

Typical antipsychotics

First-generation agents whose antipsychotic effect rests on postsynaptic blockade of dopamine D2 receptors, and whose characteristic harms follow from the same blockade reaching motor and endocrine dopamine pathways that the illness never involved.

Online guide: <https://www.medguideglobal.com/pharmacology/central-nervous-system/typical-antipsychotics>

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Quick revision

One Liner: Blocking D2 receptors treats psychosis, but the same blockade in the nigrostriatal and tuberoinfundibular pathways produces the movement disorders and the raised prolactin that define this class.

1. Postsynaptic blockade of dopamine D2 receptors in the mesolimbic system is the accepted mechanism, yet the labels themselves say the precise therapeutic mechanism is not established. [9][1][4]
2. Potency rather than chemical family predicts the side-effect profile, so learn the agents in two groups rather than by their ring structure. [9]
3. High-potency agents including fluphenazine, haloperidol, trifluoperazine, perphenazine, thiothixene, loxapine and pimozide carry a high risk of dystonia, bradykinesia, rigidity and tremor. [9]
4. Low-potency agents, chlorpromazine and thioridazine, have marked histaminic and muscarinic activity and cause more dizziness, sedation, dry mouth, urinary retention and constipation. [9]
5. The four extrapyramidal syndromes separate by timing: acute dystonia in the first few days, akathisia usually inside two weeks, parkinsonism early, and tardive dyskinesia after prolonged exposure. [1][10][5]
6. Tardive dyskinesia is the examinable one: the movements are potentially irreversible and there is no known treatment for established cases. [1]
7. Neuroleptic malignant syndrome is the class emergency, presenting with hyperpyrexia, muscle rigidity, altered mental status and autonomic instability. [1][9]
8. D2 antagonism in the tuberoinfundibular pathway raises prolactin, and the elevation persists during chronic administration rather than settling with time. [11][1]
9. Sudden death, QT prolongation and torsades de pointes have been reported with haloperidol, and the injection is not approved for intravenous administration. [1][2]
10. Prochlorperazine sits in this class but earns its place in practice as an antiemetic, and in the UK is used for vertigo and for balance problems such as Meniere's disease. [6][7]
11. Each of these agents carries a boxed warning about deaths in elderly patients with dementia-related psychosis, and none of them is approved for that use. [1][3][4][5][6]

Overview

1. The older antipsychotics were first developed in the 1950s and act primarily to reduce the effect of dopamine in the brain. Chlorpromazine is the prototype of the group and the one whose label still carries the widest set of indications, spanning psychotic disorders, the manic phase of manic-depressive illness, severe nausea and vomiting, intractable hiccups, acute intermittent porphyria and adjunctive use in tetanus. It has no medicine page on this site, but no account of the class makes sense without it. [8][3]
2. Learn these drugs by potency, not by chemical family. Antipsychotic efficacy tracks D2 receptor binding closely enough that functional imaging studies show a consistent requirement of around 65% D2 receptor occupancy, and the agents that reach that occupancy in small milligram quantities are the ones that also drive the striatum hard. High-potency members therefore carry the greater extrapyramidal burden, while low-potency members carry more histamine and muscarinic blockade and correspondingly more sedation, dizziness and dry mouth. [9][11]

3. The class harms follow the anatomy of dopamine rather than the anatomy of the illness. Blockade in the nigrostriatal pathway is held responsible for the extrapyramidal effects, and antagonism in the tuberoinfundibular pathway for the rise in prolactin. Two consequences sit above the rest for safety: tardive dyskinesia, whose movements may never resolve, and neuroleptic malignant syndrome, a rare but potentially fatal emergency that a student is expected to recognise on sight. [11][1][9]

4. Regulators have narrowed where these medicines are used. Every label in the group opens with a boxed warning on mortality in older people with dementia, and the UK regulator states that there is a clear increased risk of stroke and a small increased risk of death when antipsychotics are used in elderly people with dementia. Newer agents were developed from the 1970s onwards and are less likely to cause movement disorders, which is the practical reason the first-generation drugs have retreated to defined roles. [1][8]

Classification and drug examples

Intro: Grouped by potency, because potency is what predicts whether a given agent will trouble the patient with movement disorders or with sedation, hypotension and antimuscarinic effects. Chemical family is noted for each drug, since it still governs a few idiosyncratic toxicities.

1. Name: High-potency first-generation agents

1. Note: Effective at small milligram quantities, tightly bound to D2, and the group most commonly associated with extrapyramidal adverse effects including dystonia, bradykinesia, rigidity and tremor.

1. Name: Haloperidol

Haldol

1. Route: Oral and intramuscular

1. Note: A butyrophenone and the reference high-potency agent. Its tablet label covers the management of manifestations of psychotic disorders and the control of tics and vocal utterances of Tourette's Disorder, and states that the precise mechanism of action has not been clearly established. [1][9]

2. Name: Fluphenazine

2. Route: Oral

2. Note: A high-potency phenothiazine indicated in the management of manifestations of psychotic disorders. Its label describes activity at all levels of the central nervous system and says the mechanism by which its therapeutic action is exerted is unknown. [4][9]

3. Name: Loxapine

3. Route: Oral

3. Note: A dibenzoxazepine, described in its label as a subclass of tricyclic antipsychotic agents chemically distinct from the thioxanthenes, butyrophenones and phenothiazines. It is indicated for the treatment of schizophrenia and lowers the convulsive threshold. [5][9]

4. Name: Trifluoperazine

4. Route: Oral

4. Note: A high-potency phenothiazine. No medicine page on this site; named here because the potency grouping is incomplete without the phenothiazines that sit at the opposite end of the scale from chlorpromazine. [9]

5. Name: Perphenazine

5. Route: Oral

5. Note: Another high-potency phenothiazine, grouped with fluphenazine rather than with chlorpromazine despite sharing the same ring system. No medicine page on this site. [9]

6. Name: Thiothixene

6. Route: Oral

6. Note: The thioxanthene representative among the high-potency agents. No medicine page on this site. [9]

7. Name: Pimozide

7. Route: Oral

7. Note: A diphenylbutylpiperidine listed among the high-potency first-generation agents. No medicine page on this site. [9] [9]

2. Name: Low-potency first-generation agents

2. Note: Given in far larger milligram quantities, with high histaminic and muscarinic activity, a lower risk of extrapyramidal adverse effects and a heightened prevalence of dizziness, sedation and antimuscarinic effects.

1. Name: Chlorpromazine

Chlorpromazine hydrochloride

1. Route: Oral and parenteral

1. Note: The low-potency prototype of the whole class, described as an antipsychotic that mainly causes non-neurologic side effects. Sedation follows from histamine H1 blockade and the dry mouth, blurred vision, urinary retention and constipation from muscarinic blockade. No medicine page exists on this site. [11][9][3]

2. Name: Thioridazine

2. Route: Oral

2. Note: The second low-potency phenothiazine in the standard grouping, sharing chlorpromazine's profile of sedation and antimuscarinic burden rather than prominent extrapyramidal effects. No medicine page on this site. [9] [9]

3. Name: Phenothiazines used chiefly outside psychiatry

3. Note: Same receptor pharmacology, same boxed warning, but a different everyday job. Their inclusion here is the reminder that a patient can acquire an extrapyramidal reaction from an antiemetic.

1. Name: Prochlorperazine

Prochlorperazine maleate

1. Route: Oral

1. Note: Its US label lists control of severe nausea and vomiting first, then the treatment of schizophrenia, then short-term treatment of generalised non-psychotic anxiety. The NHS describes it as an anti-sickness medicine used for vertigo, motion sickness, sickness caused by migraines and balance problems such as Meniere's disease. [6][7]

2. Name: Chlorpromazine in its non-psychiatric roles

2. Route: Oral and parenteral

2. Note: The same drug appears twice in this table for a reason. Beyond psychosis its label covers control of nausea and vomiting, relief of intractable hiccups, acute intermittent porphyria and adjunctive treatment of tetanus. [3] [6][7]

Mechanism of action

Summary: Antipsychotic effect comes from postsynaptic D2 blockade in the mesolimbic system, and antipsychotic efficacy tracks D2 occupancy closely. Because the drugs cannot confine themselves to one dopamine pathway, the same blockade in the nigrostriatal pathway produces extrapyramidal effects and in the tuberoinfundibular pathway raises prolactin. Off-target blockade of histamine H1, muscarinic and related receptors accounts for the sedation and antimuscarinic burden that dominate the low-potency agents.

Target: Postsynaptic dopamine D2 receptors, with additional blockade of histamine H1 and muscarinic M1 receptors that varies by agent

Cidal Static: Symptom-suppressing rather than disease-modifying

Kill Kinetics: Effect maintained only while receptor occupancy is maintained

1. Step: 1

1. Title: Postsynaptic blockade of dopamine D2 receptors

1. Detail: In first-generation antipsychotic medications the postsynaptic blockade of dopamine D2 receptors in the mesolimbic system of the central nervous system is the mechanism of action. Chlorpromazine's own summary is more guarded, describing its precise mechanism as unknown while attributing the antipsychotic effect to post-synaptic blockade at the D2 receptors. [9][11]

2. Step: 2

2. Title: Receptor occupancy sets potency

2. Detail: There is a higher association between D2 receptor binding and potency, and functional imaging studies show a consistent requirement of 65% D2 receptor occupancy for antipsychotic efficacy. An agent that reaches that threshold at a small milligram quantity is by definition high potency, and it reaches the same threshold in the motor pathways at the same time. [9]

3. Step: 3

3. Title: The blockade is not confined to one pathway

3. Detail: Blocking D2 receptors in the nigrostriatal pathway is responsible for the extrapyramidal side effects, and antagonism at D2 receptors in the tuberoinfundibular pathway is believed to be responsible for the increase in prolactin level. The non-specific localisation of dopamine binding throughout the central nervous system is consistent with the risk of drug-induced parkinsonism and hyperprolactinaemia. [11][9]

4. Step: 4

4. Title: Off-target receptor blockade shapes the low-potency profile

4. Detail: Low-potency agents have high histaminic and muscarinic activity. Sedation follows blockade of histamine H1 receptors, and dry mouth, dizziness, urinary retention, blurred vision and constipation follow blockade of muscarinic receptors, which is why the same drugs that trouble the patient least in the striatum trouble them most everywhere else. [11][9]

5. Step: 5

5. Title: Antiemetic action at the vomiting centre

5. Detail: The antiemetic effect of chlorpromazine stems from the combined blockade of histamine H1, dopamine D2 and muscarinic M1 receptors in the vomiting centre. That combination, not a separate drug class, is why a phenothiazine such as prochlorperazine is indicated for the control of severe nausea and vomiting. [11][6]

6. Step: 6

6. Title: What the labels decline to claim

6. Detail: None of these labels asserts a settled mechanism. Haloperidol's states that the precise mechanism of action has not been clearly established; fluphenazine's states that the mechanism by which the therapeutic action is exerted is unknown; loxapine's states that the exact mode of action has not been established, adding only that changes in the level of excitability of subcortical inhibitory areas have been observed. [1][4][5]

Major clinical uses

1. Drug: Haloperidol

1. Organism: Not applicable

1. Indication: Management of manifestations of psychotic disorders; control of tics and vocal utterances of Tourette's Disorder

1. Line: established

1. Note: The tablet label also covers severe behaviour problems in children marked by combative, explosive hyperexcitability. Its use is constrained by extrapyramidal effects and by the cardiac signal rather than by lack of efficacy. [1]

2. Drug: Fluphenazine

2. Organism: Not applicable

2. Indication: Management of manifestations of psychotic disorders

2. Line: established

2. Note: A single-indication label, which makes fluphenazine the cleanest illustration of a high-potency agent used purely for its antipsychotic effect. [4]

3. Drug: Loxapine

3. Organism: Not applicable

3. Indication: Treatment of schizophrenia

3. Line: established

3. Note: Its dibenzoxazepine structure sets it apart chemically from the phenothiazines, butyrophenones and thioxanthenes, but it is grouped with the high-potency first-generation agents. The lowered convulsive threshold is its distinguishing caution. [5][9]
4. Drug: Chlorpromazine
4. Organism: Not applicable
4. Indication: Psychotic disorders and schizophrenia, the manic type of manic-depressive illness, severe nausea and vomiting, intractable hiccups, acute intermittent porphyria and adjunctive treatment of tetanus
4. Line: older agent, broad label
4. Note: The breadth is historical rather than a recommendation, and no medicine page exists here for it. Its label also covers relief of restlessness and apprehension before surgery. [3]
5. Drug: Prochlorperazine
5. Organism: Not applicable
5. Indication: Control of severe nausea and vomiting; treatment of schizophrenia; short-term treatment of generalised non-psychotic anxiety
5. Line: widely used as an antiemetic
5. Note: Most patients who receive this drug never receive it for a psychiatric reason, which is exactly why unexplained dystonia in a vomiting patient should prompt a look at the antiemetic chart. [6]
6. Drug: Prochlorperazine in vestibular symptoms
6. Organism: Not applicable
6. Indication: Vertigo, motion sickness, sickness caused by migraines and balance problems such as Meniere's disease
6. Line: UK practice
6. Note: The NHS lists these among the reasons prochlorperazine is prescribed, alongside sickness in pregnancy and sickness after a general anaesthetic or cancer treatment. [7]
7. Drug: The class as a whole in UK practice
7. Organism: Not applicable
7. Indication: Schizophrenia and other psychoses, agitation, severe anxiety, mania, and violent or dangerously impulsive behaviour
7. Line: regulator's summary
7. Note: The UK regulator's own description of where antipsychotic medicines are mainly used. It is deliberately narrower than the historical chlorpromazine label. [8]

Pharmacokinetics

1. No dose regimens appear on this page. Choosing an agent, titrating it, monitoring it and stopping it are decisions for the treating clinician working from a current prescribing reference and the individual patient's circumstances.
2. Potency is a receptor-affinity statement, not a statement about strength of effect. High-potency agents reach the occupancy needed for antipsychotic efficacy at small milligram quantities, while low-potency agents need far larger ones for the same occupancy. [9]
3. Route matters more than usual for haloperidol. The injection is labelled for intramuscular use and states in capitals that it is not approved for intravenous administration; where it is nonetheless given intravenously, the label directs that the ECG be monitored for QTc prolongation and arrhythmias. [2]
4. Onset of the adverse effects, rather than of the drug, is what examiners test. Dystonia appears in the first few days, akathisia usually inside the first two weeks, and the likelihood that dyskinetic movements become irreversible rises as the duration of treatment increases. [4][10][1]

Adverse effects

1. Effect: Extrapyramidal symptoms
1. Detail: Reported frequently with haloperidol, often during the first few days of treatment, and categorised generally

as Parkinson-like symptoms, akathisia, or dystonia including opisthotonos and oculogyric crisis. The side effects most frequently reported with phenothiazine compounds are extrapyramidal symptoms including pseudoparkinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos and hyperreflexia. [1][4]

2. Effect: Drug-induced parkinsonism

2. Detail: In most patients whose extrapyramidal reactions were reported with loxapine, the reactions involved parkinsonian-like symptoms such as tremor, rigidity, excessive salivation and masked facies. The pattern is a hypokinetic one and can be mistaken for the negative symptoms of the illness being treated. [5]

3. Effect: Akathisia

3. Detail: An inability to remain still, described by patients as an intense sensation of unease or inner restlessness usually involving the lower limbs and a compulsion to move, and seen as pacing, rocking and shifting position. It usually develops within the first two weeks of antipsychotic therapy or when the dose is increased. [10]

4. Effect: Sedation and drowsiness

4. Detail: With chlorpromazine, drowsiness is usually mild to moderate and may occur particularly during the first or second week, after which it generally disappears. It reflects histamine H1 blockade and is a low-potency problem rather than a class-wide one. [3][11]

5. Effect: Antimuscarinic effects

5. Detail: Occasional dry mouth, nasal congestion, nausea, constipation, adynamic ileus and urinary retention are listed for chlorpromazine, and the low-potency agents show a heightened prevalence of these effects together with dizziness. [3][9]

6. Effect: Postural hypotension

6. Detail: Postural hypotension, simple tachycardia, momentary fainting and dizziness may occur rarely with chlorpromazine after the first oral dose. Combined with somnolence and motor and sensory instability it is what makes falls a recognised hazard of this class. [3][4]

7. Effect: Raised prolactin and its consequences

7. Detail: Antipsychotic drugs elevate prolactin levels and the elevation persists during chronic administration. Disturbances such as galactorrhoea, amenorrhoea, gynaecomastia and impotence have been reported as a result. [1][3][4]

1. Effect: Increased mortality in elderly patients with dementia-related psychosis

1. Detail: The boxed warning states: "Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death." Analyses of seventeen placebo-controlled trials found a risk of death in drug-treated patients of about 1.6 to 1.7 times that in placebo-treated patients, roughly 4.5% against 2.6% over a typical ten-week trial, with deaths appearing to be either cardiovascular such as heart failure or sudden death, or infectious such as pneumonia.

1. Action: None of these agents is approved for dementia-related psychosis, and the UK regulator records a clear increased risk of stroke alongside the mortality signal. Whether an antipsychotic is appropriate for an older person with dementia is a decision for the responsible clinician. [1][3][8]

2. Effect: Tardive dyskinesia

2. Detail: A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Both the risk of developing it and the likelihood that it will become irreversible are believed to increase as the duration of treatment increases, and prevalence appears highest among the elderly and especially elderly women, although prevalence estimates cannot predict at the outset who will be affected.

2. Action: There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Any such decision belongs to the treating clinician.

[1][3][4]

3. Effect: Neuroleptic malignant syndrome

3. Detail: A potentially fatal symptom complex reported in association with antipsychotic drugs. Its clinical manifestations are hyperpyrexia, muscle rigidity, altered mental status including catatonic signs, and evidence of

autonomic instability such as irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias. Symptoms typically develop over one to three days, and reported mortality is in the range of 5% to 20%.

3. Action: It is the most life-threatening emergency associated with the use of these drugs, so the point to master is recognition: a rigid, febrile, confused patient with unstable observations who is taking an antipsychotic needs urgent medical assessment. Management is a matter for the clinical team, not for this page. [1][9][3]

4. Effect: QT prolongation, torsades de pointes and sudden death

4. Detail: Cases of sudden death, QT-prolongation and torsades de pointes have been reported in patients receiving haloperidol. Higher than recommended doses of any formulation, and intravenous administration of haloperidol injection, appear to be associated with a higher risk, and electrolyte imbalance, particularly hypokalaemia and hypomagnesaemia, is a predisposing factor.

4. Action: The injection label states in capitals that it is not approved for intravenous administration, and directs that the ECG be monitored for QTc prolongation and arrhythmias if it is nevertheless given by that route. [1][2]

5. Effect: Agranulocytosis with chlorpromazine

5. Detail: Most reported cases have occurred between the fourth and tenth weeks of therapy, which places the risk window well after the point at which a patient has stopped thinking about the medicine.

5. Action: The label directs that patients be warned to report the sudden appearance of sore throat or other signs of infection. [3]

6. Effect: Seizures with loxapine

6. Detail: Loxapine lowers the convulsive threshold, and seizures have been reported in patients receiving it at antipsychotic dose levels.

6. Action: Its label directs extreme caution in patients with a history of convulsive disorders. [5]

7. Effect: Falls and consequent injury

7. Detail: Fluphenazine may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries.

7. Action: For patients whose diseases, conditions or medicines could exacerbate these effects, the label directs that fall risk assessments are completed when antipsychotic treatment is initiated and recurrently during long-term therapy. [4]

1. Drug: Haloperidol

1. Effect: The cardiac liability of the group: sudden death, QT prolongation and torsades de pointes, with risk rising at higher than recommended doses and with intravenous administration. [1][2]

2. Drug: Chlorpromazine

2. Effect: Jaundice of low overall incidence, considered by most investigators to be a sensitivity reaction; photosensitivity of a mild urticarial type; rare skin pigmentation ranging from imperceptible darkening to a slate grey colour; and epithelial keratopathy and pigmentary retinopathy. [3]

3. Drug: Loxapine

3. Effect: A lowered convulsive threshold, with seizures reported at antipsychotic dose levels. [5]

4. Drug: Prochlorperazine

4. Effect: Children seem more prone to develop extrapyramidal reactions, even on moderate doses. The antiemetic action may also mask the signs and symptoms of overdose of other drugs and obscure the diagnosis and treatment of other conditions. [6]

5. Drug: Fluphenazine

5. Effect: A high-potency phenothiazine whose label singles out somnolence, postural hypotension and motor and sensory instability as a route to falls and fractures. [4]

Contraindications, precautions and interactions

1. None of these agents is approved for the treatment of patients with dementia-related psychosis; the boxed warning on each label says so directly. [1][3][4][5][6]

2. Haloperidol injection is not approved for intravenous administration, a restriction its label prints in capital letters, and the approved route is intramuscular. [2]

1. In elderly people with dementia there is a clear increased risk of stroke and a small increased risk of death when antipsychotics are used, and in 2004 UK advisers reported an approximately three-fold increase in stroke risk against placebo. [8]

2. Loxapine should be used with extreme caution in anyone with a history of convulsive disorders, because it lowers the convulsive threshold. [5]

3. Electrolyte imbalance, particularly hypokalaemia and hypomagnesaemia, predisposes to the QT effects seen with haloperidol. [1]

4. Older patients, and older women in particular, carry the highest apparent prevalence of tardive dyskinesia, though no prevalence estimate identifies which individual will develop it. [1]

5. Extrapyramidal reactions occur readily in children given prochlorperazine, even at moderate doses, so a child receiving it as an antiemetic warrants particular vigilance. [6]

6. Patients on chlorpromazine should be told to report a sudden sore throat or other sign of infection, since most cases of agranulocytosis appeared between the fourth and tenth weeks of treatment. [3]

1. With: Conditions and medicines that deplete potassium or magnesium

1. Effect: Electrolyte imbalance is listed as predisposing to QT prolongation and torsades de pointes with haloperidol, so anything that lowers potassium or magnesium raises the cardiac risk of the combination. [1]

2. With: Other drugs taken in overdose

2. Effect: The antiemetic action of prochlorperazine may mask the signs and symptoms of overdosage of other drugs, and may obscure the diagnosis and treatment of other conditions. [6]

3. With: Anticholinergic agents given for extrapyramidal symptoms

3. Effect: Akathisia does not generally respond to anticholinergic agents, which suggests a pathophysiological mechanism different from the other extrapyramidal syndromes; a failure to respond is therefore diagnostic information rather than a reason to escalate. [10]

4. With: Any additional agent that lowers the seizure threshold

4. Effect: Loxapine already lowers the convulsive threshold, and seizures have been reported at antipsychotic dose levels, so the combined effect is the relevant consideration. [5]

Comparison tables

1. Title: The four extrapyramidal syndromes, separated by timing

1. Caption: Timing is the discriminator examiners use. Recognition belongs to the reader; assessment and any change of treatment belong to the treating clinician.

1. Key: syndrome

1. Label: Syndrome

1. Is Row Header: true

2. Key: timing

2. Label: Typical timing

3. Key: features

3. Label: Features

4. Key: point

4. Label: The point to remember

1. Syndrome: Acute dystonia

1. Timing: First few days of treatment

1. Features: Prolonged abnormal contractions of muscle groups, including opisthotonos and oculogyric crisis

1. Point: Earliest of the four, and frightening out of proportion to its duration [4][1]

2. Syndrome: Akathisia

- 2. Timing: Usually within the first two weeks, or after a dose increase
- 2. Features: Inner restlessness felt mainly in the lower limbs, with pacing, rocking and shifting position
- 2. Point: Often underdiagnosed because it mimics psychosis, mania, ADHD or agitated depression [10]
- 3. Syndrome: Drug-induced parkinsonism
- 3. Timing: Often during the first few days, and through the early weeks
- 3. Features: Tremor, rigidity, excessive salivation and masked facies
- 3. Point: A hypokinetic picture that can be misread as the illness worsening [5][9]
- 4. Syndrome: Tardive dyskinesia
- 4. Timing: After prolonged exposure, with risk rising as treatment continues
- 4. Features: Involuntary dyskinetic movements that are potentially irreversible
- 4. Point: No known treatment once established, though it may remit if the drug is withdrawn [1]
- 2. Title: High potency against low potency
- 2. Caption: One axis explains most of what separates these drugs in practice. Representative agents are taken from the standard potency grouping.
- 1. Key: feature
- 1. Label: Feature
- 1. Is Row Header: true
- 2. Key: high
- 2. Label: High-potency agents
- 3. Key: low
- 3. Label: Low-potency agents
- 1. Feature: Representative drugs
- 1. High: Fluphenazine, haloperidol, trifluoperazine, perphenazine, thiothixene, loxapine, pimozide
- 1. Low: Chlorpromazine and thioridazine [9]
- 2. Feature: Extrapyrimal risk
- 2. High: High, with dystonia, bradykinesia, rigidity and tremor
- 2. Low: Lower risk of extrapyramidal adverse effects [9]
- 3. Feature: Sedation
- 3. High: Less prominent
- 3. Low: Heightened, reflecting histamine H1 blockade [9][11]
- 4. Feature: Antimuscarinic burden
- 4. High: Less prominent
- 4. Low: Marked: dry mouth, blurred vision, urinary retention and constipation [9][11]
- 5. Feature: Dizziness and postural effects
- 5. High: Less prominent
- 5. Low: Heightened prevalence of dizziness; postural hypotension reported after the first oral dose of chlorpromazine [9][3]
- 6. Feature: Milligram quantity required
- 6. High: Small, because the D2 occupancy needed for efficacy is reached at low doses
- 6. Low: Far larger for the same receptor occupancy [9]

High-yield exam pearls

- 1. Pearl: The likelihood that dyskinetic movements will become irreversible is believed to increase as the duration of treatment increases, and no treatment is known for established cases.
- 1. Why: Irreversibility is the single fact that distinguishes tardive dyskinesia from the other three extrapyramidal syndromes, and it is asked directly. [1]
- 2. Pearl: High-potency agents are the ones most commonly associated with extrapyramidal effects, while low-potency

agents trade those for sedation, dizziness and antimuscarinic effects.

2. Why: One rule covers the whole class and lets a candidate predict the side-effect profile of an unfamiliar first-generation agent from its potency alone. [9]

3. Pearl: Akathisia occurs more with first-generation agents, particularly high-potency ones such as haloperidol, and does not generally respond to anticholinergic agents.

3. Why: The failure to respond to an anticholinergic separates akathisia from dystonia and parkinsonism, and points to a different mechanism. [10]

4. Pearl: Haloperidol injection is labelled for intramuscular use and states that it is not approved for intravenous administration, yet intravenous use is exactly what raises the torsades risk.

4. Why: It is a rare instance of a label naming a route as both unapproved and specifically hazardous, and it is easy to examine. [2]

5. Pearl: Prolactin elevation persists during chronic administration, producing galactorrhoea, amenorrhoea, gynaecomastia and impotence.

5. Why: Students often expect tolerance to develop; the labels say the opposite, and the endocrine consequences are a common short-answer question. [1][3]

6. Pearl: The boxed warning is a class warning about older people with dementia, not a warning specific to any one drug in the group.

6. Why: It appears identically on haloperidol, chlorpromazine, fluphenazine, loxapine and prochlorperazine labels, and the UK regulator adds a clear increase in stroke risk. [6][5][8]

7. Pearl: Prochlorperazine is a first-generation antipsychotic whose everyday role is as an anti-sickness medicine, including for vertigo and Meniere's disease in the UK.

7. Why: It explains how a patient with no psychiatric history can present with an acute dystonic reaction, which is a classic vignette. [7][6]

Common exam traps

1. Trap: Sorting these drugs by chemical family and expecting the side effects to follow.

1. Correction: Fluphenazine and chlorpromazine are both phenothiazines yet sit at opposite ends of the potency scale, with opposite side-effect profiles. Potency, not the ring system, is the organising principle. [9]

2. Trap: Treating chlorpromazine as the safer option because it causes fewer movement disorders.

2. Correction: Its burden simply moves elsewhere: sedation, postural hypotension, antimuscarinic effects, jaundice, photosensitivity, skin pigmentation, pigmentary retinopathy and agranulocytosis between the fourth and tenth weeks. [3][11]

3. Trap: Reading a restless, pacing patient as worsening psychosis and pushing the antipsychotic higher.

3. Correction: Akathisia is often underdiagnosed precisely because it mimics psychosis, mania and agitated depression, and it typically appears within two weeks of starting the drug or of a dose increase. [10]

4. Trap: Assuming tardive dyskinesia resolves once the drug is stopped.

4. Correction: The movements are described as potentially irreversible. Withdrawal may produce partial or complete remission, but the label offers no guarantee and no treatment for established cases. [1]

5. Trap: Thinking this class belongs to psychiatry alone.

5. Correction: Prochlorperazine's label puts control of severe nausea and vomiting first, and chlorpromazine's covers intractable hiccups, acute intermittent porphyria and adjunctive use in tetanus. [6][3]

6. Trap: Calling loxapine atypical because it is a tricyclic compound like the second-generation agents.

6. Correction: Its label describes a dibenzoxazepine chemically distinct from the thioxanthenes, butyrophenones and phenothiazines, but it is grouped with the high-potency first-generation drugs. [5][9]

7. Trap: Believing that these agents are simply contraindicated in older people.

7. Correction: The precise position is narrower: they are not approved for dementia-related psychosis, and their use in elderly people with dementia carries a clear increased risk of stroke and a small increased risk of death. [8][4]

Self-test questions

1. Question: A patient started on a first-generation antipsychotic three days ago develops sustained painful neck twisting and an upward deviation of the eyes. Which syndrome is this?

1. Acute dystonia
2. Tardive dyskinesia
3. Akathisia
4. Neuroleptic malignant syndrome

1. Explanation: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment, and haloperidol's label lists opisthotonos and oculogyric crisis among the dystonic presentations. [4][1]

2. Question: Which statement best captures the relationship between potency and adverse effects among first-generation antipsychotics?

1. High-potency agents carry more extrapyramidal effects; low-potency agents carry more sedation and antimuscarinic effects
2. High-potency agents carry more sedation; low-potency agents carry more extrapyramidal effects
3. Potency predicts efficacy but has no bearing on the adverse-effect profile
4. Both groups carry an identical adverse-effect profile at equivalent doses

2. Explanation: High-potency agents have a high risk of extrapyramidal adverse effects including dystonia, bradykinesia, rigidity and tremor, whereas low-potency agents have high histaminic and muscarinic activity, a lower extrapyramidal risk and a heightened prevalence of dizziness, sedation and anticholinergic effects. [9]

3. Question: A patient on long-term haloperidol develops involuntary orofacial movements. What does the label say about the outlook?

1. The movements are potentially irreversible and there is no known treatment for established cases
2. The movements always resolve within days of stopping the drug
3. The movements respond reliably to an anticholinergic agent
4. The movements indicate that the dose is too low

3. Explanation: The warning describes a syndrome of potentially irreversible involuntary dyskinetic movements, states that no known treatment exists for established cases, and adds only that the syndrome may remit partially or completely if antipsychotic treatment is withdrawn. [1]

4. Question: Which combination of features should raise immediate concern for neuroleptic malignant syndrome?

1. Hyperpyrexia, muscle rigidity, altered mental status and autonomic instability
2. Bradycardia, hypothermia, flaccid paralysis and polyuria
3. Orofacial dyskinesia, galactorrhoea and photosensitive rash
4. Isolated restlessness of the lower limbs with no other findings

4. Explanation: Haloperidol's label lists hyperpyrexia, muscle rigidity, altered mental status including catatonic signs, and autonomic instability such as irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias as the clinical manifestations of this potentially fatal complex. [1][9]

5. Question: Why does D2 blockade raise serum prolactin?

1. Antagonism at D2 receptors in the tuberoinfundibular pathway removes dopaminergic inhibition of prolactin release
2. Blockade of nigrostriatal D2 receptors stimulates the anterior pituitary directly
3. Histamine H1 blockade in the hypothalamus increases prolactin secretion
4. Muscarinic blockade in the vomiting centre increases prolactin secretion

5. Explanation: Antagonism at the D2 receptors in the tuberoinfundibular pathway is believed to be responsible for the increase in the prolactin level, whereas blockade in the nigrostriatal pathway accounts for the extrapyramidal effects instead. [11]

6. Question: Which route of haloperidol injection is stated on its label to be unapproved, while also being associated

with a higher risk of QTc prolongation and torsades de pointes?

1. Intravenous
2. Intramuscular
3. Subcutaneous
4. Sublingual

6. Explanation: The injection label states that haloperidol injection is not approved for intravenous administration, that higher than recommended doses and intravenous administration appear to carry a higher risk of QTc prolongation and torsades de pointes, and that the ECG should be monitored if the drug is given intravenously. [2]

7. Question: A patient given an antiemetic in the emergency department becomes intensely restless, unable to sit still, and paces the cubicle. Which drug and syndrome best fit?

1. Prochlorperazine causing akathisia
2. Prochlorperazine causing tardive dyskinesia
3. Loxapine causing a seizure
4. Chlorpromazine causing pigmentary retinopathy

7. Explanation: Prochlorperazine is a first-generation antipsychotic indicated for control of severe nausea and vomiting, and akathisia presents as an inability to remain still with pacing and shifting position, typically soon after the drug is started. [6][10]

8. Question: Which finding is characteristic of the low-potency agents rather than the high-potency ones?

1. Dry mouth, urinary retention and constipation
2. Prominent bradykinesia and rigidity
3. Absence of any boxed warning
4. Failure to raise serum prolactin

8. Explanation: Low-potency agents show high histaminic and muscarinic activity with a heightened prevalence of dizziness, sedation and anticholinergic effects, and chlorpromazine's own label lists dry mouth, constipation and urinary retention among its reactions. [9][3]

Frequently asked questions

1. Question: Why is chlorpromazine covered here when it has no medicine page on this site?

1. Answer: Because the class cannot be described without it. Chlorpromazine is the low-potency prototype, the agent whose sedation and antimuscarinic effects define one end of the potency scale, and its label still carries the broadest indication list in the group, from psychotic disorders and mania to nausea and vomiting, intractable hiccups, acute intermittent porphyria and tetanus. [11][3]

2. Question: How do the four extrapyramidal syndromes differ?

2. Answer: Mainly by when they appear. Dystonic contractions arrive in the first few days; akathisia usually within the first fortnight or after a dose increase; drug-induced parkinsonism with tremor, rigidity, salivation and masked facies also appears early; and tardive dyskinesia emerges after prolonged treatment, with the risk of irreversibility rising the longer treatment continues. [4][10][5][1]

3. Question: Are these medicines used for behavioural symptoms in dementia?

3. Answer: They are not approved for it. Every label in this group opens with a boxed warning about increased mortality in elderly patients with dementia-related psychosis, and the UK regulator records both a clear increased risk of stroke and a small increased risk of death when antipsychotics are used in elderly people with dementia. Any decision in an individual patient rests with the responsible clinician. [5][8]

4. Question: What makes neuroleptic malignant syndrome an emergency rather than a side effect?

4. Answer: Its speed and its lethality. The picture assembles over about one to three days, combining fever, rigidity, altered mental state and unstable pulse and blood pressure, and reported mortality is in the range of 5% to 20%. Recognising it and getting the patient urgent medical assessment is the student's task; treatment is the clinical team's. [9][1]

5. Question: Do second-generation antipsychotics avoid these problems?

5. Answer: They reduce one of them. The UK regulator states that the newer antipsychotics, developed from the 1970s onwards, are less likely to cause movement disorders than the older ones. That is the main reason first-generation agents have narrowed to particular roles, but the boxed warning about older people with dementia applies to antipsychotic drugs generally. [8][1]

6. Question: Why does an antiemetic cause a movement disorder?

6. Answer: Because it is the same pharmacology. Prochlorperazine is a first-generation antipsychotic, and the antiemetic effect of this group comes from combined blockade of histamine H1, dopamine D2 and muscarinic M1 receptors in the vomiting centre. The D2 blockade does not stop at the vomiting centre, so a patient treated for sickness can acquire dystonia or akathisia, and children are described as especially prone. [11][6]

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