

# FLUPHENAZINE

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## Introduction and Classification

**Fluphenazine** is a highly potent, typical antipsychotic medication belonging to the phenothiazine class. It is classified as a first-generation antipsychotic (FGA), primarily utilized in the management of severe psychotic disorders, most notably **schizophrenia**. Its distinction as a high-potency agent signifies that it achieves therapeutic efficacy at relatively low doses, a characteristic that is frequently associated with a higher propensity for inducing neuromuscular and **extrapyramidal symptoms (EPS)** compared to lower-potency FGAs or most second-generation antipsychotics (SGAs). This profile makes careful patient selection and monitoring paramount when initiating treatment with fluphenazine.

The medication operates primarily through the antagonism of dopamine receptors in the central nervous system, particularly the D2 receptors, which is the foundational mechanism underlying its therapeutic action against positive symptoms of psychosis, such as hallucinations and delusions. While highly effective in controlling these acute symptoms, its broad dopaminergic blockade across various brain pathways contributes directly to the spectrum of adverse effects that are characteristic of this drug class. Fluphenazine is available in several formulations, including oral tablets, oral concentrate, and two injectable forms: fluphenazine hydrochloride (short-acting) and **fluphenazine decanoate** (long-acting).

In the United States, fluphenazine is widely recognized under the trade name **Prolixin**. The development of fluphenazine marked a significant advancement in psychiatric pharmacology, offering clinicians a powerful tool for managing chronic, severe mental illness. Furthermore, the development of the long-acting injectable form revolutionized adherence strategies for patients who struggle with consistent daily oral medication intake, thereby reducing rates of relapse and subsequent hospitalizations in populations with known poor compliance.

## Mechanism of Action

The primary therapeutic effect of fluphenazine is achieved through potent post-synaptic blockade of D2 dopamine receptors in the mesolimbic pathway of the brain. This blockade reduces the excessive dopaminergic activity believed to contribute to the manifestation of psychotic symptoms in disorders like schizophrenia. Fluphenazine's high binding affinity for the D2 receptor is the determinant factor in its classification as a **high-potency antipsychotic**. However, its activity is not confined solely to the dopaminergic system; like other phenothiazines, it also interacts with various other neurotransmitter systems, although these secondary effects are often responsible for some of its adverse profile rather than its primary therapeutic efficacy.

Beyond dopamine antagonism, fluphenazine exhibits varying degrees of affinity for alpha-1 adrenergic, muscarinic cholinergic, and histaminergic (H1) receptors. While antagonism at these sites contributes to certain side effects, such as orthostatic hypotension (alpha-1 blockade) and

mild anticholinergic effects (muscarinic blockade), fluphenazine possesses relatively weak anticholinergic activity compared to lower-potency agents like chlorpromazine. This relative selectivity contributes to its specific side-effect burden, strongly favoring **neuromuscular** effects and EPS over severe sedation or strong anticholinergic symptoms.

The therapeutic window relies upon achieving adequate D2 receptor occupancy--typically between 65% and 80%--to manage psychosis effectively. However, occupancy exceeding 80% significantly increases the risk of dose-dependent **extrapyramidal symptoms**. The challenge in clinical practice is titrating the dose to achieve optimal therapeutic benefit while minimizing the occupancy in the nigrostriatal pathway, the region responsible for motor control, which often becomes the site of undesirable motor side effects. Monitoring serum levels and carefully observing clinical response are essential components of high-potency antipsychotic therapy.

## Therapeutic Uses and Indications

The primary indication for fluphenazine is the management of psychotic disorders, particularly **schizophrenia**. It is highly effective for controlling acute exacerbations and maintaining stability in chronic patients. The drug is often reserved for patients who require a high-potency agent or those who have responded well to typical antipsychotics in the past. It is particularly useful for controlling positive symptoms, including disorganized thought processes, paranoia, and fixed delusions, providing significant relief where other medications may have failed to achieve adequate therapeutic response.

Due to the critical availability of the long-acting injectable formulation, fluphenazine is indispensable for improving adherence in patients with established poor compliance histories. This formulation, **fluphenazine decanoate**, allows for sustained therapeutic drug levels over periods of up to four weeks, dramatically reducing the risk of relapse associated with missed doses. Clinical guidelines often recommend the use of long-acting injectables (LAIs) for patients with recurrent psychotic episodes linked specifically to medication non-adherence, thereby improving long-term outcomes and reducing the frequency of hospital readmissions.

While schizophrenia remains the core indication, fluphenazine may also be utilized off-label for other conditions requiring potent dopamine blockade. These include severe behavioral disturbances in patients with dementia or intellectual disabilities, refractory bipolar disorder (usually in combination with mood stabilizers), and severe agitation. Its high potency and relatively rapid onset of action (for the short-acting injectable form) make it valuable in acute care settings for rapid tranquilization, though caution is always exercised due to the high risk of acute dystonic reactions, which necessitate prompt recognition and treatment.

## Pharmacokinetics and Administration

Fluphenazine is administered via oral routes (tablet, elixir) and intramuscular or subcutaneous injection. The oral forms are subject to significant first-pass metabolism, meaning that the bioavailability is lower than the injectable forms, necessitating higher oral doses compared to parenteral administration. Once absorbed, it is highly protein-bound and metabolized primarily in the liver through oxidation and conjugation, with metabolites excreted via the urine and feces, contributing to a relatively complex pharmacological profile that requires careful dosing considerations.

The critical difference in pharmacokinetics lies between the hydrochloride and the decanoate formulations. Fluphenazine hydrochloride is the active compound and is used for short-term, immediate effects. Conversely, **fluphenazine decanoate** is an esterified prodrug dissolved in a sesame or vegetable **oil-based injection** vehicle. This oily vehicle is responsible for the depot effect; after injection into the muscle, the drug is slowly released into the circulation over weeks. Once in the bloodstream, plasma esterases gradually cleave the decanoate chain, releasing the active fluphenazine compound. This slow-release mechanism is what permits the extended dosing interval, typically every two to four weeks.

The initiation of fluphenazine decanoate requires careful transition from the oral form to ensure stable therapeutic levels are maintained, often involving an overlap period. The peak plasma concentration of the decanoate formulation is typically reached 24 to 48 hours post-injection, and steady-state concentrations are usually achieved after four to five repeated injections. Monitoring of the patient's clinical response throughout this initial period is essential, as adjustments to the dosing interval or strength may be required to prevent breakthrough symptoms or excessive side effects, particularly motor disturbances.

## Side Effects: Extrapyramidal Symptoms (EPS)

As a high-potency D2 antagonist, the most prominent and concerning side effect profile associated with fluphenazine relates to the induction of **extrapyramidal symptoms (EPS)**. These motor side effects arise from dopamine blockade in the nigrostriatal pathway, which regulates voluntary movement. Clinicians categorize EPS into several distinct syndromes based on their presentation and timing relative to drug initiation. These effects necessitate immediate clinical attention and often require co-administration of anticholinergic or dopaminergic agents for management.

Acute EPS generally manifests early in treatment or following a rapid dose increase. Key examples include **acute dystonia**, characterized by sudden, sustained muscle contractions resulting in abnormal postures, often affecting the neck (torticollis), eyes (oculogyric crisis), or trunk. Another common acute presentation is **akathisia**, described as a subjective feeling of inner restlessness and an objective need to constantly move the limbs or body. Both acute dystonia and severe

akathisia are intensely distressing for the patient and require immediate intervention, often with intramuscular anticholinergics such as benztropine or antihistamines like diphenhydramine.

A chronic and potentially irreversible form of EPS is **tardive dyskinesia (TD)**. TD typically develops after months or years of cumulative exposure to typical antipsychotics like fluphenazine. It is characterized by involuntary, repetitive movements, most commonly affecting the oral-buccal-lingual region (e.g., lip smacking, tongue protrusion, facial grimacing). Given the debilitating and often permanent nature of TD, the use of fluphenazine must be continuously weighed against the risk, and patients requiring long-term treatment must undergo regular screening using standardized assessment tools, such as the AIMS scale, to detect early signs of this disorder.

## Other Adverse Reactions and Warnings

While EPS dominates the side effect landscape, fluphenazine carries risks for other significant adverse reactions. Cardiovascular effects, although less common than with low-potency FGAs, include orthostatic hypotension due to alpha-1 adrenergic blockade, leading to dizziness or fainting upon standing. There is also a notable risk of **QT interval prolongation**, which can predispose the patient to serious cardiac arrhythmias, specifically Torsades de Pointes. This risk mandates baseline and periodic electrocardiogram (ECG) monitoring, especially in elderly patients or those with pre-existing cardiac conditions or electrolyte imbalances.

A rare but potentially fatal complication associated with fluphenazine and all antipsychotics is **Neuroleptic Malignant Syndrome (NMS)**. NMS is a life-threatening idiosyncratic reaction characterized by a tetrad of symptoms: severe muscle rigidity, fever (hyperpyrexia), altered mental status, and autonomic instability (e.g., labile blood pressure, tachycardia). Immediate discontinuation of the drug and intensive supportive medical care, including cooling and hydration, are mandatory upon suspicion of NMS. Due to its severity, NMS represents a major clinical warning for all prescribers of typical antipsychotics.

Endocrine and metabolic side effects are generally less pronounced with fluphenazine compared to many SGAs, as fluphenazine has a lower propensity for causing significant weight gain or dyslipidemia. However, it can significantly elevate prolactin levels (hyperprolactinemia) due to dopamine blockade in the tuberoinfundibular pathway, leading to potential issues such as amenorrhea, galactorrhea, gynecomastia, and sexual dysfunction. Long-term hyperprolactinemia may also pose a risk to bone mineral density, necessitating periodic monitoring of prolactin levels if symptoms persist.

## Fluphenazine Decanoate (Long-Acting Injection)

The **decanoate formulation** of fluphenazine is perhaps its most distinguishing and clinically important feature. This oil-based preparation is crucial for overcoming one of the most significant

challenges in psychiatric care: medication non-adherence. Non-adherence is the leading cause of relapse in schizophrenia, and the ability to administer a medication that maintains therapeutic levels for weeks greatly mitigates this risk. The decanoate is typically administered every 14 to 28 days, depending on the patient's clinical response and tolerability, offering a substantial improvement in compliance rates.

The administration protocol for fluphenazine decanoate requires meticulous technique. It must be administered deep intramuscularly (IM) or sometimes subcutaneously, ensuring the preparation is delivered into the muscle tissue where the slow-release depot can form effectively. Since it is an **oil-based solution**, the injection process requires careful consideration of needle length and injection site rotation to prevent localized irritation, pain, or sterile abscess formation. Patients transitioning to the decanoate form must be educated thoroughly about the injection schedule and potential side effects, especially since any side effects experienced will persist for the duration of the drug's extended action.

A major clinical advantage of the LAI is the ability to confirm that the patient has received the dose, facilitating better monitoring and dose adjustments that are grounded in certainty regarding exposure. Furthermore, studies suggest that the decanoate form may lead to a more stable plasma concentration profile compared to fluctuating oral dosing, potentially reducing fluctuation-related side effects and promoting consistent symptom control, although the inherent risk of severe EPS remains high and often requires prophylactic anticholinergic management during the initial phases of treatment.

## Clinical Management and Monitoring

Effective management of fluphenazine therapy requires comprehensive monitoring throughout the course of treatment. Initially, the focus is on achieving symptom control while carefully monitoring for acute EPS, especially dystonia and akathisia, which are common with high-potency agents. For patients receiving the oral formulation, dose titration must be gradual. For those receiving the decanoate injection, the conversion ratio from oral to injectable dose must be calculated accurately, and the patient must be observed closely during the first few cycles of injection to ensure efficacy and tolerability.

Long-term monitoring protocols are essential due to the cumulative risk of irreversible **tardive dyskinesia (TD)**. Clinicians must perform periodic standardized assessments, such as the Abnormal Involuntary Movement Scale (AIMS), typically every three to six months for patients on typical antipsychotics. If signs of TD emerge, the drug must be discontinued or the dose drastically reduced, and consideration must be given to switching to an antipsychotic with a lower TD risk profile, such as a second-generation agent or a VMAT2 inhibitor, despite the complexity of managing the transition.

Additionally, routine laboratory and physical assessments are necessary. This includes monitoring of prolactin levels, particularly if symptoms of hyperprolactinemia are present, and metabolic parameters, though metabolic risk is lower than with many SGAs. Cardiovascular monitoring, including blood pressure checks and periodic ECGs, is critical, especially in the elderly or those with known cardiac risk factors, ensuring that the patient remains medically stable while benefiting from the potent therapeutic effects of fluphenazine.

## Historical Context and Regulatory Status

Fluphenazine was introduced to clinical practice in the mid-20th century, following the groundbreaking discovery of chlorpromazine, the first antipsychotic drug. Its introduction provided clinicians with a powerful, high-potency option for managing severe psychosis with less pronounced sedative effects than its predecessors. The development of the **Prolixin Decanoate** formulation solidified its place in long-term psychiatric care by successfully addressing the critical issue of adherence, transforming outpatient management for thousands of individuals previously requiring continuous institutionalization.

As a typical antipsychotic, fluphenazine's use has been somewhat tempered since the widespread introduction of second-generation antipsychotics (SGAs) in the 1990s. SGAs are often preferred as first-line treatments due to their generally lower risk of inducing severe EPS and TD, although they carry a higher risk for significant metabolic side effects. Despite this shift, fluphenazine remains a vital component of the psychiatric pharmacopeia, particularly favored in situations where cost-effectiveness, established high efficacy, and the adherence benefits of the long-acting injectable form are prioritized over minimizing metabolic risk factors.

Regulatory bodies worldwide, including the U.S. Food and Drug Administration (FDA), maintain strict guidelines regarding the use of fluphenazine, emphasizing the need for comprehensive informed consent detailing the high risks of EPS and TD. The drug is considered highly effective when used judiciously, often forming a critical part of treatment strategies in public health systems and forensic psychiatry where controlling severe, refractory symptoms and ensuring medication compliance are paramount objectives for patient and public safety.