Drugs used in schizophrenia

Dr .MD ASIF ALI ,
3rd year P.G ,
Dept of Pharmacology

- Classification
- Antipsychotic Long Acting Injections (LAI)
- Pharmacology of Individual Long Acting Antipsychotics
- Advantages & Disadvantages

Classification of Anti -psychotic drugs :

CLASS	Drugs
First generation	CHLORPROMAZINE, LEVOMEPROAZINE , FLUPHENAZINE
	LEVOMEPROMAZINE , HALOPERIDOL , PERICYAZINE
	FLUPENTIXOL/ZUCLOPENTHIXOL
	PIPOTIAZINE , PERPHENAZINE , TRIFLUOPERAZINE
	PIMOZIDE , SULPIRIDE
Second generation	RISEPERIDONE,ARPIPRAZOLE , AMISULPRIDE
	OLANAZAPINE , CLOZAPINE , QUETIAPINE , ASENAPINE
	PALIPERIDONE ,LURASIDONE , SERTINDOLE

First-generation Longer acting injections

Flupentixol:

- Thioxanthine antipsychotic.
- LAI is formulated as flupentixol decanoate .

MECHANISM

- Blockade of dopaminergic projections to the temporal and prefrontal areas constituting the limbic system and in mesocortical areas .

PHARMACOKINETIC

- Peak plasma levels 3–7 days after IM injection
- Apparent half-life of 17 days.
- Steady-state plasma levels can be expected to be achieved after 2 months .

- Initially 20 mg should be given as a test dose. If well tolerated 20-40mg may be given after 1 wk.
- Maintenance dose of 20-40 mg can be given every 2-4 wks.
- Dose of depot is 8 times of total oral dose
- It has mood elevating property, may worsen agitation.

First-generation LAIs

Fluphenazine:

- Piperazine phenothiazine compound.
- Fluphenazine decanoate is available as an LAI in sesame oil.

MECHANISM

- Mechanism not fully understood: it block postsynaptic dopamine receptors in the brain, depress the RAS, including the parts of the brain involved with wakefulness and emesis.

PHARMACOKINETICS

- Plasma levels peak within 24 h of intramuscular injection
- Half-life is approximately 7–14 days.
- Plasma levels obtained vary up to 40-fold in patients receiving the same dose.

Metabolism: Fluphenazine is extensively metabolized, undergoing "first pass" metabolism by the liver, and is excreted in both the urine and faeces .

Distribution: Crosses placenta; enters breast milk.

Excretion: Unchanged in the urine

Indication

Fluphenazine decanoate is indicated in the long-term management of psychotic disorders including schizophrenia, mania and organic brain syndrome.

It is of particular value in the treatment of chronic schizophrenia and for patients who are unreliable at taking oral medication.

Pros

- 2-4wk administration

Cons

- Risk of EPS and tardive dyskinesia
- No established loading dose option

First-generation LAIs

Haloperidol:

- Butyrophenone
- Haloperidol decanoate is a ester of haloperidol and decanoic acid dissolved in Sesame seed oil.
- After intramuscular injection, haloperidol decanoate is gradually released from muscle tissue and hydrolysed slowly into free haloperidol which enters the systemic circulation.
- Haloperidol decanoate is a potent dopamine antagonist and, therefore, a very incisive neuroleptic.

PHARMACOKINETICS

- Peak plasma levels are seen up to 7 days after intramuscular injection .
- Plasma half-life is around 3 weeks.
- Steady-state plasma levels can be expected to be reached after 2–3 months of regular dosing.

- **Distribution**: crosses the blood-brain barrier easily, Plasma protein binding is 92%
- **Metabolism**
  Metabolised by several routes including the cytochrome P450 enzyme system (particularly CYP 3A4 or CYP 2D6) and glucoronidation.
- **Elimination**: Excreted in the urine (40%) and faeces (60%).

Indication

For the maintenance therapy of psychoses, particularly for patients requiring prolonged parenteral neuroleptic therapy.

It is preferred drug for acute schizophrenia

Pros

-4wk administration
-Loading dose options

Cons

-Risk of EPS and tardive dyskinesia

First-generation LAIs

Perphenazine:

- Piperazine phenothiazine
- Perphenazine decanoate in sesame oil.

- **PHARMACOKINETICS**
- After intramuscular injection at gluteal region, peak plasma levels are obtained in 1–7 days
- Half-life is approximately 2 weeks.
- Steady-state levels are obtained after 3 months.
- Variations in plasma levels during regular dosing are small.
- Plasma levels are directly correlated with dose.

First-generation LAIs

Pipotiazine:

- Piperidine Phenothiazine Antipsychotic.
- The Lai Formulation Contains Pipotiazine Palmitate In Coconut Oil.
- Provides Peak Plasma Levels After 1–2 Weeks Although No Drug Is Released For At Least 3 Days.
- Plasma Half-life Is Around 2 Weeks
- Time To Steady State Is 2 Months.

First-generation LAIs

Zuclopenthixol:

- Thioxanthine compound.
- LAI is formulated as the decanoate ester dissolved in thin vegetable oil (fractionated coconut oil).
- Peak plasma levels of zuclopenthixol are achieved a week after injection.
- Plasma half-life has been estimated 19 days.

- Steady-state plasma levels can be expected to be achieved after 2 months .
- It can be given as 200-1200 mg at intervals of 2-4 wks.
- It is preferred in agitated and aggressive patients.

First-generation LA'S

Drug	Injection site	Test dose (mg)	Dose range (mg/week)	Dosing Interval (weeks)	Comments
Flupentixol decanoate	Gluteal or thigh	20	12.5-400	2-4	Maximum licensed dose is very high relative to other LAIs
Fluphenazine decanoate	Gluteal	12.5	6.25-50	2-5	High EPS
Haloperidol Decanoate	Gluteal	25	12.5-75	4	High EPS
Pipothiazine palmitate	Gluteal	25	12.5-50	4	? Lower incidence of EPS (unproven)
Zuclopenthixol decanoate	Gluteal or thigh	100	100-600	2-4	? Slightly higher efficacy

Second-generation LAIs

Risperidone:

- First ‘atypical’ drug to be made available as depot
- Belongs to benzisoxazole derivative class .

- **MECHANISM**

  It blocks the D2 and 5-HT2 receptor and has high affinity for alpha 1,2 and H1 receptor .

Pharmacokinetics

Absorption: The main release of the drug starts 3 wk after injection, is maintained from 4 to 6 wk, and subsides by 7 wk. Steady state is reached after 4 injections

Disutribution: Volume of distribution: 1-2 L/kg.

Plasma protein binding is 90% .

Metabolism
Extensively metabolized in the liver by CYP2D6 to major active metabolite 9-hydroxyrisperidone. 9-hydroxyrisperidone has similar activity to risperidone.

Elimination in urine (70%) and feces (14%).
The half-life of risperidone plus 9-hydroxyrisperidone is 3 to 6 days.

PROS AND CONS

- Risperidone injection is not suitable for patients with treatment-refractory schizophrenia.
- Peak release is at about 28 days.
- Doses of 25–50 mg every 2 weeks appear to be as effective as oral doses of 2–6 mg/day.
- Prolactin levels appear to reduce somewhat following a switch from oral to injectable risperidone.
- Rates of tardive dyskinesia are said to be low

Second-generation LAIs

Paliperidone:

Contains extended release intramuscular Paliperidone Palmitate .

Active paliperidone plasma levels are seen within a day or so, therefore co-administration of oral paliperidone or risperidone during initiation is not required

- Prefilled syringes and does not require reconstitution
- No oral supplementation is required on initiation for paliperidone palmitate.
- No test dose is required for paliperidone palmitate (but patients should ideally be currently stabilised on or have previously responded to oral paliperidone or risperidone).
- The maximum plasma concentrations is 13 days.

Paliperidone	**Dose**	**Route**
Initiation Day 1	150 mg IM	Deltoid only
Day 8 (+/−2 days)*	100 mg IM	Deltoid only
Maintenance Every month (+/− 7 days) thereafter		
	50–150 mg IM**	Deltoid or gluteal

Equivalent **doses**

Risperidone oral (mg/day) (bioavailability = 70%)	**Paliperidone oral (mg/day)** (bioavailability = 28%)	**Risperidone LAI (Consta) (mg/2 weeks)**	**Paliperidone palmitate (mg/month)**
2	4	25	50
3	6	37.5	75
4	9	50	100
6	12	-	150

Second-generation LAIs

Olanzapine

- Crystal salt made of Olanzapine & Palmoic acid.

Mechanism

It blocks the multiple monoaminergic (D2 , 5-HT2 ,Alpha 1,2) as well as muscuranic and H1 receptor .

- Both positive and negative symptoms of schizophrenia tend to be benifit

Parameter	Olanzapine LA IM
Metabolism	Glucuronidation, CYP1A2 and 2D6
Elimination	Urine and feces, 7% unchanged
Half-life	30 days
Protein binding	93%

- **Intramuscular gluteal injection**
  3 vial strengths (210 mg, 300 mg, 405 mg)
  Once every 2 or 4 week injection
  24 hour medication stability in vial once reconstituted
- **Pros**
  2wk or 4wk dosing options
  New second generation antipsychotic in LAI formulation
- **Cons**
  Post-injection monitoring

Second-generation LAIs

Aripiprazole LAI

It is an extended-release injectable suspension available in 400 mg or 300 mg strength vials.

its monohydrate polymorphic form

Mechanism of Action
Atypical antipsychotic; partial agonist at dopamine D2 and serotonin type 1 (5-HT1A) receptors; antagonist at serotonin type 2 (5-HT2A) receptor; also has alpha-blocking activity

Absorption
Bioavailability: 87% (tablet); 100%(IM)
Peak plasma time: 1-3 hr (IR); 5-7 hr (ER); 3-5 hr (tablet)

Distribution
Protein bound: 99%

Metabolism
Metabolized by CYP2D6 and CYP3A4
Metabolites: Dehydroaripiprazole (40%)

Elimination
Half-life: 75 hr (parent drug); 94 hr (metabolite); 30-47 days (IM); 146 hr (poor metabolizers)

Excretion: Feces (55%), urine (25%)

Advantages of depot antipsychotics over oral antipsychotic

1. Improved treatment adherence, overt non-adherence can be addressed
2. Easier early detection of relapse, improved relapse prevention and reduced rehospitalisation rates
3. Enhanced consistency between the drug prescription and drug delivery
4. More predictable and stable serum concentrations
5. Less variability between patients in steadystate blood levels for a given dose
6. Lowest effective dose principle more safely achieved with depots (step- wise reduction)
7. Reduced risk of accidental or deliberate selfpoisoning (overdose)
8. Less risk of overdose and can Bypass pharmacokinetic hurdeles of absorption & first pass

Disadvantages of LAI over oral antipsychotics

1. Understanding the pharmacokinetics & dosing require specific LAI knowledge.

    i. Delayed time until steady state is reached
    ii. Clinical improvement may be delayed after dose increase
    iii. Elimination may take weeks to months

2. Adverse effects may persist after stopping/reducing dose

3. Injection related adverse effects e.g. pain, nodules

4. Organised community system to deliver LAIs

5. LAI storage, reconstitution & administration may require special precautions, &/or training

THANK YOU !