Long-Acting Injectable (LAI) Antipsychotics: Evolution, Pharmacology, and Clinical Use

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Historical Overview

Moral Era (1825-1875): Therapeutic social settings

Biological Era (1930s to 1950s): Insulin coma therapy, ECT, psychosurgery

Deinstitutionalization (1960s-1970s): Shift to community mental health care

1825–1875 | Early 20th Century | 1930s to 1950s | 1950s-Present | 1960s-1970s

Custodial Era (Late 19th – Early 20th Century): Institutionalization

Pharmacological Era (1950s-Present): Introduction of Chlorpromazine and LAIs

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Deinstitutionalization & Community Care

- 1960s-1970s: Deinstitutionalization led to community care for schizophrenia patients.
- Challenges: Higher medication non-adherence, **increased family burden, need for integrated care**.

- 1952 – Chlorpromazine (Thorazine)
- 1958 – Haloperidol (Haldol)
- 1959 – Fluphenazine (Prolixin)
- **1966 – Fluphenazine Decanoate (LAI)**
- 1960 – Thioridazine (Mellaril)
- 1960 – Trifluoperazine (Stelazine)
- 1960 – Perphenazine (Trilafon)
- **1968 – Fluphenazine Enanthate (LAI)**
- **1969 – Haloperidol Decanoate (LAI)**
- 1970 – Thiothixene (Navane)
- 1975 – Loxapine (Loxitane)
- **1978 – Zuclopenthixol Decanoate (LAI, Europe)**
- 1989 – Clozapine (Clozaril)

Pharmacology: Oral vs. LAI

Oral Antipsychotics:

- Absorbed via gastrointestinal system, first-pass metabolism in liver.
- CYP enzymes influence drug metabolism.

LAIs:

- Gradual absorption, higher bioavailability, and more stable plasma levels.
- Bypass first-pass metabolism.

Efficacy of LAIs

- Superior real-world efficacy in preventing relapse.
- Reduced hospitalization rates, particularly for patients with poor adherence.
- Symptom reduction similar to oral antipsychotics; adherence is the key factor.

Patient Acceptability

INITIAL RESISTANCE TO INJECTIONS, BUT IMPROVED ADHERENCE ONCE INITIATED.

LAIS ARE PREFERRED FOR LONG-TERM ADHERENCE DUE TO REDUCED NON-ADHERENCE.

Side Effects Comparison

Metabolic Side Effects:
- Weight gain, lipid abnormalities, and diabetes risk were similar between LAIs and oral formulations.
- Some second-generation LAIs had a lower metabolic risk than certain oral SGAs.

Extrapyramidal Symptoms (EPS):
- First-generation LAIs had a slightly higher EPS risk compared to their oral counterparts.
- Second-generation LAIs had a similar EPS risk as oral formulations.

Sedation and Cognitive Effects:
- No significant difference was observed between OAs and LAIs.

Injection Site Reactions (specific to LAIs):
- Mild, transient pain was reported in some patients but did not lead to discontinuation in most cases.

Clinical Considerations for LAI Selection

Considerations
- Patient adherence
- Side effect profile.

Dosing:
- Some LAIs require oral supplementation, others don't.

Side effects:
- Reduced peak plasma concentrations in LAIs.

Common LAI Antipsychotics

Drug	Brand Name	Dosing Interval	Metabolism	Half-Life	Notes
Risperidone LAI	Risperdal Consta	Every 2 weeks	Hepatic (CYP2D6)	~3- days	Requires oral supplementation initially
Paliperidone Palmitate	Invega Sustenna / Trinza / Hafyera	Every 4–12 weeks	Minimal hepatic metabolism	~25–49 days	No need for oral supplementation
Aripiprazole LAI	Abilify Maintena / Aristada	Every 4–8 weeks	Hepatic (CYP2D6, CYP3A4)	~45–55 days	Requires oral supplementation initially
Olanzapine Pamoate	Zyprexa Relprevv	Every 2–4 weeks	Hepatic (CYP1A2)	~30 days	Risk of PDSS (Post-injection delirium/sedation syndrome)
Haloperidol Decanoate	**Haldol Decanoate**	**Every 4 weeks**	**Hepatic (CYP3A4)**	**~21 days**	**Older, first-generation LAI**

LAIs in Schizophrenia vs. Bipolar Disorder

Schizophrenia:
- ~17% of patients use LAIs.

Bipolar Disorder:
- (~11.6%) of patients use LAIs.
- Increasing use especially for recurrent episodes in Bipolar I.

Demographic & Disparities in LAI Use

- Younger patients (18-30) more likely to receive LAIs.
- Men more likely to receive LAIs.
- Racial/ethnic disparities: Black patients more likely to use LAIs.
- Geographic Disparities: Urban areas had higher rates of LAI prescribing compared to rural settings.

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Impact of Insurance and Access

Private insurance: Higher LAI utilization.

Medicaid/low-income: Limited access due to insurance or specialist availability.

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Oil-Based Formulations

- These are the most traditional lipid-based LAI formulations and involve dissolving lipophilic drugs in biocompatible oils such as sesame, castor, or soybean oil.
    - The slow diffusion of the drug from the oil depot into surrounding tissues leads to prolonged drug release.
- Advantages:
    - Simple formulation process
    - Proven safety and efficacy
    - Minimal risk of burst release
- Challenges:
    - Limited to highly lipophilic drugs
    - Injection site pain due to oil viscosity

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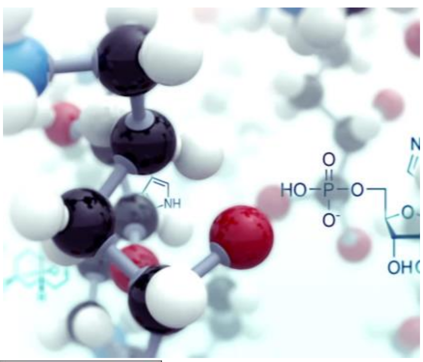
Lipid-Based Nanoparticles



- **Definition:**
    - Advanced drug delivery system in which drugs are encapsulated within lipid-based carriers to enhance bioavailability and provide controlled release.
- **Subtypes:**
    - **SLNs:** Solid lipids for sustained release.
    - **NLCs:** Flexible structure with higher drug loading.
- **Advantages:**
    - Encapsulate hydrophilic and lipophilic drugs
    - Enable targeted delivery
    - Greater stability than emulsions
- **Clinical Potential:**
    - Investigated for antipsychotic, antiviral, and cancer therapies

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Advantages of Lipid-Based LAIs

- BIOCOMPATIBILITY: NATURALLY OCCURRING LIPIDS, WELL-TOLERATED.
- SUSTAINED RELEASE: REDUCES FREQUENT DOSING.
- VERSATILITY: SUITABLE FOR A WIDE RANGE OF DRUGS, INCLUDING POORLY SOLUBLE ONES.

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Clinical Applications of Lipid-Based LAIs

- Psychiatry: Schizophrenia, bipolar disorder (e.g., Paliperidone Palmitate).
- HIV Treatment: Cabotegravir for sustained antiviral action.
- Hormonal Therapies: Testosterone Undecanoate for replacement.
- Pain Management: Buprenorphine LAIs for opioid addiction.

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Challenges & Future Directions

Challenges: Stability, injection site reactions, drug loading limitations.

Future Directions: Improved lipid carriers, personalized medicine, combination therapies.

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Questions

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