

Atypical antipsychotics

Second-generation antipsychotics that act on dopamine D2 receptors alongside serotonin 5-HT_{2A} receptors, whether by antagonism, partial agonism or inverse agonism, and which trade a smaller burden of movement disorder for a larger metabolic one, with clozapine standing apart as the agent for treatment-resistant illness and the only member whose neutrophil count must be watched for as long as it is taken.

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

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Quick revision

One Liner: These agents were designed to spare the motor system, and largely do, but they moved the cost to metabolism; clozapine is the exception that works where nothing else has, and it is the exception that is watched most closely.

1. Every member of this class carries a boxed warning about excess deaths when antipsychotics are given to elderly people with dementia-related psychosis, and none of them is approved for that use. [1][3][4][10]
2. The pooled evidence behind that warning covers seventeen placebo-controlled trials, with mortality in drug-treated patients 1.6 to 1.7 times that of placebo, about 4.5% against 2.6% over a ten-week trial. [5]
3. Clozapine is the only agent here indicated for schizophrenia that has already failed standard antipsychotic treatment, and for reducing the risk of recurrent suicidal behaviour. [1]
4. Its price is a five-part boxed warning: severe neutropenia, orthostatic hypotension with bradycardia and syncope, seizure, myocarditis and cardiomyopathy, and the class mortality signal in dementia. [1]
5. Before clozapine is started the absolute neutrophil count must be at least 1500 per microlitre, or at least 1000 per microlitre where benign ethnic neutropenia is documented. [1]
6. Weight gain, hyperglycaemia and dyslipidaemia run through the whole class, but the rates in the labels are strikingly unequal, with olanzapine and clozapine at the heavy end. [3][2][9]
7. Movement disorders are less frequent than with the older agents rather than absent, and risperidone, paliperidone and lurasidone all report extrapyramidal effects that rise with dose. [11][5][6][9]
8. Risperidone is associated with higher prolactin elevation than other antipsychotic agents, and paliperidone, which is its major active metabolite, behaves similarly. [5][6]
9. Aripiprazole works as a partial agonist at dopamine D2 rather than as a pure blocker, and pimavanserin acts at 5-HT_{2A} with no appreciable dopamine affinity at all. [8][10]
10. Tardive dyskinesia and neuroleptic malignant syndrome are still described in these labels, so the second-generation name does not mean the older hazards were left behind. [2][3]

Overview

1. The atypical antipsychotics are grouped by what they do at dopamine and serotonin receptors rather than by chemistry, and the single statement they all share sits at the top of every label in the group: "Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death." That warning is quantified from seventeen placebo-controlled trials, in which the risk of death among drug-treated patients ran at 1.6 to 1.7 times the placebo risk, roughly 4.5% against about 2.6% over a typical ten-week study, with most deaths appearing cardiovascular or infectious. No agent in this class is approved for dementia-related psychosis, and pimavanserin is licensed only where the hallucinations and delusions arise from Parkinson's disease. [5][10][4]
2. What made these drugs "atypical" was the promise of antipsychotic effect without the motor toxicity of the first-generation agents. UK regulators put the comparison plainly, describing the newer antipsychotics as less likely to

cause movement disorders as a side effect than the older ones. The promise was partly kept. Akathisia, dystonia and parkinsonism still appear in the labels of risperidone, paliperidone and lurasidone, and in each case the incidence climbs as the dose climbs, so a patient on a high dose of an atypical agent may be no better protected than one on a modest dose of an older drug. [11][5][6][9]

3. The cost that replaced it is metabolic. Hyperglycaemia severe enough to reach ketoacidosis, hyperosmolar coma or death has been reported with these agents, alongside adverse shifts in lipids and substantial weight gain. The size of the problem is not uniform: in six-week adult schizophrenia trials 22.2% of olanzapine-treated patients gained at least 7% of their baseline weight against 3% on placebo, while a lurasidone schizophrenia programme recorded 4.8% reaching the same threshold. Those figures come from separate trial programmes rather than from head-to-head comparison, so they show that the burden differs by agent without ranking the agents precisely. [3][9][4]

4. Clozapine sits outside this pattern and deserves separate study. It is reserved for severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatment, and it is the only antipsychotic indicated for reducing the risk of recurrent suicidal behaviour in schizophrenia or schizoaffective disorder. Because of severe neutropenia it is supplied only through a restricted programme under a Risk Evaluation and Mitigation Strategy, and the whole of its use is organised around blood counts, slow re-titration after any interruption, and vigilance for myocarditis. Learning clozapine well means learning what a genuinely effective drug looks like when its safety demands are non-negotiable. [1]

Classification and drug examples

Intro: Divided by how each agent engages the dopamine D2 receptor, because that is what predicts prolactin behaviour, movement-disorder risk and whether an agent can be used in Parkinson's disease at all. Breadth of binding at histamine, muscarinic and adrenergic receptors then predicts most of the remaining adverse-effect profile.

1. Name: Clozapine, the restricted treatment-resistant agent

1. Note: A class of one. Its efficacy where other antipsychotics have failed is matched by a boxed warning with five headings and a mandatory monitoring programme.

Name: Clozapine

Clozaril

Route: Oral

Note: Its label states that therapeutic efficacy in schizophrenia is mediated through antagonism of the dopamine type 2 and serotonin type 2A receptors. Severe neutropenia is defined there as an absolute neutrophil count below 500 per microlitre, and supply runs through a restricted programme. [1][2] [1]

2. Name: Broad multi-receptor antagonists

2. Note: Agents that bind widely across dopaminergic, serotonergic, histaminergic, muscarinic and adrenergic receptors. Sedation and metabolic change dominate their profile.

1. Name: Olanzapine

Zyprexa

1. Route: Oral and intramuscular

1. Note: The heaviest labelled weight burden in this group: 22.2% of adults gained at least 7% of baseline weight over six weeks, and in longer exposure of 48 weeks or more the figures reached 64%, 32% and 12% for gains of at least 7%, 15% and 25%. [3]

2. Name: Quetiapine

1. Seroquel

2. Quetiapine fumarate

2. Route: Oral

2. Note: Notable for orthostatic hypotension with dizziness, tachycardia and sometimes syncope during initial titration, for dose-related falls in thyroxine of about 20% at the higher end of the therapeutic range, and for lens changes on long-term use whose causal link is not established. [4] [3][4]

3. Name: Serotonin-dopamine antagonists

3. Note: Tighter D2 blockade with 5-HT2A antagonism. Prolactin elevation and dose-dependent motor effects are the recurring themes here rather than sedation.

1. Name: Risperidone

Risperdal

1. Route: Oral and long-acting injection

1. Note: Metabolised by CYP2D6 to 9-hydroxyrisperidone, and the parent drug together with that metabolite forms the active moiety. Its label states that it is associated with higher levels of prolactin elevation than other antipsychotic agents. [5]

2. Name: Paliperidone

1. Invega

2. 9-hydroxyrisperidone

2. Route: Oral extended-release and long-acting injection

2. Note: The major active metabolite of risperidone, marketed in its own right. The oral tablet is delivered by an osmotic system whose shell is non-deformable, so it must be swallowed whole and avoided where there is severe gastrointestinal narrowing. [6]

3. Name: Lurasidone

Latuda

3. Route: Oral

3. Note: Antagonises dopamine D2 and serotonin 5-HT2A receptors with affinity also for 5-HT7, 5-HT1A and alpha-2 adrenergic receptors. Its labelled metabolic figures are among the lightest in the class, but akathisia reached 13% overall against 3% on placebo. [9] [5][9]

4. Name: Dopamine D2 partial agonists

4. Note: Agents that stabilise rather than simply block dopaminergic transmission, behaving as agonists where dopamine tone is low and as antagonists where it is high.

Name: Aripiprazole

Abilify

Route: Oral and long-acting injection

Note: The label states that its efficacy could be mediated through a combination of partial agonist activity at dopamine D2 and serotonin 5-HT1A receptors and antagonist activity at 5-HT2A receptors. Postmarketing reports describe intense urges, particularly for gambling, that patients could not control. [8][7] [8]

5. Name: Serotonin-selective agents without dopamine blockade

5. Note: The newest departure from the class template: antipsychotic effect pursued through serotonin receptors alone, which is what makes use in Parkinson's disease possible.

Name: Pimavanserin

Nuplazid

Route: Oral

Note: Described in its label as possibly acting through a combination of inverse agonist and antagonist activity at serotonin 5-HT2A receptors, and to a lesser extent at 5-HT2C receptors, with no appreciable affinity above a Ki of 300 nanomolar for dopaminergic receptors including D2. [10] [10]

Mechanism of action

Summary: The unifying action is engagement of the dopamine D2 receptor together with serotonin 5-HT2A, but the class contains three different ways of doing it: straightforward antagonism, partial agonism, and serotonergic inverse agonism with the dopamine arm removed altogether. Several labels state that the precise mechanism of antipsychotic benefit is not established, and the page follows them in saying so.

Target: Dopamine D2 receptors and serotonin 5-HT2A receptors, with variable additional binding at 5-HT1A, 5-HT2C,

5-HT₇, histaminergic, muscarinic and alpha-adrenergic receptors

Cidal Static: Symptom-suppressing rather than curative

Kill Kinetics: Effect maintained only while receptor occupancy is maintained

1. Step: 1

1. Title: Antagonism at dopamine D₂ receptors

1. Detail: Blockade of D₂ receptors in mesolimbic pathways is the common route to reducing hallucinations and delusions. The clozapine label attributes its therapeutic efficacy in schizophrenia to antagonism of the dopamine type 2 and serotonin type 2A receptors, and the lurasidone label states that the drug antagonises dopamine D₂ and serotonin 5-HT_{2A} receptors. [2][9]

2. Step: 2

2. Title: Simultaneous blockade of serotonin 5-HT_{2A} receptors

2. Detail: Adding 5-HT_{2A} antagonism to D₂ blockade is the defining structural feature of the second-generation agents and is the usual explanation offered for their lighter motor burden. Lurasidone extends this further, with affinity also for 5-HT₇, 5-HT_{1A} and alpha-2 adrenergic receptors. [9][2]

3. Step: 3

3. Title: Partial agonism as an alternative to blockade

3. Detail: Aripiprazole does not simply occupy the D₂ receptor and silence it. Its label describes efficacy that could be mediated through a combination of partial agonist activity at dopamine D₂ and serotonin 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors, which is a different pharmacological proposition from pure antagonism. [8]

4. Step: 4

4. Title: Serotonergic action with the dopamine arm removed

4. Detail: Pimavanserin abandons dopamine blockade entirely. Its label calls the mechanism unclear but suggests a combination of inverse agonist and antagonist activity at serotonin 5-HT_{2A} receptors, and to a lesser extent at 5-HT_{2C} receptors, while recording no appreciable affinity, defined as a K_i value above 300 nanomolar, for dopaminergic receptors including D₂. [10]

5. Step: 5

5. Title: Blockade of the tuberoinfundibular pathway raises prolactin

5. Detail: Dopamine restrains prolactin release, so D₂ blockade lifts that restraint. The olanzapine label notes that, as with other drugs that antagonise dopamine D₂ receptors, prolactin rises and the elevation persists during chronic administration, and the paliperidone label carries the same observation with a comparison to risperidone. [3][6]

6. Step: 6

6. Title: Off-target binding generates most of the tolerability problems

6. Detail: Affinity outside the dopamine and serotonin systems is where much of the harm originates. Clozapine has potent anticholinergic effects that produce gastrointestinal hypomotility ranging from constipation to paralytic ileus, and quetiapine induces orthostatic hypotension with dizziness, tachycardia and in some patients syncope during the initial titration period. [2][4]

Major clinical uses

1. Drug: Clozapine

1. Organism: Not applicable

1. Indication: Treatment-resistant schizophrenia, and reduction of the risk of recurrent suicidal behaviour in schizophrenia or schizoaffective disorder

1. Line: reserved, after failure of standard treatment

1. Note: Indicated for severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatment, with the label stating that because of the risks of severe neutropenia and of seizure it should be used only in those patients. The suicidality indication was demonstrated over a two-year treatment period in the InterSePT trial. [1]

2. Drug: Olanzapine

2. Organism: Not applicable

2. Indication: Schizophrenia in adults and adolescents, and acute manic or mixed episodes in bipolar I disorder

2. Line: first-line option

2. Note: Also used intramuscularly for acute agitation associated with schizophrenia and bipolar I mania. Fasting glucose and a lipid profile are recommended at the start of treatment and periodically during it. [3]

3. Drug: Quetiapine

3. Organism: Not applicable

3. Indication: Schizophrenia and mood episodes in bipolar disorder

3. Line: first-line option

3. Note: Its boxed warning pairs the dementia mortality signal with the antidepressant suicidality warning, reflecting its use in depressive as well as psychotic illness. Lens examination is recommended when treatment starts and at six-month intervals thereafter. [4]

4. Drug: Risperidone

4. Organism: Not applicable

4. Indication: Schizophrenia, bipolar I mania, and irritability associated with autistic disorder

4. Line: first-line option

4. Note: Its paediatric indications are unusually broad for this class, covering bipolar I mania from ten years of age and irritability in autistic disorder from five, which is one reason its prolactin behaviour matters so much. [5]

5. Drug: Paliperidone

5. Organism: Not applicable

5. Indication: Schizophrenia in adults and adolescents, and schizoaffective disorder in adults

5. Line: first-line option

5. Note: Used alone or with mood stabilisers or antidepressants in schizoaffective disorder. The extended-release tablet must be swallowed whole, and its long-acting injectable forms are widely used where adherence is the main obstacle. [6]

6. Drug: Lurasidone

6. Organism: Not applicable

6. Indication: Schizophrenia in adults and adolescents, and depressive episodes of bipolar I disorder

6. Line: first-line option, favoured where metabolic risk dominates

6. Note: Approved for bipolar depression as monotherapy in adults and in patients aged ten to seventeen, and as adjunctive therapy with lithium or valproate in adults. Its light labelled metabolic profile is the usual reason it is chosen. [9]

7. Drug: Aripiprazole

7. Organism: Not applicable

7. Indication: Schizophrenia, bipolar I disorder, and adjunctive treatment of major depressive disorder

7. Line: first-line option

7. Note: Its partial agonism is often preferred where prolactin elevation or sedation would be unwelcome, but prescribers are directed to ask specifically about new or intense gambling urges and other compulsive behaviours. [8][7]

8. Drug: Pimavanserin

8. Organism: Not applicable

8. Indication: Hallucinations and delusions associated with Parkinson's disease psychosis

8. Line: the only agent licensed for this indication

8. Note: Its lack of dopamine blockade is precisely what allows it to be used in a disease already defined by dopaminergic loss. Its boxed warning excludes patients with dementia-related psychosis unless the symptoms arise from Parkinson's disease. [10]

Pharmacokinetics

1. No dose regimens appear on this page. Choosing an antipsychotic, titrating it, monitoring it and stopping it are decisions for the treating clinician working from a current prescribing reference, because they turn on diagnosis, previous response, metabolic risk, comorbidity and what the patient can tolerate.
2. Risperidone and paliperidone are one pharmacological story told twice: CYP2D6 converts risperidone into 9-hydroxyrisperidone, parent and metabolite together make up the active moiety, and that metabolite is paliperidone sold as a drug in its own right. [5][6]
3. Paliperidone therefore behaves quite differently from its parent in the body, with 59% of a dose excreted unchanged into urine and only a limited role for CYP2D6 and CYP3A4 in its overall elimination. [6]
4. The oral paliperidone tablet is a shell that does not appreciably change shape in the gastrointestinal tract, so it should ordinarily be avoided where there is pre-existing severe gastrointestinal narrowing and must be swallowed whole. [6]
5. Clozapine's tolerability is time-dependent as well as concentration-dependent: orthostatic hypotension, bradycardia, syncope and cardiac arrest are described as most likely during initial titration, and the label warns that they can recur when treatment restarts after even a brief interruption. [1]

Adverse effects

1. Effect: Weight gain
 1. Detail: Common enough to be treated as expected rather than exceptional, and unequal between agents. Quetiapine trials in schizophrenia recorded 23% of patients gaining at least 7% of body weight against 6% on placebo, risperidone trials 18% against 9%, and a lurasidone programme 4.8% with a mean change of 0.43 kg against a small mean loss on placebo. [4][5][9]
2. Effect: Sedation and orthostatic hypotension
 2. Detail: Prominent with the broadly binding agents. Quetiapine may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, and paliperidone lists somnolence and orthostatic hypotension among the reactions whose incidence rose with dose. [4][6]
3. Effect: Akathisia and other extrapyramidal effects
 3. Detail: Less frequent than with first-generation drugs but clearly present. In adult schizophrenia studies lurasidone produced akathisia in 13% of patients against 3% on placebo and extrapyramidal symptoms in 14% against 6%, both rising with dose, while risperidone's fixed-dose trials ran from 11% on placebo up to 31% at the highest dose studied. [9][5][11]
4. Effect: Raised prolactin
 4. Detail: A predictable consequence of D2 blockade that varies by agent. Quetiapine shifted prolactin to a clinically significant value in 3.6% of treated patients against 2.6% on placebo, and lurasidone produced a median rise of 0.4 nanograms per millilitre with 2.8% of patients reaching five times the upper limit of normal against 1.0% on placebo. [4][9]
1. Effect: Increased mortality in elderly patients with dementia-related psychosis
 1. Detail: The class boxed warning, and the most important safety statement on this page. Seventeen placebo-controlled trials, mostly of atypical agents, produced a risk of death in drug-treated patients of between 1.6 and 1.7 times the placebo risk, about 4.5% against 2.6% over a ten-week trial, with most deaths cardiovascular or infectious in nature. Cerebrovascular events including fatal stroke were reported in risperidone trials in elderly patients with dementia-related psychosis, at a significantly higher incidence than on placebo, and UK regulators describe an approximately three-fold increase in stroke risk against placebo.
 1. Action: No agent in this class is approved for dementia-related psychosis, and prescribing in that setting sits outside the licence; the decision and any review of it belong to the treating clinician. [5][11]
 2. Effect: Severe neutropenia with clozapine

2. Detail: Defined in the label as an absolute neutrophil count below 500 per microlitre, and capable of leading to serious infection and death. The count must be at least 1500 per microlitre before treatment begins, or at least 1000 per microlitre in documented benign ethnic neutropenia, and regular monitoring continues throughout treatment.
2. Action: Supply is restricted to a programme under a Risk Evaluation and Mitigation Strategy, and patients are told to report fever, weakness, lethargy or sore throat immediately. [1]
3. Effect: Myocarditis, pericarditis and cardiomyopathy with clozapine
3. Detail: Fatal myocarditis and cardiomyopathy have occurred during clozapine treatment. The label directs that these be considered if chest pain, tachycardia, palpitations, dyspnoea, fever, flu-like symptoms, hypotension or ECG changes appear, and eosinophilia above 700 per microlitre has been linked to myocarditis, pancreatitis, hepatitis, colitis and nephritis.
3. Action: The label directs that clozapine is stopped and a cardiac evaluation obtained on suspicion, and that patients affected should generally not be rechallenged. [1][2]
4. Effect: Seizures with clozapine
4. Detail: Listed in the boxed warning as dose-related. The label directs caution where there is a history of seizures or other predisposing factors such as central nervous system pathology, medicines that lower the seizure threshold, or alcohol misuse.
4. Action: Patients are cautioned about activities in which a sudden loss of consciousness would put them or others at serious risk. [1]
5. Effect: Hyperglycaemia, diabetes and dyslipidaemia
5. Detail: Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported with these agents. In clozapine data, 27% of treated patients showed a categorical shift in fasting glucose from normal to high against 10% on chlorpromazine, mean total cholesterol rose by 13 mg/dL and mean triglycerides by 71 mg/dL, an increase of 54%.
5. Action: Fasting glucose and a lipid profile at the start of treatment and periodically thereafter are recommended, with the interpretation and any change of agent resting with the treating clinician. [2][3]
6. Effect: Neuroleptic malignant syndrome
6. Detail: A potentially fatal symptom complex reported with antipsychotic drugs including these agents, whose clinical features are hyperpyrexia, muscle rigidity, altered mental status and autonomic instability.
6. Action: Recognition is urgent and management is a clinical emergency handled by the treating team. [2][3]
7. Effect: Tardive dyskinesia
7. Detail: A syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic drugs. Both the risk and the likelihood of irreversibility are believed to increase with longer treatment and higher cumulative dose.
7. Action: Labels direct that the smallest dose and the shortest duration of treatment producing a satisfactory clinical response be sought; that judgement belongs to the prescriber. [2][5]
8. Effect: Severe gastrointestinal hypomotility with clozapine
8. Detail: Driven by potent anticholinergic effects, with reported consequences running from constipation to paralytic ileus, and complications including faecal impaction, megacolon, intestinal obstruction, ischaemia, infarction, perforation, ulceration and necrosis.
8. Action: Bowel function is monitored actively during clozapine treatment rather than waited upon, and caution applies where there is existing constipation, urinary retention or significant prostatic hypertrophy. [2]
9. Effect: QT interval prolongation
9. Detail: Paliperidone causes a modest increase in the corrected QT interval, and the pimavanserin label states plainly that the drug prolongs the QT interval and should be avoided in patients with known QT prolongation.
9. Action: Concurrent use with other QT-prolonging medicines is avoided, which matters most where several psychotropics are being combined. [6][10]
1. Drug: Clozapine

1. Effect: The only member requiring a documented neutrophil count before and throughout treatment, and the only one whose supply runs through a restricted programme. [1]
2. Drug: Olanzapine
2. Effect: The largest labelled weight gain in this class: 22.2% of adults gained at least 7% of baseline weight in six-week trials against 3% on placebo, rising to 64% at that threshold with 48 weeks or more of exposure. [3]
3. Drug: Quetiapine
3. Effect: Dose-related decreases in thyroid hormone, with total and free thyroxine reduced by roughly 20% at the higher end of the therapeutic range, plus lens changes on long-term treatment and a need to monitor blood counts where there is pre-existing leucopenia or neutropenia. [4]
4. Drug: Risperidone
4. Effect: Associated with higher levels of prolactin elevation than other antipsychotic agents, with galactorrhoea, amenorrhoea, gynaecomastia and impotence reported. [5]
5. Drug: Paliperidone
5. Effect: The same prolactin liability as its parent drug, plus a non-deformable tablet shell that makes severe gastrointestinal narrowing a reason to avoid the oral extended-release form. [6]
6. Drug: Aripiprazole
6. Effect: Postmarketing reports of intense urges, particularly for gambling, and of an inability to control them; less frequently reported urges include sexual urges, shopping, and eating or binge eating. [7]
7. Drug: Pimavanserin
7. Effect: QT prolongation is its principal labelled hazard, which is unsurprising for an agent whose whole selling point is the absence of dopaminergic effects. [10]

Contraindications, precautions and interactions

1. Clozapine must not be started where the baseline absolute neutrophil count is below the labelled threshold, which is 1500 per microlitre for the general population and 1000 per microlitre where benign ethnic neutropenia is documented. [1]
2. No agent in this class is approved for the treatment of patients with dementia-related psychosis, and pimavanserin's approval reaches such patients only when the hallucinations and delusions are related to Parkinson's disease. [10][4]
1. Patients who develop clozapine-related myocarditis or cardiomyopathy should generally not be rechallenged with the drug, which effectively closes off the most effective option in treatment-resistant illness. [1]
2. Clozapine is used cautiously in cardiovascular or cerebrovascular disease and in conditions predisposing to hypotension such as dehydration or concurrent antihypertensive treatment. [1]
3. The oral extended-release paliperidone tablet should ordinarily not be given to patients with pre-existing severe gastrointestinal narrowing, and it can only be used by someone able to swallow it whole. [6]
4. Quetiapine requires frequent blood-count monitoring during the first months of treatment where there is a pre-existing low white cell count or a history of leucopenia or neutropenia. [4]
5. Abrupt cessation of an atypical antipsychotic has been followed by withdrawal symptoms including insomnia, nausea and vomiting, so stopping is a planned clinical decision rather than a simple omission. [4]
6. Because patients often do not recognise compulsive behaviour as abnormal, prescribers are directed to ask aripiprazole-treated patients and their carers directly about new gambling, sexual, shopping or eating urges. [7]
1. With: Other medicines that prolong the QT interval
1. Effect: Pimavanserin should be avoided in combination with them, and paliperidone's own modest QTc increase makes such combinations a reason for caution rather than a routine choice. [10][6]
2. With: CYP2D6 inhibitors
2. Effect: Risperidone depends on CYP2D6 for conversion to 9-hydroxyrisperidone, so inhibition of that polymorphic enzyme shifts the balance between parent drug and metabolite within the active moiety. [5]
3. With: Antihypertensives and other hypotensive agents

3. Effect: They compound the orthostatic hypotension, bradycardia and syncope that clozapine can cause during titration, and add to quetiapine's postural effects. [1][4]
4. With: Medicines that lower the seizure threshold
4. Effect: Listed in the clozapine boxed warning among the predisposing factors that call for caution, alongside central nervous system pathology and alcohol misuse. [1]
5. With: Anticholinergic medicines
5. Effect: They add to clozapine's own potent anticholinergic effect and so to the risk of the gastrointestinal hypomotility that can progress to ileus and its complications. [2]

Comparison tables

Title: The trade-off each agent makes

Caption: Metabolic and motor figures are drawn from each product's own trial programme, not from head-to-head studies, so they show that agents differ without ranking them precisely. Choice of agent belongs to the treating clinician.

1. Key: drug
1. Label: Drug
1. Is Row Header: true
2. Key: receptor
2. Label: Action at the dopamine receptor
3. Key: metabolic
3. Label: Labelled metabolic signal
4. Key: signature
4. Label: Signature problem
1. Drug: Clozapine
1. Receptor: D2 and 5-HT2A antagonism
1. Metabolic: 35% gained at least 7% of baseline weight; triglycerides up by a mean of 54%
1. Signature: Severe neutropenia, myocarditis, seizure and ileus, all under mandatory monitoring [2][1]
2. Drug: Olanzapine
2. Receptor: Broad antagonism including D2
2. Metabolic: 22.2% gained at least 7% over six weeks, reaching 64% with longer exposure
2. Signature: The heaviest weight and glycaemic burden in routine use [3]
3. Drug: Quetiapine
3. Receptor: Broad antagonism including D2
3. Metabolic: 23% gained at least 7% against 6% on placebo
3. Signature: Orthostatic hypotension, reduced thyroxine, and lens changes on long-term use [4]
4. Drug: Risperidone
4. Receptor: D2 and 5-HT2A antagonism
4. Metabolic: 18% gained at least 7% against 9% on placebo
4. Signature: The highest prolactin elevation of the antipsychotics, and dose-related motor effects [5]
5. Drug: Paliperidone
5. Receptor: D2 and 5-HT2A antagonism
5. Metabolic: Not separately quantified in the material reviewed here
5. Signature: Prolactin elevation like risperidone, modest QTc increase, non-deformable tablet [6]
6. Drug: Lurasidone
6. Receptor: D2 and 5-HT2A antagonism with 5-HT7 affinity
6. Metabolic: 4.8% gained at least 7%, with cholesterol and triglycerides falling on average
6. Signature: Dose-related akathisia in 13% of adults, against a light metabolic profile [9]

- 7. Drug: Aripiprazole
- 7. Receptor: Partial agonism at D2 and 5-HT1A
- 7. Metabolic: Class metabolic warning applies; no distinct figure quoted in the material reviewed
- 7. Signature: Impulse-control behaviours, particularly gambling urges [7][8]
- 8. Drug: Pimavanserin
- 8. Receptor: None; no appreciable D2 affinity
- 8. Metabolic: Not a dopamine blocker, and metabolic change is not its labelled concern
- 8. Signature: QT prolongation, and a licence confined to Parkinson's disease psychosis [10]

High-yield exam pearls

- 1. Pearl: The dementia boxed warning is a class statement, not a property of one drug, and it appears on clozapine, olanzapine, quetiapine, risperidone, paliperidone, lurasidone, aripiprazole and pimavanserin alike.
- 1. Why: Questions often attach the warning to a single agent to see whether the candidate knows it belongs to the whole class. [1][4][10][9]
- 2. Pearl: Clozapine's boxed warning has five headings, and severe neutropenia is only the first of them; orthostatic collapse, seizure, myocarditis with cardiomyopathy, and the dementia mortality signal complete it.
- 2. Why: Candidates who remember only the blood count miss the cardiac and seizure hazards that shape day-to-day clozapine practice. [1]
- 3. Pearl: Paliperidone is 9-hydroxyrisperidone, the major active metabolite of risperidone, which is why their prolactin behaviour matches.
- 3. Why: It converts a fact that looks like rote memory into a deduction, and explains why switching between the two rarely solves a prolactin problem. [6][5]
- 4. Pearl: Aripiprazole is a partial agonist at dopamine D2 and 5-HT1A receptors with antagonist activity at 5-HT2A, not a pure D2 blocker.
- 4. Why: The distinction explains its different prolactin and sedation profile and is the single most commonly tested mechanism point in this class. [8]
- 5. Pearl: Pimavanserin has no appreciable affinity for dopaminergic receptors including D2, which is exactly why it can be given in Parkinson's disease psychosis.
- 5. Why: It is the cleanest available illustration that antipsychotic effect and dopamine blockade are not the same thing. [10]
- 6. Pearl: Extrapyramidal effects in this class are dose-related, so an atypical agent at a high dose does not automatically carry less motor risk than an older agent at a modest one.
- 6. Why: The rates rise with dose in the risperidone, paliperidone and lurasidone labels, which is the evidence behind the frequent examination stem about a patient who develops akathisia after a dose increase. [5][6][9]

Common exam traps

- 1. Trap: Believing that second-generation agents do not cause tardive dyskinesia or neuroleptic malignant syndrome.
- 1. Correction: Both remain in these labels. Tardive dyskinesia is described as potentially irreversible, with risk rising with treatment duration and cumulative dose, and neuroleptic malignant syndrome is described as a potentially fatal symptom complex. [2][3]
- 2. Trap: Treating all atypical antipsychotics as equally likely to cause weight gain and diabetes.
- 2. Correction: The labelled proportions differ by agent, from 22.2% of olanzapine-treated adults gaining at least 7% of baseline weight in six-week trials down to 4.8% in a lurasidone programme, although these come from separate trials rather than direct comparison. [3][9]
- 3. Trap: Assuming an atypical agent is the safe choice for behavioural symptoms in an elderly person with dementia.
- 3. Correction: That is the population the boxed warning exists for. Mortality ran at 1.6 to 1.7 times placebo across seventeen trials, cerebrovascular events including fatal stroke were reported in risperidone dementia trials, and no

agent is approved for the indication. [5][11]

4. Trap: Describing every drug in this class as a dopamine receptor blocker.

4. Correction: Aripiprazole is a partial agonist at D2, and pimavanserin has no appreciable affinity for dopaminergic receptors at all, acting instead as an inverse agonist and antagonist at 5-HT2A. [8][10]

5. Trap: Thinking clozapine monitoring is only about the blood count.

5. Correction: Its label also requires slow initial titration because of orthostatic collapse, re-titration after even a brief interruption, active attention to bowel function because of anticholinergic hypomotility, and cardiac evaluation on suspicion of myocarditis. [1][2]

6. Trap: Assuming raised prolactin is a uniform class effect of the same magnitude.

6. Correction: Risperidone is described as associated with higher prolactin elevation than other antipsychotic agents and paliperidone matches it, whereas quetiapine shifted prolactin to a clinically significant value in only 3.6% of patients against 2.6% on placebo. [5][6][4]

Self-test questions

1. Question: Which single statement appears in the boxed warning of every atypical antipsychotic covered on this page?

1. Elderly patients with dementia-related psychosis have an increased risk of death when treated with antipsychotic drugs
2. Severe neutropenia requires an absolute neutrophil count before every dose
3. The drug prolongs the QT interval in all patients
4. Weight gain of at least 7% occurs in most treated patients

1. Explanation: The dementia mortality statement is the shared boxed warning across the class, quantified from seventeen placebo-controlled trials at 1.6 to 1.7 times the placebo risk of death. Neutropenia monitoring is specific to clozapine, and the QT and weight statements are agent-specific. [5][1][10]

2. Question: A patient with schizophrenia has failed two adequate trials of different antipsychotics. Which agent's label is written for exactly this situation?

1. Clozapine
2. Lurasidone
3. Pimavanserin
4. Paliperidone

2. Explanation: Clozapine is indicated for severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatment, and its label states that because of the risks of severe neutropenia and of seizure it should be used only in such patients. [1]

3. Question: Which of these is NOT one of the headings in clozapine's boxed warning?

1. Permanent visual field constriction
2. Severe neutropenia
3. Myocarditis, pericarditis and cardiomyopathy
4. Orthostatic hypotension, bradycardia and syncope

3. Explanation: Clozapine's boxed warning covers severe neutropenia, orthostatic hypotension with bradycardia and syncope, seizure, myocarditis with pericarditis and cardiomyopathy, and increased mortality in elderly patients with dementia-related psychosis. Visual field constriction belongs to a different drug entirely. [1]

4. Question: A patient develops galactorrhoea and amenorrhoea after starting an antipsychotic. Which agent is most characteristically implicated?

1. Risperidone
2. Aripiprazole
3. Pimavanserin
4. Quetiapine

4. Explanation: Its label states that risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents, and lists galactorrhoea, amenorrhoea, gynaecomastia and impotence among the reported consequences. Quetiapine shifted prolactin to a clinically significant value in only 3.6% of patients. [5][4]

5. Question: Which description of aripiprazole's mechanism matches its label?

1. Partial agonist activity at dopamine D2 and serotonin 5-HT_{1A} receptors with antagonist activity at 5-HT_{2A} receptors
2. Irreversible blockade of dopamine D2 receptors in the striatum
3. Selective inverse agonism at serotonin 5-HT_{2A} receptors with no dopamine affinity
4. Inhibition of dopamine reuptake at the presynaptic transporter

5. Explanation: The label states that the efficacy of aripiprazole could be mediated through a combination of partial agonist activity at dopamine D2 and serotonin 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. The third option describes pimavanserin instead. [8][10]

6. Question: Why can pimavanserin be used for psychosis in Parkinson's disease when most antipsychotics cannot?

1. It has no appreciable affinity for dopaminergic receptors including D2
2. It is a more potent D2 blocker and therefore acts at a lower receptor occupancy
3. It is cleared renally and so avoids central accumulation
4. It is given only for a short course, limiting motor harm

6. Explanation: Its label records no appreciable affinity, defined as a K_i value above 300 nanomolar, for dopaminergic receptors including D2, and attributes any effect to inverse agonist and antagonist activity at serotonin 5-HT_{2A} receptors. Sparing dopaminergic transmission is precisely the point in a disease of dopamine loss. [10]

7. Question: Which pair of agents shares a prolactin-elevating effect because one is the active metabolite of the other?

1. Risperidone and paliperidone
2. Olanzapine and quetiapine
3. Clozapine and aripiprazole
4. Lurasidone and pimavanserin

7. Explanation: Paliperidone is the major active metabolite of risperidone, formed by CYP2D6 as 9-hydroxyrisperidone, and its label states that its prolactin-elevating effect is similar to that seen with risperidone. [6][5]

8. Question: A patient stabilised on clozapine misses several days of treatment and wants to restart at the previous dose. What does the label say about this situation?

1. Orthostatic hypotension, bradycardia and syncope can recur even after a brief interruption, so slow re-titration is required
2. Restarting at the previous dose is safe provided the neutrophil count is normal
3. The drug can be restarted at any dose because tolerance to hypotension is permanent
4. No neutrophil count is needed on restarting within one week

8. Explanation: The boxed warning states that these reactions can occur with the first dose, at very low doses, or when restarting patients who have had even a brief interruption in treatment, and directs slow titration with divided dosing. Any decision about restarting rests with the treating clinician. [1]

Frequently asked questions

1. Question: What actually makes an antipsychotic "atypical"?

1. Answer: Historically it meant a lower burden of movement disorder, and UK regulators still describe the newer agents as less likely to cause movement disorders than the older ones. Pharmacologically the group is held together by action at serotonin 5-HT_{2A} receptors alongside dopamine, but the members do not share one mechanism: most are antagonists, aripiprazole is a partial agonist at D2, and pimavanserin does not engage dopamine receptors at all. [11][8][10]

2. Question: If clozapine works where other antipsychotics fail, why is it not used first?

2. Answer: Because of what its label demands in return. Severe neutropenia restricts supply to a monitoring programme with a defined neutrophil threshold before treatment starts; seizures are dose-related; fatal myocarditis and

cardiomyopathy have occurred; and orthostatic collapse limits how quickly it can be introduced. Its indication is therefore written for patients who have already failed standard antipsychotic treatment. [1]

3. Question: Are the metabolic effects the same for every drug in this group?

3. Answer: No, and the differences are large enough to drive prescribing. The labelled proportion of adults gaining at least 7% of baseline weight ranges from 22.2% in six-week olanzapine trials and 23% in quetiapine trials down to 4.8% in a lurasidone programme, and clozapine data show a mean triglyceride rise of 54%. These come from separate trial programmes, so they establish that agents differ rather than fixing an exact order. [3][4][9][2]

4. Question: Why are these drugs not used for agitation in dementia?

4. Answer: Because the evidence of harm in that population is what produced the class boxed warning. Pooled trials showed death rates of about 4.5% against 2.6% on placebo over ten weeks, cerebrovascular events including fatalities were reported in risperidone trials in elderly patients with dementia-related psychosis, and UK regulators describe a clear increase in stroke risk. No agent in this class holds an approval for that indication. [5][11]

5. Question: Does the lower rate of movement disorders mean extrapyramidal effects can be ignored?

5. Answer: No. Akathisia occurred in 13% of adults in lurasidone schizophrenia studies against 3% on placebo, with the rate rising as the dose rose, risperidone's fixed-dose trials ran up to 31% for extrapyramidal symptoms at the highest dose against 11% on placebo, and paliperidone lists akathisia, dystonia and parkinsonism among the reactions that increased with dose. [9][5][6]

6. Question: Is a raised prolactin level always a reason to change drug?

6. Answer: Not automatically, and the page does not offer a rule. What the labels establish is that the liability differs sharply: risperidone is associated with higher prolactin elevation than other antipsychotic agents, paliperidone behaves similarly as its metabolite, and long-standing hyperprolactinaemia with hypogonadism has been linked to reduced bone density. Whether that matters for a given patient, and what follows, is a judgement for the treating clinician. [5][6]

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[11] Antipsychotic medicines: licensed products, uses and side effects. Medicines and Healthcare products Regulatory Agency (GOV.UK) .

<https://www.gov.uk/government/publications/antipsychotic-medicines-licensed-products-uses-and-side-effects/antipsychotic-medicines>

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