to the injection?

Case

a.) Start fluphenazine decanoate 12.5 mg IM Q28 days with one week of po overlap

b.) Start 25 mg IM fluphenazine hydrochloride IM Q 21 days with one week of po overlap

c.) Start 37.5 mg IM fluphenazine hydrochloride IM q 14 days with two weeks of po overlap

d.) Start 25 mg IM fluphenazine decanoate q 21 days with one week of po overlap

Haloperidol Decanoate

DRAMA

- Oral form discovered by Janssen Pharmaceutica (1958)- marketed in Europe the following year
- Very **successful in Europe**, but not approved in US for ~10 years!
  - Structurally **flawed clinical trial**
  - Approval hampered by new laws following the **Thalidomide disaster** (1962)
  - Case of **industrial espionage:** confidential info regarding haloperidol was passed to another pharm company prior to approval
    - → **Janssen awarded** the right to register oral haloperidol in US in **1969**

De Risio and Lang, 2014

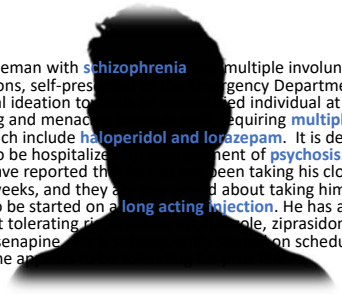
Haloperidol Decanoate

	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

Case



A 42 year-old gentleman with **schizophrenia** multiple involuntary treatment admissions, self-pres gency Department reporting homicidal ideation to ed individual at his group home. He is pacing and menac equiring **multiple prn** medications of which include **haloperidol and lorazepam**. It is determined that he will need to be hospitalize ment of **psychosis**. Staff at the group home have reported th been taking his clozapine reliably in recent weeks, and they a d about taking him back unless he agrees to be started on a **long acting injection**. He has a history of either failing or not tolerating ri ole, ziprasidone, olanzapine, and asenapine on scheduled oral **haloperidol** since he a

Case

The patient is titrated up to **15 mg po haloperidol** daily over the course of 2 weeks and appears to be **stabilizing**. He complains of some akathisia, which has responded well to propranolol, however is agreeable to a **long acting injection**. You are wondering how to transition him to haloperidol **decanoate**.

a.) Give 150 mg IM haloperidol decanoate now and stop the oral in one week. Continue with 150 mg IM every month.

b.) Give 100 mg IM haloperidol decanoate now and another 200 mg IM in one week. Taper the oral over the next 1-2 weeks. His monthly dose would be 150 mg IM.

c.) LAI not indicated at this time since he has not been on oral for long enough

d.) Give 300 mg of haloperidol decanoate IM x 1 now and start 150 mg IM monthly in 4 weeks. We do not need oral overlap at this time.

Long Acting Risperdal Consta (Risperidone)

All doses administered **every two weeks**

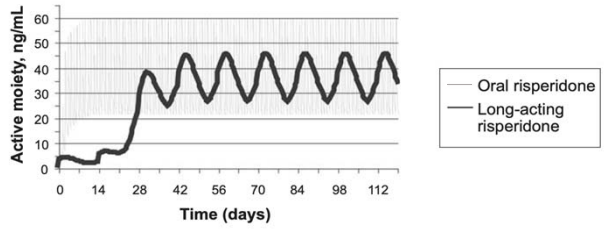
Requires **oral overlap** for at least 3 **weeks**

Deltoid and gluteal **sites interchangeable** and bioequivalent

Disconnect between $t_{1/2}$ and tss (monograph states that the half life = 3-6 days)

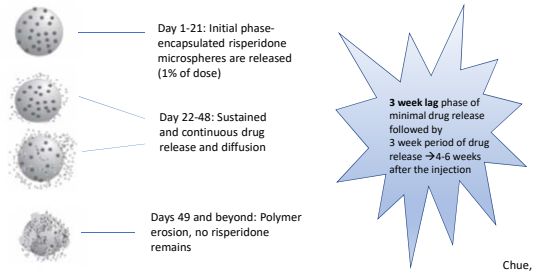
Steady state plasma concentrations achieved **after 4 injections** (8 weeks)

Long Acting Risperdal Consta (Risperidone)



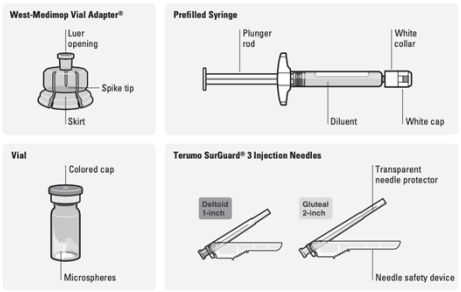
Chue, 2007

Long Acting Risperdal Consta (Risperidone)



Chue, 2007

Long Acting Risperdal Consta (Risperidone)



Risperidone Consta Package Insert

Long Acting Risperdal Consta (Risperidone)

- **PO to IM conversion:**

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)

- Package insert advises reduced dose with **renal impairment**
- Extensively metabolized by **CYP2D6**

Long Acting Perseris (Risperidone)

1st **subcutaneous** 2nd generation LAI antipsychotic
Available as an extended release injectable suspension of risperidone
Administered in the **abdomen**
Once **monthly** injection
18 gauge needle!!
Manufacturer claims **no overlap** required with oral therapy
No loading dose available

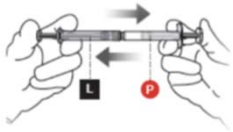
Long Acting Perseris (Risperidone)

- First establish tolerability with at least 3 mg of po risperidone

PO Risperidone	SubQ Perseris	IM Paliperidone
3 mg	90 mg	78 mg
4 mg	120 mg	156 mg

- Has **not been studied** in renal or hepatic impairment
- Use caution if on **CYP2D6** inhibitor or **3A4** inducer
- 2 absorption peaks (1st at 4-6 hours, 2nd at 10-14 days)
- T½ ranges between 9 and 11 days on average

Long-Acting Perseris (Risperidone)



- Requires refrigeration and thorough mixing for **60 cycles** transferring between two syringes
- Have patient lay in supine position for administration
- Delivery system solidifies upon contact with bodily fluid
- Patient may experience lump for several weeks

Long Acting Invega Sustenna (Paliperidone)

- Paliperidone palmitate is a prodrug that is hydrolyzed to paliperidone
- Major **active metabolite of risperidone** (9-hydroxyrisperidone)
- Available as a white sterile aqueous extended release **suspension**
- Prefilled syringe
- Administered as a **once monthly** IM injection
- Median apparent **half-life** after a single dose = **25-49 days**
- Not extensively metabolized in the liver

Long Acting Invega Sustenna(Paliperidone)

- Manufacturer **claims no overlap required** with oral therapy
  - Following a single IM dose, the plasma concentrations gradually rise to reach max plasma concentrations at 13 days (tmax)
  - First establish tolerability with po risperidone or paliperidone

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

Long Acting Invega Sustenna (Paliperidone)

	deltoid	deltoid	deltoid or gluteal
CrCl > 80 mL/min:	Begin with initial loading dose of **234** mg	Give second shot of **156** mg 7 days later (+/- 4 days)	Start maintenance dose 36 days after first shot (+/- 7 days)
CrCl 50-79 mL/min:	Begin with initial loading dose of **156** mg	Give second shot of **117** mg 7 days later (+/- 4 days)	Start maintenance dose 36 days after first shot (+/- 7 days)

CrCl < 50 mL/min: use not recommended
Has not been studied in dialysis

Long Acting Invega Trinza (Paliperidone)

- Long acting injectable **paliperidone** as a **3 month** formulation
- Initiate only after **4 consecutive monthly injections** of Invega Sustenna (Last two doses must be the same strength)
- May administer in **deltoid or gluteal** muscle
- Median T ½ = **84-95 days** with **deltoid** injection, **118-139** with **gluteal**

Long Acting Invega Trinza (Paliperidone)

Invega Trinza dose equals **3.5 times** the 1-month Invega Sustenna dose, given every 3 months

IM Invega Trinza	IM Invega Sustenna
273 mg	78 mg
410 mg	117 mg
546 mg	156 mg
819 mg	234 mg

Can be given 2 weeks early or late without altering kinetics

Case

You are on the inpa
injectable options
antipsychotic after
been **hospitalized 4**
with his medication
month, mainly beca
insight presently to
meds to stay stable
risperidone 6 mg p

taking his
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Case

a.) Tell him that there is a 4 month IM formulation of paliperidone that he can receive the month after he is loaded with Invega Sustenna

b.) Inform him that the only options available to him at this time are risperidone Consta, (administered IM every 2 weeks) or risperidone Perseris (administered sub-q monthly)

c.) Discuss with him the option of Invega Trinza, and let him know that he would be eligible after 4 consecutive months of Invega Sustenna (with the last two doses being of the same strength)

d.) Tell him that there is a transdermal option of risperidone that has recently been approved

Long Acting Zyprexa Relprevv (Olanzapine)

- **Gluteal** injection only
- Not to be confused with short-acting IM Zyprexa
- Slow dissolution of a **crystalline salt**
- Crystals are micron-sized and suspended in water
- **Black box warning** includes **post injection syndrome**

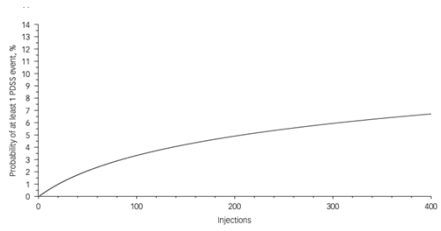
LA Zyprexa Relprevv (Olanzapine)

Black Box Warning

Post-injection Delirium/Sedation Syndrome:
- Consistent with olanzapine overdose (sedation, coma, delirium)
- Must be administered in a registered healthcare facility with ready access to emergency response services

Risk per injection = 0.07%

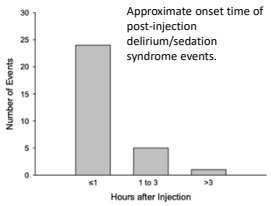
LA Zyprexa Relprevv (Olanzapine)
Post Injection Delirium Sedation Syndrome (PDSS)

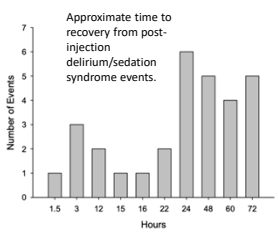


Plot of cumulative estimated risk of PDSS event. The probability of having at least 1 PDSS event increases over time and reaches approximately 6 to 7% after 400 injections.

Meyers et al, 2017

LA Zyprexa Relprevv (Olanzapine)
Post Injection Delirium Sedation Syndrome (PDSS)





Detke, 2010

Long Acting Zyprexa Relprevv (Olanzapine)

✓**Observe patient** for at least **3 hours**
✓Available through a **restricted distribution** program - Zyprexa Relprevv Patient Care Program
✓**Required enrollment**
- Prescriber
- Healthcare facility
- Patient
- Pharmacy

Long Acting Zyprexa Relprevv (Olanzapine)

- ½ life of Zyprexa Relprevv is 30 days
- Plasma concentrations peak within a week and are at trough level immediately prior to next injection

PO olanzapine/day	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**

Long Acting Abilify Maintena (Aripiprazole)

Starting and **maintenance dose = 400 mg** intramuscularly every month (**deltoid or gluteal**)

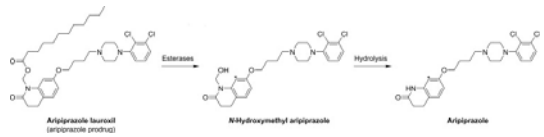
Can **reduce dose to 200 or 300 mg** if adverse effects occur

Steady state concentrations after the **4th** dose

Long Acting Aripiprazole

	Abilify Maintena	Aripiprazole Aristada
PO to IM Conversion	No	Yes
Loading Dose Available	No	Yes
Site	Deltoid or Gluteal	Deltoid or Gluteal for 441 mg dose only Gluteal for all other strengths
Frequency of Injections	Every 4 weeks	Every 4-8 weeks
Oral Overlap Required	14 days	None- if loading dose used 21 days - if no loading dose used
$T_{1/2}$	**29.9 days** for 300 mg and **46.5 days** for 400 mg	Ranges from **29 to 35 days**
Elimination	3A4 and 2D6	3A4 and 2D6
Supplied As	Vials or Prefilled Syringes	Prefilled Syringes

Long Acting Aripiprazole Aristada (Aripiprazole lauroxil)



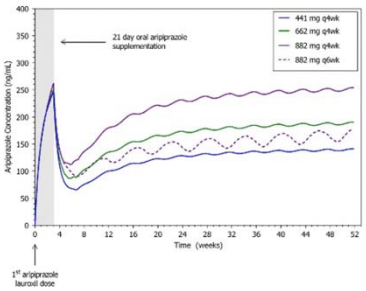
Aripiprazole lauroxil (prodrug) is converted by enzyme-mediated hydrolysis to N-hydroxymethyl aripiprazole, which is then hydrolyzed to aripiprazole

Long Acting Aripiprazole Aristada (Aripiprazole lauroxil)

PO Abilify	IM Abilify Aristada
10 mg/day	441 mg/4 weeks
15 mg/day	662 mg/4 weeks or 882 mg/6 weeks or 1064 mg/8 weeks
20 mg/day	882 mg/4 weeks

Do not administer earlier than 14 days following the previous injection.

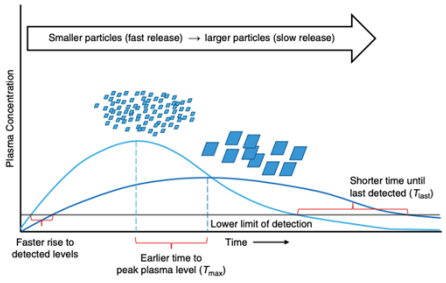
Long Acting Aripiprazole Aristada (Aripiprazole lauroxil)



Long Acting Aripiprazole Aristada Initio (Aripiprazole Lauroxil Initiation Dose)

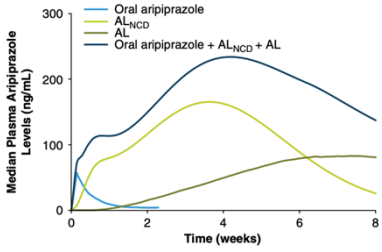
- Administer first **Aristada IM injection** with **675 mg** of Initio and one **30 mg tablet** of aripiprazole (in place of 21 day oral overlap)
- First Aristada injection may be administered on the **same day** as Initio or up to 10 days thereafter
- Avoid injecting into the same deltoid for concomitant administration (can also use gluteal muscle)

Long Acting Aripiprazole Aristada Initio (Aripiprazole Lauroxil Initiation Dose)



Jain et al, 2019

Long Acting Aripiprazole Aristada Initio (Aripiprazole Lauroxil Initiation Dose)



Jain et al, 2019

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

Case

A 24 year old female presents to the clinic today for a regular appointment. She has been taking **15 mg of aripiprazole** daily for paranoia and auditory hallucinations associated with her schizophrenia. She seems to be doing **fairly well** on this regimen and is asking about getting an **injection**, since she has a hard time remembering to take her dose every day. She does mention that she doesn't like needles, so the longer she can go between injections, the better. After discussing the options with her, you decide on the following plan.

Case

a.) Abilify Maintena 400 mg IM q month with 14 days of oral overlap

b.) Aripiprazole Aristada 882 mg IM q 8 weeks with 14 days of oral overlap

c.) Aripiprazole Aristada 1064 mg IM q 8 weeks with Aristada Initio 675 mg IM x 1 on day one to be taken with a 30 mg tablet of aripiprazole po x 1

d.) Abilify Maintena 300 mg IM q month with Aristada Initio 675 mg IM x 1 on day one to be taken with a 15 mg tablet of aripiprazole po x 1

Do You Want Chips With That?

- Digital pill combining aripiprazole with **ingestible chip** approved
- Proteus worked with Otsuka to develop 1 mm ingestible chip that **emits** a unique code when **wetted in the digestive system**
- Band-aid sized **patch** applied to the skin that picks up **signal** and relays to **smartphone** or tablet tracking adherence
- Technology initially developed/approved in 2012 as inert pill to be taken with another active drug
- Patch replaced **once/week**

Mullard, 2015

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