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HALOPERIDOL: A COMPREHENSIVE REVIEW OF ITS PHARMACOLOGICAL AND CLINICAL USE

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ABSTRACT

Haloperidol stands out as a high-potency, first-generation antipsychotic from the butyrophenone class. Clinicians use it often to treat schizophrenia, acute psychosis, and delirium. The main way it works? It blocks central dopamine D_2 receptors, especially in the mesolimbic and mesocortical pathways. This blockade suppresses positive psychotic symptoms (Adams et al., 2013). But there's a tradeoff blocking dopamine in the nigrostriatal pathway brings on extrapyramidal side effects like dystonia, akathisia, and parkinsonism. Haloperidol also binds moderately to α_1-adrenergic receptors, but it barely touches histaminergic or muscarinic receptors. That's why it causes little sedation or anticholinergic effects (Dold et al., 2015).

After you give haloperidol by mouth or injection, the body absorbs it pretty well. Still, only about 60% actually makes it into circulation because the liver breaks down a big chunk right away. Most of the drug latches onto plasma proteins in the blood. The liver does most of the heavy lifting here, mainly through the CYP3A4 and CYP2D6 enzymes, turning haloperidol into inactive forms (Kane & Correll, 2019). The drug sticks around for quite a while the elimination half-life runs anywhere from 12 up to 36 hours. That's why you can usually get away with dosing once or twice a day. The decanoate ester version works differently: it lets the drug out slowly and keeps blood levels steady for weeks, which really helps people stick with their maintenance therapy.

KEY WORDS: *Haloperidol, Mode of action of Haloperidol, Pharmacokinetics of Haloperidol*

INTRODUCTION

Haloperidol first appeared in the late 1950s and quickly became a cornerstone among high-potency first-generation antipsychotics, especially in the butyrophenone class. Decades later, researchers still turn to it as a benchmark when measuring the effects of new dopaminergic antagonists (Adams et al., 2013). Clinicians rely on haloperidol mainly for schizophrenia, acute psychosis, and delirium. Its main action? It blocks dopamine D_2 receptors in the mesolimbic and mesocortical pathways, which helps dial down positive psychotic symptoms. The problem is, when it blocks D_2 receptors in the nigrostriatal pathway too, patients often deal with extrapyramidal side effects dystonia, akathisia, parkinsonism [1].

Haloperidol isn't just about blocking dopamine; it barely touches histaminergic H_1, muscarinic M_1, or serotonergic 5-HT_2 receptors. That's why it doesn't sedate or cause anticholinergic side effects as much as many atypical antipsychotics (Kane & Correll, 2019). After someone takes it by mouth, the body absorbs it moderately well. Most of it binds to proteins in the blood, and the liver specifically the CYP3A4 and CYP2D6 enzymes handles most of the breakdown. It sticks around for quite a while, with a half-life somewhere between 12 and 36 hours. The decanoate ester version is different: it keeps drug levels steady over time, which really helps people stick with their treatment in the long run [2].

Even with newer atypical agents that are easier to tolerate, haloperidol still matters in clinical practice. It works reliably, costs little, and you can give it as a pill or injection simple as that. Researchers keep looking at how best to dose it and where it fits, especially for tough cases like delirium, agitation, or psychosis that resists other treatments [3].

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1. MODE OF ACTION

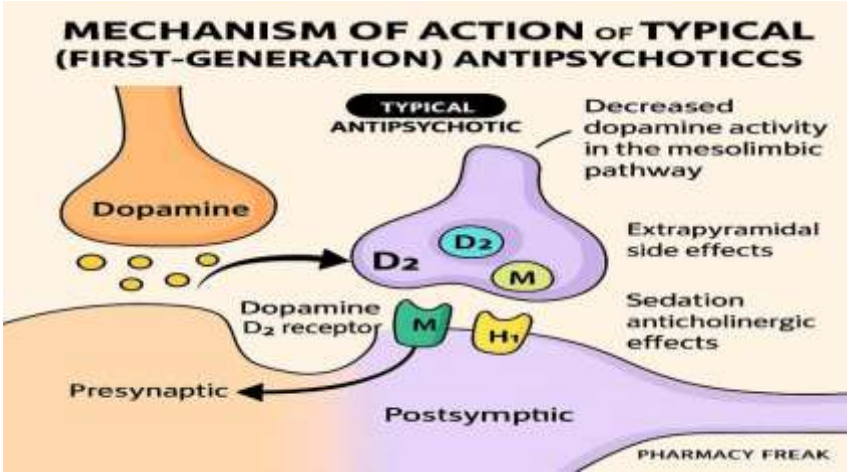

Figure 1: Mode of action of Haloperidol

- Blocking dopamine D2 receptors in the mesolimbic pathway drives the antipsychotic effect this action cuts down on positive symptoms like hallucinations and delusions in schizophrenia.
- D2 receptor blockade doesn't just happen there. In the nigrostriatal pathway, it triggers extrapyramidal symptoms: parkinsonism, dystonia, akathisia. In the tuberoinfundibular pathway, blocking D2 ramps up prolactin, so you see things like galactorrhea and gynecomastia. In the mesocortical pathway, D2 antagonism can actually make negative symptoms and cognitive problems worse.
- When you get into additional receptor blockade, especially with low-potency first- generation antipsychotics, other side effects pop up. Blocking alpha-1 adrenergic receptors drops blood pressure, leading to orthostatic hypotension. H1 histamine blockade means sedation and weight gain. Muscarinic blockade brings on dry mouth, constipation, and urinary retention [4].

2. CHEMICAL AND PHARMACOLOGICAL PROFILE

2.1 Chemical Class- Haloperidol owes its pharmacological punch to its p-fluor butyrophenone core. That's the backbone driving its strong dopamine D_2 receptor antagonism. The butyrophenone side chain those three carbons between the phenyl ring and the tertiary amine hits the sweet spot for binding tightly to the receptor and ramping up antipsychotic effects (Richelson, 2010). Its piperidine ring isn't just for show; it boosts lipophilicity and helps the drug slip across the blood– brain barrier, making haloperidol act fast in the brain. The para-fluoro group on the phenyl ring matters, too. It toughens the molecule against metabolism and sharpens its receptor affinity, setting haloperidol apart from weaker relatives. If you mess with that carbon chain or tinker with the aromatic ring, you usually lose some dopaminergic power and clinical punch. Altogether, these features make haloperidol the classic high-potency butyrophenone antipsychotic, a blueprint for drugs like droperidol and spiperone [5].

2.2 Molecular Formula -Haloperidol's molecular formula is $C_{18}H_{21}ClFNO_2$, and it weighs about 375.8 g/mol. The structure features a butyrophenone backbone, topped off with a p-fluorophenyl group and a piperidinyl ring classic markers of the butyrophenone class of antipsychotics (PubChem, 2024). This arrangement gives haloperidol its high lipid solubility and lets it bind strongly to central dopamine D_2 receptors. Its IUPAC name, 4-[4-(p-chlorophenyl)-4- hydroxypiperidino]-4'-fluorobutyrophenone, captures the complexity of the molecule and points to the functional groups that drive its pharmacological effects [6].

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2.3 Structure

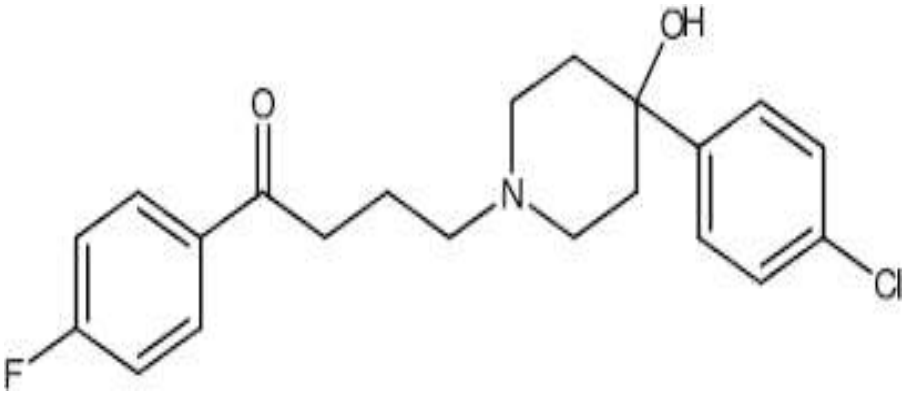

Figure 2: Structure of Haloperidol.

IUPAC NAME: 4-[4-(4-chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone [7].

Haloperidol belongs to the butyrophenone class. Its structure features a p-fluorophenyl group connected to the butyrophenone chain. There's also a piperidine ring, which carries a p- chlorophenyl group, plus a hydroxyl group attached directly to the nitrogen. The backbone includes a carbonyl group this C=O bond is a hallmark of butyrophenone antipsychotics [8].

2.4 Pharmacological Category

Haloperidol is a typical, first-generation antipsychotic and a butyrophenone derivative. It works by blocking dopamine D_2 receptors, which gives it both antipsychotic and antiemetic effects [9].

3. PHARMACOKINETICS

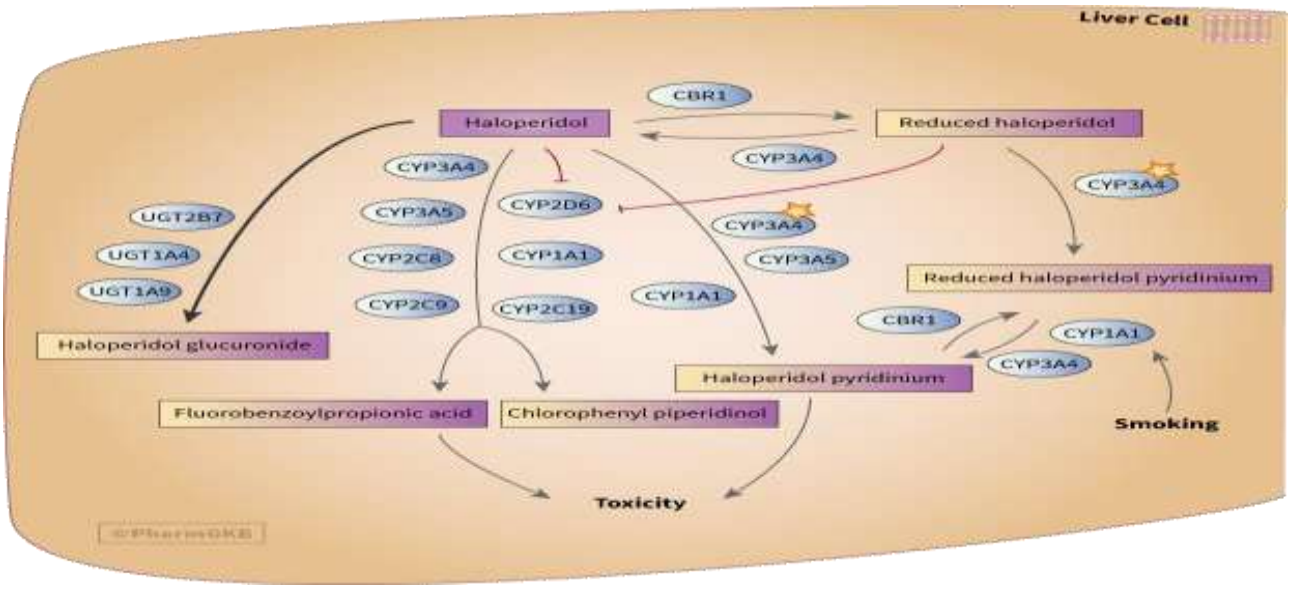

Figure 3: Pharmacokinetics Of Haloperidol [10].

3.1 Absorption

Oral bioavailability of HAL tablets or oral solution sits at about 60 to 70%. After you take it by mouth, the drug usually reaches its peak plasma concentration in 2 to 6 hours.

If you give HAL by intramuscular injection (using non-depot formulations), the absorption happens much faster peak levels show up in around 20 minutes.

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Depot formulations, like the decanoate form, release HAL much more slowly. Absorption stretches out over days, leading to long-lasting effects [11].

3.2 Distribution

In plasma, HAL is heavily protein-bound (about 88–92% in adults).
It has a large volume of distribution (V_nd); depending on the model, it has been reported in non- ICU studies to be between 9.5 and 21.7 L/kg (1000–3000 L total).
Because it is lipophilic, HAL diffuses into tissues and passes through the blood-brain barrier [12].

3.3 Metabolism

The liver metabolizes HAL extensively; the main processes are pyridinium metabolite formation, oxidative N-dealkylation (CYP3A4, CYP2D6), glucuronidation, and ketone-reduction (to "reduced HAL").
CYP3A4 is the main cytochrome P450 enzyme implicated, but CYP2D6 also plays a role (genetic polymorphism may influence HAL concentrations).
It is not completely impossible for reduced HAL to back-convert to HAL [13]

3.4 Elimination

The terminal elimination half-life (oral dosing) is on average ~ 24 hours (range ~15–37 h) in adults.
Apparent clearance (after extravascular dosing) is ~ 0.9-1.5 L h^{-1} kg^{-1}; high inter-subject variability.
After intravenous dosing, studies (in Chinese schizophrenic patients) reported a three- compartment model with mean $t_{1/2}$ ~ 54.8 h (59.9 h by non-model analysis).
Excretion: Less than 3% of an administered dose is excreted unchanged in the urine; ~21% of IV dose in faeces and ~33% in urine (metabolites) in one SmPC [14].

4. PHARMACODYNAMIC

Haloperidol works mainly by blocking dopamine D_2 receptors, especially in the mesolimbic pathway. This strong blockade cuts down on positive symptoms of schizophrenia think delusions and hallucinations. But it doesn't stop there. When haloperidol blocks D_2 receptors in the nigrostriatal pathway, it often triggers extrapyramidal symptoms (EPS), the movement issues you see in patients. Blockade in the tuberoinfundibular pathway drives up prolactin levels, leading to hyperprolactinemia [15].

As for other receptors, haloperidol barely touches them. Its action at α_1-adrenergic receptors is minimal, but even a little can cause orthostatic hypotension. It barely affects muscarinic (M_1) receptors, so anticholinergic side effects stay low. Same story with histamine H_1 sedation is mild at best [16].

What really stands out about haloperidol is how selective it is. Compared to other typical antipsychotics, it sticks close to D_2 and doesn't wander much to other receptors. That makes it powerful for controlling psychosis but also means it's notorious for causing EPS. On the neurochemical level, haloperidol reduces dopamine neurotransmission, which underpins its antipsychotic effect. This dopamine drop pushes up acetylcholine in the basal ganglia, leading to those parkinsonian side effects. There's also some weak antagonism at sigma receptors, which might help explain haloperidol's calming or sedative qualities [17].

5. ADVERSE EFFECT OF HALOPERIDOL

5.1. Extrapyramidal Symptoms (EPS)
These pop up most often because of strong D_2 blockade in the nigrostriatal pathway.
a. Acute Dystonia
Sudden muscle spasms neck, face, back or eyes rolling upward (oculogyric crisis). Shows up within hours to a few days.
b. Parkinsonism
Slow movement, stiff muscles, and tremor. Usually starts days to weeks after starting treatment.
c. Akathisia
Restless feeling, can't sit still. This kicks in within days to weeks.
d. Tardive Dyskinesia
Involuntary movements think lip smacking or odd, dance-like motions. Appears after months or years, and sometimes it doesn't go away.

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5.2. Neuroleptic Malignant Syndrome (NMS)
This is a medical emergency. High fever, "lead-pipe" stiff muscles, unstable blood pressure and heart rate, high CK levels (rhabdomyolysis), and changes in mental status.

5.3. Cardiovascular Effects
Longer QT interval, risk of Torsade's de Pointes, blood pressure drops when standing up (thanks to α_1 blockade), and a fast heart rate.

5.4 Endocrine & Metabolic Effects (from increased prolactin)
Milk production (galactorrhea), missed periods, breast enlargement in men, sexual problems, and lower fertility.

5.5 Neurocognitive & Psychiatric Effects
Drowsiness (not as bad as with low-potency antipsychotics), trouble thinking clearly, and feeling down.

5.6 Anticholinergic Effects (less than low-potency drugs)
Dry mouth, blurry vision, trouble peeing, constipation, and a racing heart.

5.7 Weight & Metabolic Effects
Some weight gain, but usually not as much as with atypical antipsychotics.

5.8 Hepatic Effects
Liver enzymes can go up. Rarely, you might see cholestatic jaundice.

5.9 Hematologic Effects
Low white blood cells (leukopenia, neutropenia), and rarely, dangerous drops (agranulocytosis).

5.10 Dermatologic & Miscellaneous
Sensitive to sunlight, skin rashes, skin darkening, trouble regulating body temperature, and a higher risk of seizures [18].

6. THERAPEUTIC USES OF HALOPERIDOL

Haloperidol packs a punch as a high-potency antipsychotic, hitting those dopamine D_2 receptors hard, especially in the brain's mesolimbic pathway. People reach for it in psychiatry, neurology, and during emergencies.

6.1. Schizophrenia & Other Psychotic Disorders
Honestly, this is where Haloperidol really shines. Doctors us it for:
- Schizophrenia (both sudden flare-ups and long-term cases)
- Schizoaffective disorder
- Psychosis from drugs
- Delusional disorders

Why? Because it blocks dopamine signals, which helps cut down hallucinations, delusions, agitation basically those "positive" psychotic symptoms.

6.2. Acute Agitation & Violent Behavior
In a crisis, when someone's agitated or aggressive (especially if it's tied to a mental health issue), haloperidol steps in fast. People often get it as an injection, which calms things down quickly.

6.3. Acute Mania in Bipolar Disorder
When mania kicks in hyperactivity, irritability, that restless energy haloperidol helps settle things down. It's the go-to when you need someone to regain control, and you need it now.

6.4. Tourette Syndrome & Severe Tics
Haloperidol actually FDA-approved for this. It helps with both motor and vocal tics in tourette, since it quiets overactive signals in

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the brain movement centers

6.5. Severe Nausea & Vomiting

Here's a lesser-known use: haloperidol blocks dopamine in the brain's nausea control center (the CTZ), which can stop stubborn nausea and vomiting, like after chemo or surgery especially when other meds haven't worked. Still, it's not the first thing people try these days [19].

6.6. Delirium (Especially in the ICU or Palliative Care)

It's pretty common to use haloperidol for hyperactive delirium, terminal restlessness, or agitation at the end of life. It's a popular pick in these situations because it doesn't have strong anticholinergic side effects.

6.7. Behavioral Problems in Dementia (Use with Caution)

Sometimes, when a person with dementia gets really aggressive or starts having hallucinations or delusions, haloperidol can help. But you have to be careful there's a higher risk of stroke and even death in elderly patients, so doctors only use it when absolutely necessary.

6.8. Palliative Care (Adjunct Use)

In palliative settings, haloperidol can ease delirium, restlessness, anxiety, and stubborn nausea or vomiting. It works whether you give it by mouth, injection, or IV.

6.9. Huntington's Disease

Finally, haloperidol helps manage the movement problems (chorea) and behavioral symptoms that come with Huntington's disease. It doesn't cure the disease, but it can make life a bit easier [20].

7. DRUG INTERACTION OF HALOPERIDOL

Haloperidol gets tangled up with a lot of other drugs, mostly because of how it's broken down by CYP450 enzymes and how it blocks dopamine. The main enzymes handling haloperidol are CYP3A4 and CYP2D6. So, if someone's taking drugs that block those enzymes like macrolide antibiotics (erythromycin, clarithromycin), azole antifungals (ketoconazole), SSRIs (fluoxetine, paroxetine), or HIV protease inhibitors haloperidol levels shoot up. That's when you really start to worry about things like extrapyramidal symptoms, neuroleptic malignant syndrome, or heart issues.

But it goes the other way too. When people take drugs that ramp up CYP3A4, like carbamazepine, phenytoin, phenobarbital, or rifampicin, haloperidol gets cleared out faster. That means it might not work as well.

There's also the whole problem with the heart. Haloperidol itself stretches out the QT interval, so piling on other QT-prolonging meds think amiodarone, sotalol, methadone, macrolides, or fluoroquinolones just boosts the risk for dangerous arrhythmias like torsade de pointe [21].

CNS depressants are another headache. If someone's mixing haloperidol with alcohol, benzodiazepines, opioids, or antihistamines, they'll feel even more sedated.

And then dopamine haloperidol blocks it, so if a patient's also on levodopa or other dopamine agonists, their Parkinsonian symptoms get worse.

One combo to really look out for is haloperidol with lithium. Together, they can trigger neurotoxicity: tremor, confusion, shaky walking, even encephalopathy.

Anticholinergic drugs like benztropine or trihexyphenidyl? They help with EPS, but they can also make constipation, memory issues, or trouble peeing worse.

Bottom line, haloperidol's interactions are no joke. Prescribers need to keep a close eye on anyone taking it, especially if they're on other meds [22].

8. RECENT ADVANCEMENTS OF HALOPERIDOL

Lately, haloperidol a classic antipsychotic has made something of a comeback. People are paying more attention to it, both in clinics and in research labs, because we're finding new ways to use it, getting a better handle on its safety, and seeing some interesting

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updates in how it's delivered. One of the big changes is how we give long-acting injectable haloperidol decanoate. With smarter dosing and better pharmacokinetic models, doctors are managing schizophrenia more effectively, cutting down on relapses and making it easier for patients to stick with their treatment.

There's also a lot more evidence backing up haloperidol in treating acute agitation, especially in emergency settings. Pairing it with benzodiazepines like haloperidol and lorazepam together has become a go-to approach. It works fast, it's reliable, and the safety profile is clear [23].

But haloperidol's story doesn't stop there. It's become a key player in managing delirium, especially for people in the ICU or under palliative care. New research shows that even low doses can help, but it also flags risks like QT prolongation, so monitoring recommendations keep getting updated. In oncology and critical care, studies show haloperidol helps with chemotherapy or opioid-induced nausea, pointing to more off-label uses [24].

We're also learning more about how haloperidol works at a cellular level. Researchers are digging into its effects on neuroinflammation, microglia, and oxidative stress trying to understand not just how it helps, but also why it can cause problems if used long-term. And on the innovation front, there's active work on nanoparticle-based delivery systems. The hope here is to target the drug more directly to the brain and cut down on those tough side effects like movement disorders.

All in all, haloperidol isn't just sticking around as an old-school antipsychotic. It's evolving finding new roles in emergency rooms, critical care, palliative medicine, and even experimental drug delivery. Its story's far from over [25].

9. CONCLUSION

Haloperidol still matters in clinical practice, even with all the newer antipsychotics around. Its strong D_2-receptor blocking power makes it a go-to choice for acute psychosis, severe agitation, delirium, and schizophrenia, especially when things get urgent in the ER or ICU. Research and current guidelines back up its value, as long as you watch the dosing, keep an eye on the ECG, and stay alert for movement side effects. There's also progress better long-acting injectables, broader use for delirium in intensive care, and new delivery options. All this just shows haloperidol isn't going anywhere. Sure, you have to manage the side effects, especially movement disorders and heart rhythm changes, but when you need a fast, strong antipsychotic, haloperidol gets the job done. So, with smart monitoring and dosing, it stays a key, reliable tool in both psychiatry and emergency medicine [26].

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