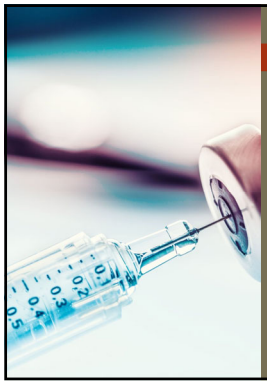

Essential Long-Acting Injectable Antipsychotic Concepts for Clinicians: A Review

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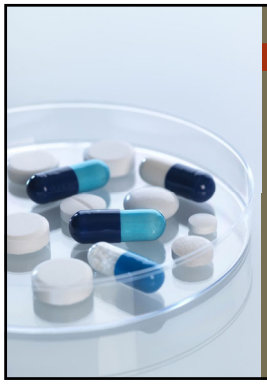
Conflict of Interest

None to disclose



Order of presentation

- Introduction
- Pharmacodynamic considerations for switching between antipsychotics
- Pharmacokinetic considerations to consider when switching to LAIs
- General Considerations with LAIs
- FGA LAIs and Loading Strategies
- SGA LAIs and Loading Strategies
- Management of Missed LAI Doses

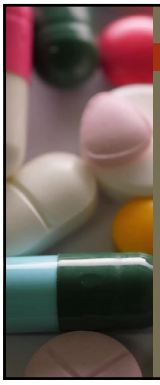
Topics not covered

- Pharmacokinetics/Pharmacodynamics of each LAI
- Mechanisms of action of each LAI
- Drug interactions
- Contraindications
- Use of LAIs in co-morbid medical illnesses
- Use during pregnancy/lactation

Introduction

- Several antipsychotics (APs) are available as LAIs
- Enhance treatment adherence and potentially improve outcomes for SMI
- LAIs lower all-cause discontinuation, hospitalization rates and all-cause as well as specific-cause mortality
- Tolerability is a significant concern as release of the active drug is sustained for several weeks after injection------result in long-lasting S/E
- Due to gradual release, LAIs in general have not been associated with an increased risk of S/E
- LAIs prescribed to small portion of SCZ patients
- Barriers: negative attitudes of patients, stigma, underappreciation, fear of occurrence of injection related pain, lack of experience, cost and treatment access, insufficient knowledge related to transition

Kishimoto T et al, 2013



Pharmacodynamic considerations for switching between antipsychotics

- Receptor binding properties of an AP could help predict therapeutic as well as adverse effects
- Receptor binding profile informs about the potential rebound effects occurring during switching from one AP to another
- Rebound symptoms (psychosis, agitation, restlessness, insomnia and anxiety) are connected to receptor supersensitivity
- Rebound symptoms: Might be related to higher antidopaminergic, antihistaminergic, or anticholinergic blockade of the pre- vs post-switch AP
- Dopaminergic rebound: occurs when postsynaptic dopamine blocking AP is discontinued or switched too abruptly to a postsynaptic dopamine blocking AP with lower affinity for dopaminergic receptors than previous AP

Buckley PF, Correll CU et al, 2006

Pharmacodynamic considerations for switching between APs

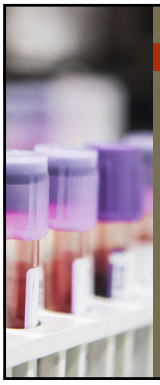
- Histaminergic (Hista) and cholinergic(chol) rebound occurs when switching from APs with potent antihista or anti-chol properties (e.g. clozapine, OLZ or quetiapine) to APs with lower affinity (risperidone or aripiprazole)
- Hista and Chol. blockade: calms anxiety, agitation, improves sleep and counter EPS
- Abrupt discontinuation can result in opposite symptoms (rebound anxiety, agitation, insomnia, akathisia)
- Becoz an increased number of hista/chol receptors may be in a high-affinity state suddenly are left free to stimulation by endogenous Histamine and Ach

Correll CU et al, 2006

Pharmacokinetic considerations when switching to LAIs

- Switching strategies involving LAIs differ from switching strategies b/n oral APs
- Oral APs: plasma t ½ determined by elimination rate. Absorption from intestine is relatively quick (hours)
- LAIs: plasma t ½ determined by absorption rate from the injection site that is slower than hepatic/renal elimination time (**flip-flop kinetics**)
- Absorption from injection site to circulation is slow (days or weeks) as AP is gradually released when injected particles slowly dissolve
- Steady-state plasma levels are achieved after approx. five half-lives
- Oral APs: steady-state achieved within weeks
- LAIs: steady state achieved in months

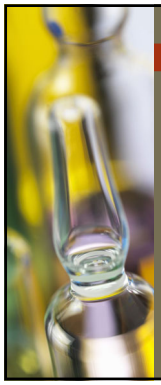
Jann MW, Ereshefsky L et al, 1985



Pharmacokinetics considerations when switching to LAIs

- LAIs are oil or water-based
- FGAs: esterified with decanoic acid to make them oil soluble
- After injection, decanoic acid is slowly absorbed from oil to bloodstream and subsequently hydrolyzed, leaving free AP to become active
- SGAs: encapsulated in a polymer matrix (risperidone microspheres/gel) or formulated as crystals (OLZ, paliperidone and aripiprazole)
- Formulation may involve a prodrug (e.g. Aripiprazole lauroxil) which needs enzymatic breakdown and hydrolyzation to become active AP
- Dosing interval: function of particle size for salt-based LAIs, with larger particles taking longer to break down

Meyer JM, 2013



Pharmacokinetic considerations

- OLZ pamoate crystals: immediately start to dissolve after injection releasing OLZ to blood
- Switching to OLZ LAI does not require considerable overlap/oral supplementation
- Risperidone microspheres: disintegrates upon injection, but significant amounts released after 2-3 weeks
- Switching to risperidone microspheres requires several weeks of oral supplementation or continuation of pre-switch oral AP
- Some LAIs can be loaded to increase plasma levels rapidly to clinically effective levels (e.g. FGA LAIs, paliperidone-LAI, risperidone long-acting subcutaneous AP formulations, certain Aripiprazole-LAI initiation strategies)

Correll CU, Kim E at al, 2021

General Considerations

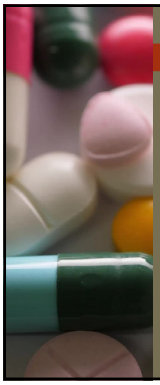
- 2 FGAs (haloperidol and fluphenazine) and 4 SGAs (aripiprazole, olanzapine, paliperidone and risperidone) are available in LAIs
- FGA LAIs: relatively cheap and might have lower risk of metabolic S/E compared with some SGA LAIs (OLZ, paliperidone and risperidone)
- FGA LAIs: higher risk of EPS and injection site irritation due to sesame oil vehicle
- Tolerability and efficacy generally equivalent to oral formulations of AP if the oral AP is taken as prescribed
- Basic tolerability and efficacy should be established for oral AP before initiating corresponding LAI
- Tolerability established by administering few doses of oral AP
- No clear consensus on how long the oral AP should last before initiating LAI (4 days- 6 weeks proposed)

Taylor D, 2009; Citrome L, 2013

Pharmacokinetics	HPL Decanoate	FFZ decanoate
Dosing interval	Q4 weeks	Q2-4 weeks
Plasma peak after administration	6 days	1 day
Time to reach steady state	3-4 months	4-6 weeks
Half-life	3 weeks	8-14 days
Therapeutic window	3-15ng/ml	0.2-2 ng/ml

Pharmacokinetic properties of haloperidol and fluphenazine decanoate

Carpenter J, Kit Wong K, 2018



UAB Hospital P&T Committee Medication Guidelines

- LAI APs should be administered IM in deltoid or gluteal muscle
- Please note when the LAI AP dose was given for timing of the next dose
- Paliperidone palmitate (PP) loading doses should be given in deltoid muscle
- Subsequent PP doses may be given in deltoid or gluteal muscle
- HPL and FFZ decanoate require z-track administration to prevent spillage

Package inserts of pharmaceuticals, Carpenter J, Wong KK, 2018

LAIs: General Dosing Recommendations- First Generation Antipsychotics

Medication	Indication	Initial dose	Maintenance Dose	Interval	Notes
FFZ Dec	Schizophrenia	6.25mg-25mg (1.25 times daily oral dose)	6.25-100mg	Every 2-4 weeks	• Oral overlap may be necessary until 2nd or 3rd injection • Q 3wks standard • SubQ or IM • 20mg oral= 25mg IM FFZ/3weeks
HPL Dec	Schizophrenia	Loading dose is 10-20 times the daily oral dose	50-450mg(usually 10-15 times daily oral dose)	Q 4 weeks	• If loading doses>100mg, dose must be divided • 100mg initially and then remainder of dose 3-7 days after 1st injection • Do not exceed 250mg/injection

Alternative Loading Dose (LD) strategies- HPL Dec- Method 1 Ereshefsky A et al, 1993

- Calculated LD is based on target Maintenance Dose (MD)
- Daily oral dose 10-15mg/d: target MD 100-150mg/ Q4weeks
- Daily oral dose 20mg/d: target MD is 200mg/Q4 weeks
- Daily oral dose >20mg/d: target MD is >200mg/Q 4weeks
- Total LD = Target MD X 2.5
- Total LD should be administered in 3 doses on day 0,7 and 21

-1st LD should be a test dose of 50-100mg
-Remainder given on day 7 and 21
-Oral HPL dose decreased by 50% after 2nd LD on day 7 and stopped after 3rd LD on day 21
Example: Patient with oral dose of 20mg/d
-Target MDD= 200mg, Calculated LD= 200 X 2.5= 500mg
-Day 0 = 100mg
-Day 7 = give 200mg and decrease oral dose by 50%
-Day 21 = give 200mg and stop oral HPL if able to

LD Strategies for HPL Dec- Ereshefsky et al, 1993

- Stop oral Haloperidol upon 1st Loading dose

-LD is 20 X the oral daily dose (1-3 doses administered within 7-day span, with first dose not more than 100mg

-First maintenance dose (starting 4 weeks after load completed) = loading dose X 0.75

-Subsequent maintenance doses (given Q 4 weeks) = 10 X oral daily dose

-Example

- Oral daily dose = 15mg HPL
- HPL Dec LD = 300mg (15mg X 20)
- Day 0: give 100mg
- Day 7: give 200mg
- 1st MD: give 225mg (300 X 0.75)
- Subsequent Maintenance Doses: 150mg Q 4 weeks

LAI General dosing recommendations: SGAs

Medication	Indication	Initial dose	Maintenance Dose	Interval	Notes
Paliperidone palmitate	Schizophrenia Schizoaffective disorder CrCl<80ml/min and >50ml/min	234mg:day 0 followed by 156mg on day 7 156mg day 0 followed by 117 on day 7	117mg (max 234mg) 78-234mg Max 78mg	Q 4 weeks	• 2nd dose may be given 4 days before or after weekly time point • 1st MD given 5wks after day 0 • Monthly doses may be given 7 days before or after • Oral overlap not required • Can stop oral after 1st LAI dose

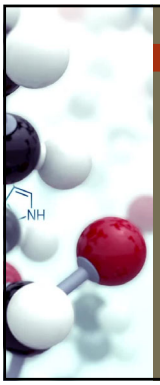
Switching to Paliperidone LAI 3M and 6M

- Paliperidone LAIs consist of paliperidone palmitate crystals in aqueous suspension and administered quarterly PP3M or half-yearly PP6M
- Administered by deltoid or gluteal injection depending on the dose
- PP3M requires ≥ 4 monthly injections of PP1M before PP3M can be initiated
- PP6M requires four monthly injections with PP1M or ≥1 injection of PP3M before PP6M can be initiated
- PP6M is marketed in doses equivalent to 156-234mg PP1M or 546-819mg PP3M without options for individuals on lower doses of PP1M/3M
- After injection, PP crystals are slowly dissolved, releasing PP into the circulation-----then subsequently hydrolyzed to free paliperidone
- Paliperidone (9-hydroxy-risperidone) is the active metabolite of risperidone

Invega Sustenna prescribing information, 2022

LAI General dosing: SGAs

Medication	Indication	Initial dose	Maint Dose	Interval	Notes
Risperidone Consta	Bipolar I disorder Schizophrenia	12.5-25mg	25mg (max 75mg)	Q 2 weeks	• 12.5mg initial dose approp for patients with h/o poor tolerability • Oral overlap for 3 weeks
Aripiprazole LAI	Bipolar I Schizophrenia	300-400mg	160-400mg	Q4 weeks	Oral overlap for 14 days after 1st shot



Switching to Risperidone LAI

- Risperidone was the first SGA to be marketed as LAI in 2003
- 5 formulations of LAI risperidone are available
- 2018: gel-based formulation for SC administration Q4 weeks was marketed not requiring oral cotreatment
- 2022: Additional formulation of risperidone for IM injection Q 4 weeks was approved. Does not require oral cotreatment
- 2023: Two additional formulations of risperidone have been approved(FDA)
  - Microsphere formulations of risperidone for IM Q2 weeks: 1 week of oral Rx
  - One- monthly or two-monthly version of risperidone for SC injection: no oral cotreatment is required

Risperdal Consta prescribing information, 2022

Converting from oral paliperidone to IM Paliperidone (Carpenter J, Kit Wong K, 2018)

Daily dose of oral Paliperidone	Daily dose of oral risperidone	Monthly Paliperidone maintenance dose
12mg	6mg	234mg
9mg	4-5mg	156mg
6mg	3mg	117mg
3mg	1-2mg	39-78mg

Converting from oral risperidone to IM risperidone (Carpenter J, Kit Wong K, 2018)

Daily dose of oral risperidone	Every 2-week IM risperidone MD*
≥ 6mg	75mg
5mg	62.5mg
4mg	50mg
3mg	37.5mg
2mg	25mg
1mg	12.5mg

* Steady state of risperidone IM occurs after the fourth consecutive injection (approximately 2 months)

Converting from IM risperidone to IM Paliperidone (Carpenter J, Kit Wong K, 2018)

Risperidone injection (Q 2 weeks)	Paliperidone Injection MD Q 4 weeks
12.5mg	39mg
25mg	78mg
37.5mg	117mg
50mg	156mg
75mg	234mg

Switching to Aripiprazole(Arip) LAI

- Arip LAI available in three different formulations:

-Arip monohydrate (AM), administered Q4 weeks (AM1M)

-AM2-monthly (AM2M)

-Arip Lauroxil (AL), administered Q4, 6 or 8 weeks depending on dose

- AM1M and AL: effective for maintenance Rx and acute exacerbation of schizophrenia (SCZ)
- AM2M tested for maintenance Rx in SCZ or Bipolar disorder

Citrome L, 2016; Meltzer HY et al, 2015

Aripiprazole Monohydrate 1-monthly (AM1M)

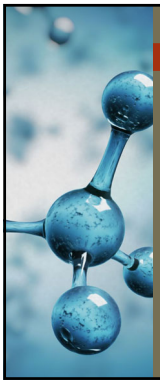
- AM1M consists of crystals, administered Q4 weeks IM in deltoid/gluteal
- Starting dose 400mg= 20mg of oral Aripiprazole
- Lower doses (160-300mg) used if 400mg IM is not tolerated or enzyme inhibiting drugs are used concurrently
- Time to peak is 4-7 days and four injections required to achieve SS
- Oral supplementation with oral Arip(10-20mg) for ≥14 days required following first injection
- Tolerability to Arip should be established before 1st injection of Arip LAI with oral doses of 2.5-5mg/d for ≥2-3 day

Citrome L, 2016; Meltzer HY et al, 2015

Aripiprazole monohydrate 2-monthly (AM-2M)

- FDA approved in April 2023
- Arip released from the injection site after first injection, but oral Arip should be continued for 14 days after 1st injection of AM-2M
- Starting dose is 960mg of AM as crystals
- Dose is reduced to 720mg during maintenance Rx if patient is known to be cytochrome P450 2D6 poor metabolizer or treated with enzyme-inhibiting drugs
- If the patient is not known to tolerate Arip, test doses should be given

Otsuka Pharmaceutical Co, Ltd



Aripiprazole lauroxil (AL)

- AL: prodrug of Arip---converted to N-hydroxymethyl arip by enzymatic hydrolysis and subsequently hydrolyzed by water to free Aripiprazole
- AL LAI administered Q 4, 6 or 8 weeks depending on the dose
- Lowest dose (441mg) administered by injection in deltoid muscle, while other doses injected in gluteal muscle
- Oral supplementation with Arip is necessary for ≥21 days following 1st injection of AL LAI (time to peak for AL LAI is 44-50 days)
- 2018: FDA approved AL Nanocrystal Dispersion (AL NCD)
- AL NCD contains 675mg of small particles of AL LAI and given with one dose of 30mg of Arip, followed by planned dose of AL LAI within 10 days
- Faster release of AL from AL NCD is a result of smaller crystal size, reaching therapeutic plasma levels within four days

Hard ML et al, 2017

Management of missed doses of LAIs

- **Haloperidol decanoate**

-At steady state and <6 weeks since last dose: Administer LAI as soon as possible

- Steady state not reached or has been >6 weeks to 12 weeks since last dose
  - Give next dose ASAP
  - Provide oral haloperidol supplementation if symptoms recur
- If >13 weeks since last dose:
  - Stabilize patient on oral haloperidol
  - Reinitiate IM loading dose sequence

Carpenter J, Wong KK, 2018

Management of missed doses of LAIs

-**Fluphenazine decanoate**

- At steady state and <6 weeks since last dose

-Give long-acting injectable dose ASAP

- Steady state not reached, or it has been > 6 weeks to 24 weeks since last dose
  - Give next dose ASAP
  - Provide oral fluphenazine if symptoms recur
- If >25 weeks since last dose:

-Stabilize patient on oral fluphenazine

-Reinitiate IM loading dose

Carpenter J, Wong KK, 2018

Management of missed initiation doses- Paliperidone Palmitate

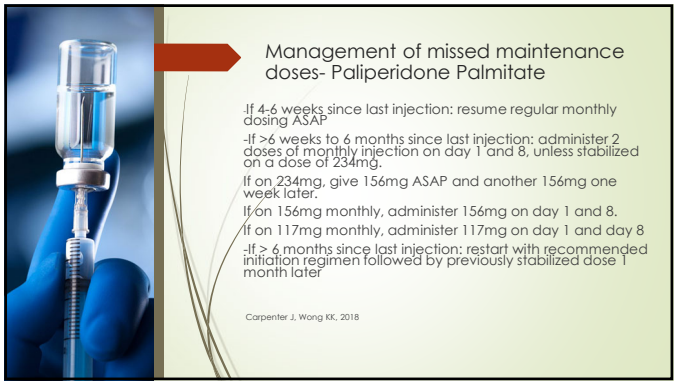
- Missed 2nd initiation dose

-If <4 weeks since 1st injection, administer 2nd initiation dose of 156mg ASAP.

A third dose of 117mg is recommended 5 weeks after the first injection regardless of the timing of the second dose

- If 4-7 weeks since 1st injection: resume with one 156mg injection ASAP, then second 156mg injection one week later
- If > 7 weeks since first injection: restart with recommended initiation regimen

Carpenter J, Wong KK, 2018



Management of missed maintenance doses- Paliperidone Palmitate

-If 4-6 weeks since last injection: resume regular monthly dosing ASAP

-If >6 weeks to 6 months since last injection: administer 2 doses of monthly injection on day 1 and 8, unless stabilized on a dose of 234mg.

If on 234mg, give 156mg ASAP and another 156mg one week later.

If on 156mg monthly, administer 156mg on day 1 and 8.

If on 117mg monthly, administer 117mg on day 1 and day 8

-If > 6 months since last injection: restart with recommended initiation regimen followed by previously stabilized dose 1 month later

Carpenter J, Wong KK, 2018

Management of missed doses-Risperdal injection

- Steady state not reached and > 2 weeks since last dose
  - Give next injection ASAP + oral overlap for 3 weeks
- At steady state and ≤ 6 weeks since last dose:
  - Give injection ASAP
- At steady state and > 6 weeks since last dose

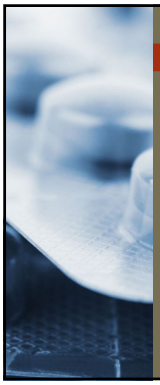
-Give next injection ASA P + oral overlap for 3 weeks

Carpenter J, Wong KK, 2018

Management of missed doses-Aripiprazole injection

- Second or Third Doses Missed:
  - If > 4 and < 5 weeks since last injection: administer injection ASAP
  - If > 5 weeks since last injection: restart oral overlap for 14 days with next injection
- Fourth or Subsequent Doses Missed:
  - If > 4 weeks and < 6 weeks since last injection: administer injection ASAP
  - If > 6 weeks since last injection: restart oral overlap for 14 days with next injection

Carpenter J, Wong KK, 2018



Conclusion

- LAIs are an effective treatment in individuals with SMI where non-adherence issues are very common
- Rebound symptoms in connection to AP discontinuation or switching may occur due to greater Dopa, Hista, or Chol antagonism of the pre-switch compared to post-switch AP
- Absorption from injection site into blood stream determines plasma levels and time to steady state for LAIs
- Most LAI formulations require loading regimens or oral supplementation, except for newer subcutaneous and microparticle injection formulations
- Switching to LAIs can be done from corresponding oral formulation

- Thank you
- Questions???
- Email: bbirur@uabmc.edu (Badari Birur)
- Email: bradleyburk@uabmc.edu (Bradley G. Burk)

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