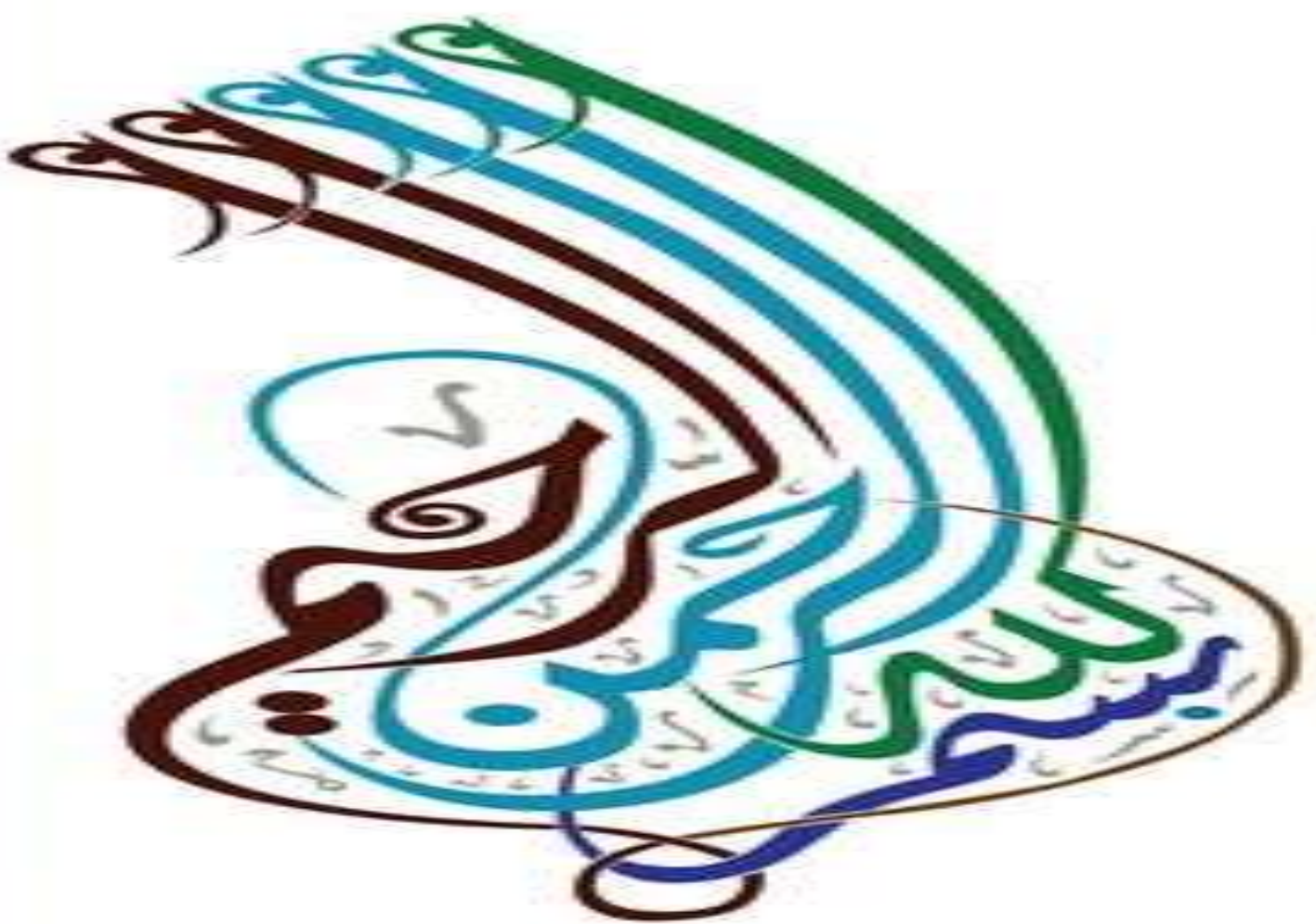




Clinical Psychopharmacology

A Practical Approach in the Hospitalized Patient

From Pharmacology to Better Patient Care



Antipsychotics

Psychosis • Agitation • Delirium

- FGA vs SGA
- Mechanism & dopamine pathways
- PK, dose adjustment, drug interactions
- Adverse effects & monitoring
- Clozapine
- Use in inpatient setting

Right patient. Right drug. Right monitoring.



Anxiolytics

Anxiety • Agitation • Insomnia

- Benzodiazepines
- Non-benzodiazepine anxiolytics (buspirone, hydroxyzine)
- PK and clinical differences
- Adverse effects, dependence & withdrawal
- Use in acute vs chronic anxiety
- Role in hospitalized patients

Relieve distress. Minimize harm.



Stimulants

ADHD • Narcolepsy • Special Indications

- Methylphenidate
- Amphetamines (including lisdexamfetamine)
- Mechanism & clinical uses
- PK, metabolism & elimination
- Adverse effects & misuse potential
- Cardiovascular and psychiatric risks
- Use and monitoring in clinical practice

Focus on benefit. Be alert to risk.



Pharmacokinetics & Pharmacodynamics

What the body does to the drug and what the drug does to the body



Hepatic Impairment

Drug-specific dose adjustment



Renal Impairment

Drug-specific dose adjustment



Older Adults

Greater sensitivity, unique risks



Drug Interactions

Think beyond the prescription



Inpatient Considerations

Agitation • Delirium
Medical comorbidities
Practical decision-making



Evidence. Clinical Judgment. Individualized Care.



*Safer Patients
Healthier Tomorrows*



Presented by: **Dr. Soha Solgi**
Pharmacist, PhD candidate of toxicology



Main References:

- Goodman & Gilman, 14th ed.
- UpToDate
- NICE Guidelines

*Knowledge Today
Better Patient Care Tomorrow*

*Same
Patients
Better
Outcomes*

*Better
Choices
for
Real Patients*

Roadmap & Learning Objectives

A Structured Approach for Real-World Practice

*Same
Patients
Better
Outcomes*

One Patient
Many Decisions
Pharmacology
Makes a Difference



*"Better
Pharmacology.
Safer Patients."*

- 1 **Antipsychotics**
Mechanism, clinical use, PK, adverse effects, and inpatient application 
- 2 **Anxiolytics**
Benzodiazepines and non-benzodiazepines, PK, clinical use and risks 
- 3 **Stimulants**
Mechanism, indications, PK, adverse effects and misuse potential 
- 4 **Pharmacokinetics & Pharmacodynamics**
What the body does to the drug – and what the drug does to the body 
- 5 **Special Populations & Organ Impairment**
Older adults, renal and hepatic impairment, dose adjustment 
- 6 **Drug Interactions**
Pharmacodynamic and pharmacokinetic interactions in clinical practice 
- 7 **Clinical Application in the Hospitalized Patient**
Agitation, delirium, comorbidities, monitoring and practical decision-making 



Learning Objectives

- 1 Select the most appropriate antipsychotic, anxiolytic, or stimulant based on patient characteristics and clinical context.
- 2 Apply key pharmacokinetic and pharmacodynamic principles to dose selection and monitoring.
- 3 Recognize and manage major adverse effects and drug interactions.
- 4 Adjust therapy in special populations (older adults, renal and hepatic impairment).
- 5 Use a practical, evidence-based approach in the hospitalized patient (e.g., agitation, delirium).
- 6 Improve patient safety and outcomes through individualized, rational pharmacotherapy.



Different Drugs. Different Patients. A Smarter, Safer Approach.



Presented by: **Dr. Soha Solgi**
Pharmacist, PhD candidate of toxicology



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Antipsychotics

Classification, Mechanism and Clinical Uses

From Dopamine to Better Outcomes

Same
Patients
Better
Outcomes



What are antipsychotics?

- Medications that primarily reduce the positive symptoms of psychosis (e.g., hallucinations, delusions) by modifying dopaminergic and other neurotransmitter systems.
- Also used for agitation, acute mania, and adjunctive therapy in selected conditions.
- Choice of agent depends on efficacy, side effect profile, patient characteristics, and prior response.



Mechanism of action

- Most antipsychotics antagonize dopamine D₂ receptors (particularly in mesolimbic pathway) → reduction in positive symptoms.
- Many second-generation agents (SGAs) also antagonize 5-HT_{2A} receptors → may improve efficacy and reduce EPS risk.
- Aripiprazole is a D₂ partial agonist (stabilizes dopaminergic signaling).
- Additional actions: antagonism at α₁-adrenergic, histamine H₁, and muscarinic receptors (vary by agent and contribute to both therapeutic effects and adverse effects).



Major clinical uses



Schizophrenia
(acute and maintenance)



Other psychotic disorders
(e.g., schizoaffective disorder)



Acute mania (bipolar disorder)



Severe agitation (selected situations)



Delirium (short-term use in specific cases)



Adjunctive use (e.g., treatment-resistant schizophrenia: clozapine)



"Target symptoms.
Individualize care.
Minimize harm."

Classification of Antipsychotics

First-Generation Antipsychotics (FGA)		Second-Generation Antipsychotics (SGA)		D ₂ Partial Agonist	
Typical Antipsychotics		Atypical Antipsychotics		Atypical Antipsychotic	
Mechanism	D ₂ receptor antagonism (high potency)	Mechanism	D ₂ antagonism + 5-HT _{2A} antagonism (variable receptor profile)	Mechanism	Partial agonism at D ₂ receptors (+ 5-HT _{1A} agonism, 5-HT _{2A} antagonism)
Examples	Haloperidol, Chlorpromazine, Fluphenazine, Perphenazine	Examples	Risperidone, Olanzapine, Quetiapine, Clozapine, Ziprasidone, Aripiprazole, Lurasidone, Paliperidone, Asenapine, Iloperidone	Example	Aripiprazole
Key features	- Higher risk of EPS - Higher prolactin elevation - Generally less metabolic effects	Key features	- Lower risk of EPS (except some, e.g., risperidone) - Greater metabolic risk (e.g., olanzapine, clozapine) - Variable effects on prolactin and QT	Key features	- Lower risk of EPS and prolactin elevation - Lower metabolic risk (compared with some SGAs) - May be activating (insomnia, akathisia)
Common brand examples	Haldol® (haloperidol), Largactil® (chlorpromazine), Prolixin® (fluphenazine)	Common brand examples	Risperdal® (risperidone), Zyprexa® (olanzapine), Seroquel® (quetiapine), Clozaril® (clozapine), Abilify® (aripiprazole)	Common brand example	Abilify® (aripiprazole)



Key Points

- Efficacy and side effect profile vary between individual drugs.
- Antipsychotics are not a routine treatment for all cases of delirium.
- Selection should be based on patient characteristics, prior response, risk factors, and treatment setting.
- Always consider monitoring for metabolic, neurologic, endocrine, and cardiac adverse effects.



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Main References:

- Goodman & Gilman, 14th ed. (Ch. 19)
- UpToDate – Antipsychotic medications: Overview
- NICE Guideline CG178 – Psychosis and schizophrenia in adults

Knowledge Today
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Dopamine Pathways in the Brain

Functions, Clinical Relevance, and Effects of Antipsychotics

Same Patients
Better Outcomes



Mesolimbic Pathway

(VTA → Nucleus accumbens, limbic structures)

- **Function:** reward, motivation, salience, emotion.
- **Hyperactivity:** associated with positive symptoms of schizophrenia (hallucinations, delusions).
- **Effect of antipsychotics:** D₂ receptor antagonism reduces dopaminergic activity → improves positive symptoms.



Mesocortical Pathway

(VTA → Prefrontal cortex)

- **Function:** cognition, executive function, affect, motivation.
- **Hypoactivity:** associated with negative symptoms (apathy, avolition, social withdrawal) and cognitive impairment.
- **Effect of antipsychotics:** D₂ blockade may be ineffective or potentially worsen negative and cognitive symptoms; clinical effects vary by agent. Agents with 5-HT_{2A} antagonism or D₂ partial agonism (e.g., aripiprazole) may have beneficial effects in some patients.



Nigrostriatal Pathway

(Substantia nigra → Dorsal striatum)

- **Function:** motor control, habit formation.
- **Effect of D₂ blockade:** extrapyramidal symptoms (EPS) including acute dystonia, parkinsonism, akathisia, and tardive dyskinesia.
- **Risk:** higher with high-potency FGAs; lower with most SGAs (except risperidone and some others).

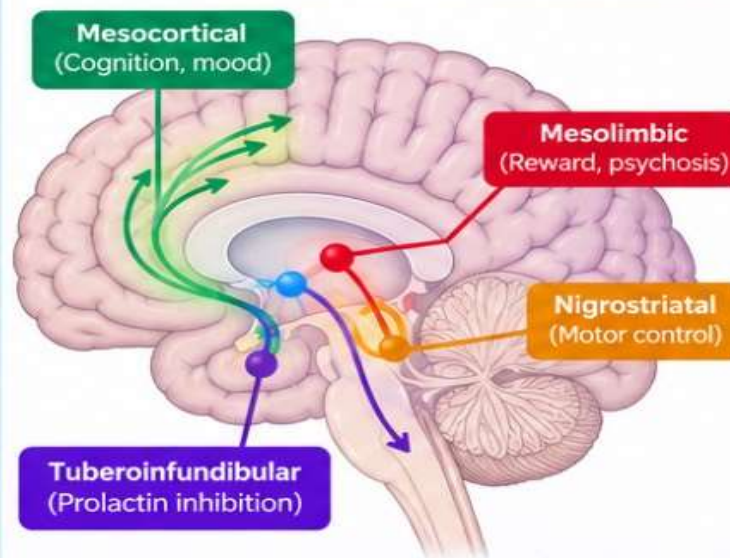


Tuberoinfundibular Pathway

(Hypothalamus → Anterior pituitary)

- **Function:** inhibits prolactin release (tonic dopaminergic inhibition).
- **Effect of D₂ blockade:** hyperprolactinemia (galactorrhea, amenorrhea, gynecomastia, sexual dysfunction).
- **Risk:** higher with FGAs and risperidone; lower with quetiapine, clozapine, and aripiprazole.

Major Dopaminergic Pathways



Different pathways. Different effects.
Individualized treatment.



Key Points

- Antipsychotics primarily reduce positive symptoms by blocking D₂ receptors in the mesolimbic pathway.
- Negative and cognitive symptoms are related to mesocortical hypodopaminergia and are less responsive to D₂ blockade.
- EPS result from D₂ blockade in the nigrostriatal pathway (risk varies by agent and dose).
- D₂ blockade in the tuberoinfundibular pathway can cause hyperprolactinemia.
- Antipsychotics also act on 5-HT_{2A}, histamine H₁, muscarinic, and α₁-adrenergic receptors, which contribute to both therapeutic effects and adverse effects.
- Understanding dopamine pathways helps guide drug selection and anticipate adverse effects.

Summary of Clinical Consequences

Pathway	Normal function	Effect of ↑ dopamine activity (e.g., in psychosis)	Effect of D ₂ blockade (antipsychotics)
Mesolimbic	Reward, motivation	Positive symptoms (hallucinations, delusions)	↓ Positive symptoms (therapeutic effect)
Mesocortical	Cognition, executive function, affect	— (often decreased activity in schizophrenia)	May be neutral, beneficial with some agents, or potentially worsen negative/cognitive symptoms
Nigrostriatal	Motor control	—	EPS (dystonia, parkinsonism, akathisia, tardive dyskinesia)
Tuberoinfundibular	Inhibits prolactin release	—	Hyperprolactinemia (endocrine adverse effects)



Clinical Pearl

- The therapeutic effects and adverse effects of antipsychotics are largely, but not exclusively, related to their effects on dopaminergic pathways. Serotonergic, histaminergic, muscarinic, and adrenergic actions also play important roles.
- Choice of antipsychotic should be individualized based on patient characteristics, symptom profile, and risk of adverse effects.



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- UpToDate: Antipsychotic medications: Overview of use and mechanism of action
- NICE Guideline CG178: Psychosis and schizophrenia in adults

Knowledge Today
Better Patient Care Tomorrow

Antipsychotic Pharmacokinetics

Absorption, Distribution, Metabolism, Elimination and Common Brands (Evidence-Based)

Same Patients Better Outcomes

Absorption

- Most antipsychotics are well absorbed after oral administration, but bioavailability varies by agent (~9–95%).
- Time to peak concentration (Tmax) is typically 0.5–6 hours (varies by agent).
- Food effects are drug-specific** (e.g., lurasidone must be taken with food; others: minimal or no significant effect).
- Onset of clinical effect: typically 1–2 weeks; full effect may take 4–6 weeks.

Distribution

- Widely distributed throughout the body, including the brain (crosses the blood–brain barrier).
- Large apparent volume of distribution (Vd) (varies by agent; e.g., 3–20 L/kg).
- Protein binding is high for most agents (range ~20–99%); quetiapine and paliperidone have lower binding.
- Crosses the placenta; present in breast milk (concentrations vary by drug).

Metabolism

- Most antipsychotics are metabolized in the liver, mainly by CYP enzymes.
- Common enzymes: CYP1A2, CYP2D6, CYP3A4 (agent-specific).
- Some agents have active metabolites (e.g., risperidone → 9-OH-risperidone; cariprazine → desmethyl-cariprazine, didesmethyl-cariprazine).
- CYP inhibitors or inducers can significantly alter plasma concentrations.
- Paliperidone is minimally metabolized and is primarily renally excreted.

Elimination

- Elimination occurs via renal and/or fecal routes (varies by agent).
- Terminal half-life (t½) ranges from ~1 hour to several days (agent-specific).
- Steady state is typically reached in 4–5 half-lives (longer for agents with long t½).
- Dose adjustment may be required in hepatic or renal impairment (agent-specific).
- Many antipsychotics and their metabolites are excreted in urine; clozapine and quetiapine have more fecal elimination.

Pharmacokinetic Properties of Common Antipsychotics (Based on UpToDate, 2024)										
	Drug (Class)	Oral Bioavailability (%)	Tmax (hours)	Protein Binding (%)	Major Metabolism (CYP)	Active Metabolite(s)	Elimination t½ (hours)	Primary Route(s) of Elimination	Food Effect	Common Brand Name(s)
First-Generation Antipsychotics (FGAs)	Haloperidol	~60–70	2–6	~92	CYP3A4, CYP2D6	No (inactive metabolites)	12–36	Renal (metabolites)	None significant	Haldol®
	Chlorpromazine	~20–35	2–6	~95	CYP2D6, CYP1A2, CYP3A4	No (inactive)	16–30	Renal and fecal	May ↑ absorption (with food)	Largactil®
	Fluphenazine	~60–70	2–4	~90	CYP2D6	No (inactive)	14–24	Renal (metabolites)	None significant	Prolixin®
	Perphenazine	~60–70	2–4	~93	CYP2D6	No (inactive)	9–12	Renal (metabolites)	None significant	Trilafon®
Second-Generation Antipsychotics (SGAs)	Risperidone	~70	1	~90	CYP2D6 (major), CYP3A4	9-OH-risperidone (active)	Parent: ~3 Active moiety: ~20	Renal (mostly as metabolites)	None significant	Risperdal®
	Paliperidone	~28	1–3	~74	Minimal metabolism	No (active parent)	~23	Renal (unchanged)	None significant	Invega®
	Olanzapine	~60	5–8	~93	CYP1A2 (major), UGT1A4	No (inactive)	21–54	Renal and fecal	None significant	Zyprexa®
	Quetiapine	~9	1–2	~83	CYP3A4	No (inactive)	6–7	Renal (metabolites)	None significant	Seroquel®
	Clozapine	~27–50	1.5–3	~95	CYP1A2 (major), CYP3A4, CYP2D6	No (inactive)	~12	Renal and fecal	None significant	Clozaril®
	Ziprasidone	~60	6–8	~99	Aldehyde oxidase (minor), CYP3A4	No (inactive)	7–10	Fecal (major), renal	Take with food (↑ ~50% exposure)	Geodon®
	Aripiprazole	~87	3–5	~99	CYP2D6, CYP3A4	Dehydroaripiprazole (active)	~75	Renal (metabolites)	None significant	Abilify®
	Lurasidone	Not reported*	1–3	~99	CYP3A4	No (inactive)	~18	Renal (metabolites)	Must be taken with food (≥350 kcal)	Latuda®
	Iloperidone	~60	1–3	~93	CYP2D6, CYP3A4	No (inactive)	18–30	Renal (metabolites)	None significant	Fanapt®
	Asenapine	~35	0.5–1.5 (sublingual)	~95	CYP1A2 (major), UGT1A4	No (inactive)	~24	Fecal (major)	Avoid food/drink 10 min after dose	Saphris®
	Brexipiprazole	~95	4	~99	CYP2D6, CYP3A4	No (inactive)	~91	Renal (metabolites)	None significant	Rexulti®
	Cariprazine	~>90	1–4	~99	CYP3A4	Desmethyl-cariprazine (active) didesmethyl-cariprazine (active)	Parent: 2–4 days Active metabolites: 1–3 weeks	Fecal (major)	None significant	Vraylar®

Key Points

- Pharmacokinetic parameters vary considerably among antipsychotics; always consider agent-specific characteristics.
- CYP450 inhibitors/inducers and patient factors (age, smoking, hepatic/renal impairment, pregnancy) can alter plasma concentrations.
- Formulation and route (oral, ODT, IM, LAI) and food effects should be considered to optimize efficacy and adherence.
- Dose adjustment may be necessary in hepatic or renal impairment, depending on the agent.
- Therapeutic drug monitoring is not routinely required, but may be useful for clozapine and in special circumstances.

Clinical Pearl

- When selecting an antipsychotic, consider pharmacokinetics, drug–drug interactions, patient characteristics, and formulation options to individualize treatment and minimize adverse effects.
- Lurasidone must be taken with food; asenapine is sublingual.
- Paliperidone is primarily renally excreted.
- Cariprazine has a long half-life (active metabolites) and reaches steady state slowly.
- TDM is recommended for clozapine and may be useful for others.

* For lurasidone, oral bioavailability is not well defined; a fraction absorbed of ~9–19% has been reported. Food increases systemic exposure (Cmax and AUC) significantly.

Adverse Effects of Antipsychotics

Recognize, Monitor, and Manage for Safer and Better Outcomes (Based on UpToDate 2024; NICE CG178, 2014/2019)

Same Patients
Better
Outcomes



Extrapyramidal Symptoms (EPS)

- **Risk is agent- and dose-dependent.**
- **FGAs** have higher EPS liability, but some SGAs (e.g., risperidone, paliperidone, iloperidone) can cause clinically significant EPS, especially at higher doses.
- **Includes:** acute dystonia (hours-days), parkinsonism (days-weeks), akathisia (days-weeks), and tardive dyskinesia (months-years; may be irreversible).
- **Risk factors:** high D2 blockade, higher doses, older age, female sex, prior EPS, organic brain disease.
- **Management:** dose reduction, switch agent, anticholinergics (for acute dystonia/parkinsonism), β -blockers (for akathisia), VMAT2 inhibitors (for TD).



Metabolic Effects

- **Weight gain** (variable; highest with clozapine and olanzapine).
- **Dyslipidemia** ($\uparrow$ triglycerides, LDL; $\downarrow$ HDL).
- **Hyperglycemia** and increased risk of type 2 diabetes.
- **Metabolic syndrome and cardiovascular risk.**
- **Risk factors:** clozapine/olanzapine, baseline obesity, family history, older age.
- **Management:** baseline and periodic monitoring (weight/BMI, waist circumference, BP, fasting glucose/HbA1c, lipids); lifestyle interventions; consider switching to lower-risk agent if needed.



Hyperprolactinemia

- Caused by D2 receptor blockade in the tuberoinfundibular pathway.
- **Clinical effects:** amenorrhea, galactorrhea, gynecomastia, sexual dysfunction, infertility, decreased bone mineral density (with long-term use).
- **Highest risk:** risperidone, paliperidone, amisulpride.
- **Moderate risk:** typical antipsychotics, iloperidone.
- **Low/minimal risk:** clozapine, olanzapine, quetiapine, aripiprazole (may lower prolactin).
- **Management:** consider dose reduction or switch to lower-risk agent (e.g., aripiprazole).



Cardiac Effects (QT Prolongation)

- Many antipsychotics can increase QT interval; risk is drug- and dose-dependent.
- **Higher risk:** ziprasidone, iloperidone, (thioridazine – not available in many countries), high-dose IV haloperidol.
- **Moderate risk:** quetiapine, risperidone, paliperidone, clozapine, chlorpromazine.
- **Lower risk:** aripiprazole, lurasidone, olanzapine, asenapine, brexpiprazole, cariprazine.
- **Risk factors:** pre-existing cardiac disease, electrolyte abnormalities ($\downarrow$ K, $\downarrow$ Mg), concomitant QT-prolonging drugs.
- **Management:** avoid high-risk combinations, correct electrolytes, consider baseline and follow-up ECG in at-risk patients.



Anticholinergic Effects

- Due to muscarinic receptor blockade.
- **Common effects:** dry mouth, blurred vision, constipation, urinary retention, tachycardia, cognitive impairment (especially in older adults).
- **Higher anticholinergic burden:** clozapine, olanzapine, chlorpromazine, quetiapine (moderate); lower with aripiprazole, lurasidone, ziprasidone.
- Risk of delirium and worsening cognition in elderly patients.
- **Management:** choose lower-burden agent in high-risk patients; monitor bowel and urinary function.



Neuroleptic Malignant Syndrome (NMS)

- **Rare** but life-threatening idiosyncratic reaction (D2 blockade).
- **Features:** hyperthermia, "lead-pipe" rigidity, altered mental status, autonomic instability, $\uparrow$ CK, leukocytosis.
- **Risk factors:** high-potency agents, rapid dose escalation, dehydration, parenteral use, agitation.
- **Management:** immediate discontinuation, supportive care (IV fluids, cooling), consider dantrolene or bromocriptine.



Hematologic Toxicity (Clozapine)

- **Agranulocytosis risk is greatest during the first several months** (especially first 18 weeks), but can occur later.
- **Other:** neutropenia, seizures (dose-related), myocarditis (typically early in treatment), cardiomyopathy, severe constipation/ileus, sialorrhea, metabolic effects.
- **ANC monitoring:** still recommended (frequency per guidelines; REMS no longer required in the U.S. since 2025, but monitoring remains standard practice).



Other Important Adverse Effects

- **Sedation:** common with clozapine, quetiapine, olanzapine, chlorpromazine.
- **Orthostatic hypotension:** higher with FGAs, clozapine, quetiapine.
- **Lower seizure threshold:** clozapine (highest), others (dose-related).
- **Sexual dysfunction:** may occur with many agents.
- **Hyponatremia (SIADH):** reported with some SGAs (e.g., risperidone, olanzapine).
- **Hepatic effects:** usually mild, monitor LFTs if risk factors.
- **Falls and fractures:** increased risk, especially in elderly.

Relative Risk of Major Adverse Effects by Antipsychotic (Evidence-Based, Approximate)

	Drug (Class)	EPS	Metabolic Effects (Weight Gain/Diabetes)	Hyperprolactinemia	QT Prolongation	Anticholinergic Effects	Notable Specific Risks/Comments
First-Generation Antipsychotics (FGAs)	Haloperidol	High	Low	Moderate	Moderate	Low	High EPS risk; consider ECG with IV/high doses
	Chlorpromazine	Moderate	Moderate	Moderate	Moderate	High	Sedation, hypotension, anticholinergic effects
	Fluphenazine	High	Low	Moderate	Low-Moderate	Low	High EPS risk
	Perphenazine	Moderate-High	Low	Moderate	Low-Moderate	Low	High EPS risk
Second-Generation Antipsychotics (SGAs)	Risperidone	Moderate	Moderate	High	Moderate	Low	Dose-related EPS and prolactin increase
	Paliperidone	Moderate	Moderate	High	Moderate	Low	Renal elimination; dose adjustment
	Olanzapine	Low	High	Low	Low-Moderate	Moderate	High metabolic risk
	Quetiapine	Low	Moderate	Low	Moderate	Moderate	Sedation, orthostatic hypotension
	Clozapine	Low	High	Low	Low	High	Agranulocytosis, myocarditis, seizures, severe constipation
	Ziprasidone	Low	Low	Low	High	Low	Take with food ($\uparrow$ absorption)
	Aripiprazole	Low	Low	Low (may $\downarrow$ prolactin)	Low	Low	Akathisia (common)
	Lurasidone	Low	Low	Low	Low	Low	Take with food ($\uparrow$ absorption)
	Iloperidone	Moderate	Moderate	Moderate	High	Low	Orthostatic hypotension, QT risk
	Asenapine	Low	Low-Moderate	Low	Low-Moderate	Low	Sublingual (avoid food/drink 10 min)
	Brexpiprazole	Low	Low	Low	Low	Low	Akathisia (less than aripiprazole)
	Cariprazine	Low	Low	Low	Low	Low	Long half-life (active metabolites)



Key Points

- Adverse effect profiles are agent-specific; avoid overgeneralization within FGAs or SGAs.
- Monitor at baseline and periodically: weight/BMI, waist circumference, BP/pulse, fasting glucose/HbA1c, lipid profile, prolactin (if symptomatic), and movement disorders (AIMS).
- Consider baseline ECG in at-risk patients (cardiac history, electrolyte abnormalities, concomitant QT-prolonging drugs, or inpatient admission).
- Use the lowest effective dose and individualize treatment based on patient factors and adverse effect risk.
- Early recognition and proactive management improve adherence and long-term outcomes.



Clinical Pearl

- No antipsychotic is free of adverse effects.
- Choose the right agent for the right patient, not the "strongest" agent.
- Regular monitoring and patient education are essential.
- Address modifiable risk factors (e.g., weight, smoking, drug interactions).
- When adverse effects occur, consider dose reduction, switching, or adjunctive treatments rather than automatic discontinuation.



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Key References:

- UpToDate. Antipsychotic medications: Adverse effects. (2024).
- NICE Guideline CG178: Psychosis and schizophrenia in adults. (2014, updated 2019).
- Stahl SM. Prescriber's Guide to Antipsychotics. (7th ed. 2024).

Knowledge Today
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Baseline Assessment

- Clinical:** psychiatric history, previous response, adverse effects, comorbidities, concomitant medications, substance use (including smoking), pregnancy status (if relevant).
- Physical:** weight (BMI), waist circumference, blood pressure, pulse, temperature (if infection suspected).
- Laboratory:** fasting glucose (or HbA1c), fasting lipid profile, prolactin, U&E, LFTs (and FBC if clozapine).
- Cardiac:** ECG if indicated (see below).
- Movement assessment:** baseline for EPS/tardive dyskinesia (e.g., AIMS if appropriate).

Ongoing Monitoring

- Weight:** weekly for first 6 weeks, then at 12 weeks, 1 year, and annually.
- Waist circumference:** at baseline, 1 year, and annually.
- Blood pressure and pulse:** at 12 weeks, 1 year, and annually (more often during titration/dose changes if indicated).
- Fasting glucose or HbA1c:** at 12 weeks, 1 year, and annually.
- Fasting lipid profile:** at 12 weeks, 1 year, and annually.
- Prolactin:** if symptomatic or using high-risk agent (e.g., risperidone, paliperidone, amisulpride).
- Movement disorders:** regular assessment (e.g., AIMS) at least annually and more often if symptoms emerge.
- ECG:** as clinically indicated (see below).

When to Take Action

- Significant weight gain** (e.g., $\geq 7\%$ of baseline): consider lifestyle intervention, review drug choice, or switch.
- New-onset diabetes or dyslipidemia:** manage according to guidelines; consider switch to lower-risk agent.
- Elevated prolactin with symptoms** (e.g., amenorrhea, sexual dysfunction): consider dose reduction, switch to lower-prolactin agent (e.g., aripiprazole), or endocrine referral.
- Emerging or troublesome EPS/tardive dyskinesia:** adjust dose, consider switch, or add symptomatic treatment.
- Marked QT prolongation:** review risk factors, correct electrolytes, review interacting drugs, consider dose reduction or switch; seek cardiology advice when appropriate.
- Signs of NMS:** immediate discontinuation and urgent medical management.

Patient Education

- Explain expected benefits and possible adverse effects.
- Discuss the importance of adherence and not stopping medication abruptly.
- Advise on **healthy lifestyle:** balanced diet, regular physical activity, weight control, and avoiding excessive alcohol.
- Inform about symptoms to report early (e.g., muscle stiffness, fever, palpitations, sexual dysfunction, menstrual changes).
- Discuss the impact of **smoking** on drug levels (may require higher doses of some antipsychotics, e.g., clozapine, olanzapine).
- Provide written information and involve family/carers when appropriate.

Monitoring Schedule by Parameter (Based on NICE CG178, 2014/2019)						
Parameter	Baseline	First 6 Weeks	12 Weeks	1 Year	Annually	Additional Notes
Weight / BMI	✓	Weekly	✓	✓	✓	Monitor more frequently if rapid weight gain.
Waist circumference	✓	–	–	✓	✓	Use in addition to BMI.
Blood pressure / Pulse	✓	–	✓	✓	✓	More often during titration/dose changes or if clinically indicated.
Fasting glucose or HbA1c	✓	–	✓	✓	✓	Follow diabetes management guidelines if abnormal.
Fasting lipid profile	✓	–	✓	✓	✓	Manage according to cardiovascular risk guidelines.
Prolactin	✓	–	–	–	If indicated	Repeat if symptoms or high-risk agent.
Movement disorders (e.g., AIMS)	✓	Regularly (clinical review)	✓	Regularly	Regularly	More frequent if symptoms or high-risk agent.
ECG	If indicated	–	–	–	As indicated	If cardiovascular risk, QT-prolonging drugs, inpatient, or symptoms (e.g., syncope).

Key Points

- Monitoring should be individualized based on patient risk factors, the specific antipsychotic, and clinical context.
- Follow NICE-recommended schedule for metabolic, cardiovascular, and movement-disorder monitoring.
- Use the lowest effective dose and consider switching to a lower-risk agent when clinically appropriate.
- Early detection and management of adverse effects improves adherence and long-term outcomes.
- Collaborate with primary care, cardiology, endocrinology, and other specialists as needed.

Clinical Pearl

- Do not stop antipsychotics abruptly (risk of relapse, withdrawal, or NMS).
- Address modifiable risk factors (obesity, smoking, sedentary lifestyle).
- Regular monitoring is a clinical priority, not optional.
- Clozapine requires ongoing ANC monitoring (per local guidelines), even though REMS was discontinued in the U.S. (2025).

Cytochrome P450–Mediated Interactions

Enzyme	Antipsychotics (clinically relevant)	Effect of inhibitors	Effect of inducers
CYP1A2	Clozapine, Olanzapine	↑ levels (risk of toxicity)	↓ levels (e.g. smoking ¹)
CYP2D6	Risperidone (→ paliperidone), Aripiprazole, Haloperidol	↑ levels (risk of EPS, prolactin elevation)	↓ levels (reduced efficacy)
CYP3A4	Quetiapine, Lurasidone, Cariprazine, Asenapine (minor), Ziprasidone (minor)	↑ levels (e.g. ketoconazole, clarithromycin)	↓ levels (e.g. carbamazepine, St John's wort)

- **Paliperidone** is not significantly metabolised by CYP enzymes (primarily renal excretion); therefore, CYP interactions are not clinically relevant for paliperidone.
- The extent of interaction varies between agents; always check the specific product information (SmPC).

Important Interacting Drugs

Interacting drug/class	Effect and clinical recommendation
Strong CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)	↑ clozapine/olanzapine levels → consider dose reduction and monitor for toxicity.
Strong CYP2D6 inhibitors (e.g. fluoxetine, paroxetine, bupropion, quinidine)	↑ risperidone, aripiprazole, haloperidol levels → consider dose reduction and monitor for adverse effects.
Strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin)	↑ quetiapine, lurasidone, cariprazine (and others) → consider dose reduction. Lurasidone: contraindicated with strong CYP3A4 inhibitors.
CYP inducers (e.g. carbamazepine, phenytoin, rifampicin, St John's wort)	↓ levels of many antipsychotics → often avoid combination. If co-administration is unavoidable, close monitoring and dose adjustment based on clinical response (and TDM where available).
Lithium	May increase risk of neurotoxicity and NMS-like reactions → use with caution and monitor closely.



Smoking and Antipsychotics

- Cigarette smoke (polycyclic aromatic hydrocarbons) induces CYP1A2 → ↓ clozapine and olanzapine levels (may decrease exposure substantially, ~30–50%; magnitude varies).
- Nicotine itself (e.g. NRT, e-cigarettes) does not induce CYP1A2.
- If a patient stops or reduces smoking, antipsychotic levels may increase → consider dose reduction and closer monitoring.



Other Clinically Relevant Interactions

- Additive CNS depression with alcohol, benzodiazepines, opioids and sedating antihistamines.
- Additive hypotensive effect with antihypertensives.
- Increased risk of QT prolongation with other QT-prolonging drugs (e.g. antiarrhythmics, macrolides, fluoroquinolones) → review risk factors and monitor (e.g. ECG).
- Metabolic effects may be additive with other weight-promoting or dyslipidaemia-inducing drugs (e.g. corticosteroids, valproate).



Key Points for Clinical Practice

- Always review the full medicine list (including OTC and herbal products).
- Check the specific product information for each antipsychotic (interaction profile varies).
- Consider therapeutic drug monitoring (TDM) (e.g. clozapine, where available) in complex situations.
- Monitor for loss of efficacy or adverse effects when starting, stopping or changing interacting drugs.
- Educate patients about smoking, alcohol and potential interactions.

Drug–Drug and Other Important Interactions with Antipsychotics (2/2)

Special situations and practical considerations

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(of 2)



Smoking and Antipsychotics

- Cigarette smoke (polycyclic aromatic hydrocarbons) **induces CYP1A2** → ↓ **clozapine** and **olanzapine** levels (may decrease exposure by ~30–50%; magnitude varies).
- Nicotine replacement therapy (NRT), e-cigarettes and other nicotine-containing products do **not induce** CYP1A2.
- If a patient stops or reduces smoking, antipsychotic levels may **increase** → monitor and consider dose reduction.



CNS Depressants

- Additive CNS depression with benzodiazepines, opioids, alcohol and sedating antihistamines.
- Increased risk of sedation, respiratory depression and psychomotor impairment.
- Use the lowest effective doses and monitor.
- Advise patients to avoid hazardous activities (e.g. driving).



General Points

- **Interactions** are often **drug-specific** – not all antipsychotics are affected in the same way.
- Check for interactions with all prescribed, OTC and herbal medicines (e.g. St John's wort).
- Consider **therapeutic drug monitoring (TDM)** where available (e.g. clozapine, and in complex situations).
- Monitor for clinical response and adverse effects after starting, stopping or changing interacting drugs.
- Always review the full **medication list**, including OTC and herbal products.
- Provide **patient education** on potential interactions (e.g. smoking, alcohol, OTC drugs) and the importance of adherence and informing healthcare providers about all medicines.



Lithium and Antipsychotics

- Combination may increase risk of neurotoxicity and NMS-like reactions (e.g. confusion, encephalopathy, EPS).
- Use with caution, especially in older adults or those with medical comorbidity.
- Monitor closely for signs of toxicity (clinical status, renal function, lithium levels).



QT-Prolonging Drugs

- Additive effect → ↑ risk of QT prolongation and *torsades de pointes*.
- Examples: class Ia/III antiarrhythmics, macrolides, fluoroquinolones, methadone and other QT-prolonging drugs.
- Review all risk factors, correct electrolyte abnormalities, consider ECG monitoring and use alternative drugs where possible.

Monitoring and Safety of Antipsychotics

What to monitor, when to monitor, and why

Slide 10
(of 2)



Clinical Response and Adverse Effects

- **Assess efficacy:** positive, negative and affective symptoms using a standardized scale (e.g. PANSS, CGI).
- **Monitor for adverse effects:** EPS, sedation, metabolic, endocrine (e.g. hyperprolactinaemia), anticholinergic effects, and others (e.g. orthostatic hypotension).
- **When:** baseline and at each visit (especially first 6–12 weeks, then regularly).
- Use the lowest effective dose and regularly reassess the need for ongoing treatment.



Metabolic Monitoring

- **Parameters:** weight/BMI, waist circumference, blood pressure, fasting glucose or HbA1c, and fasting lipid profile.
- **When:** baseline, at 4, 8, 12 weeks, then at least annually (more frequently with clozapine and olanzapine or if high risk).
- **Rationale:** antipsychotics (especially clozapine and olanzapine) are associated with weight gain, insulin resistance/diabetes and dyslipidaemia.
- **Interventions:** lifestyle advice, consider switching to a lower-risk antipsychotic or add-on treatment if needed.



Cardiac Monitoring (QT Interval)

- **Obtain a baseline ECG** in patients with cardiovascular risk factors (e.g. age > 65, cardiac disease, electrolyte abnormalities) or when using higher-risk antipsychotics (e.g. ziprasidone, iloperidone, high-dose haloperidol) or other QT-prolonging drugs.
- **Repeat ECG** after dose increases or when adding other QT-prolonging drugs.
- **If QTc $\geq$ 500 ms** or an increase $\geq$ 60 ms from baseline $\rightarrow$ reconsider treatment and correct modifiable risk factors.
- Also monitor and correct **electrolytes** (K^+ , Mg^{2+} , Ca^{2+}).



Other Laboratory Monitoring

- **Complete blood count (CBC):** baseline, then regularly (for clozapine: per local guidelines, e.g. weekly $\rightarrow$ monthly).
- **Liver function tests (LFTs):** baseline, then periodically (e.g. annually or more often if indicated).
- **Renal function:** baseline, then periodically (especially for renally cleared drugs, e.g. paliperidone, amisulpride).
- **Prolactin:** baseline, then if symptoms (e.g. sexual dysfunction, menstrual changes, galactorrhoea).
- **Thyroid function:** baseline, then periodically (particularly relevant with lithium augmentation).
- **Consider additional tests:** e.g. serum lithium levels (if applicable), drug levels (e.g. clozapine), or other tests based on clinical context.



Key Take-Home Messages

- 1 Monitor efficacy and adverse effects regularly using standardized tools.
- 2 Metabolic, haematological, cardiac and endocrine monitoring are essential.
- 3 Tailor monitoring to the **individual drug**, dose, patient risk factors and comorbidities.
- 4 Early detection and management of adverse effects improves adherence and outcomes.
- 5 Educate patients about the importance of regular monitoring.

Anxiolytics: Overview, Mechanisms and Clinical Use

Slide 11

Evidence-based approach to the pharmacological management of anxiety disorders



What Are Anxiolytics?

- Medications that reduce excessive anxiety, tension and associated symptoms (e.g. restlessness, autonomic arousal, insomnia).
- Used alongside psychological therapies (e.g. CBT).
- Choice of agent depends on the disorder, severity, comorbidities and risk of misuse.



Main Clinical Indications

Condition	Role of Anxiolytics
Generalized Anxiety Disorder (GAD)	- First-line pharmacological treatment: SSRI or SNRI (with psychological therapy). - If SSRI/SNRI not tolerated or ineffective: consider pregabalin (where available). - Benzodiazepines: only for short-term use in severe anxiety or crisis.
Panic Disorder	- First-line: SSRI (with or without CBT). - Benzodiazepines are not recommended for long-term treatment (risk of dependence; poorer long-term outcomes). - May be considered short-term in selected cases (e.g. severe distress at initiation of SSRI).
Social Anxiety Disorder	- First-line: SSRI (with CBT). - Alternatives: SNRI (e.g. venlafaxine). - Benzodiazepines are generally not recommended (risk of dependence, especially with chronic use).
Specific Phobias (e.g. flying, dental)	- Short-term benzodiazepine may be considered situationally (e.g. single dose for acute anxiety). - Psychological therapy is first-line.
Anxiety associated with medical conditions	Treat the underlying cause; short-term anxiolytic may be used when clinically indicated.



Key Benefits

- Reduction in anxiety symptoms and autonomic arousal.
- Can improve sleep and short-term functioning.
- Useful as short-term adjuncts while waiting for the effect of first-line treatments (e.g. SSRIs).



Important Limitations

- Do not treat the underlying psychological cause.
- Risk of tolerance, dependence and withdrawal (especially benzodiazepines).
- Sedation, cognitive impairment and increased risk of falls (especially in elderly).
- Potential for misuse and diversion (benzodiazepines, pregabalin).
- Should be used as part of a comprehensive treatment plan.



Mechanisms of Action

Benzodiazepines

Positive allosteric modulators of GABA_A receptors → ↑ frequency of Cl⁻ channel opening → increased inhibitory neurotransmission.

Buspirone

Partial agonist at 5-HT_{1A} receptors (presynaptic and postsynaptic).

Hydroxyzine

H₁ histamine receptor antagonist (central); also has anticholinergic properties.

Pregabalin

Binds to α2δ subunit of voltage-gated Ca²⁺ channels → ↓ release of excitatory neurotransmitters (e.g. glutamate, noradrenaline).



Place in Therapy (Guideline-Based)

- Psychological interventions (e.g. CBT) are first-line for most anxiety disorders.
- SSRIs are first-line pharmacological treatment for GAD, panic disorder and social anxiety disorder (NICE CG113).
- Benzodiazepines are not first-line and should generally be limited to short-term use (typically 2–4 weeks) in cases of severe anxiety or crisis.
- Pregabalin may be considered for GAD if SSRI/SNRI are not tolerated or ineffective (where licensed).
- Hydroxyzine can be used for short-term symptomatic relief of anxiety (evidence for GAD is limited).
- Long-term use of benzodiazepines is associated with tolerance, dependence and withdrawal and is not recommended.



Key Take-Home Messages

- SSRIs and psychological therapy are first-line for most anxiety disorders.
- Benzodiazepines are not recommended for long-term use.
- Pregabalin is an alternative for GAD if SSRIs/SNRIs are not suitable (where available).
- Always consider risks (dependence, sedation, falls) and individual patient factors.
- Use the lowest effective dose for the shortest duration, with regular review.

Anxiolytics: Pharmacokinetics (ADME) and Common Brands

Slide 12

Key pharmacokinetic properties and commonly used agents

Common Anxiolytics: ADME and Brand Names							
Drug (class)	Oral bio-availability (%)	Tmax (h)	Half-life (h)	Metabolism (major)	Active metabolites (if any)	Elimination	Common brand name(s)
Benzodiazepines (BZD)							
Diazepam (BZD)	~90–100	0.5–2	20–50	Hepatic (CYP2C19, CYP3A4)	Yes (desmethyldiazepam, oxazepam, temazepam)	Renal (as metabolites)	Valium®
Lorazepam (BZD)	~90	1–2	10–20	Hepatic (UGT glucuronidation)	No	Renal (as conjugate)	Ativan®
Alprazolam (BZD)	~80–90	1–2	10–15	Hepatic (CYP3A4)	No	Renal (as metabolites)	Xanax®
Clonazepam (BZD)	~90	1–4	18–50	Hepatic (CYP3A4)	No (inactive metabolites)	Renal (as metabolites)	Klonopin® (Rivotril®)
Oxazepam (BZD)	~90	1–2	4–15	Hepatic (UGT glucuronidation)	No	Renal (as conjugate)	Serax®
Temazepam (BZD)	~90–100	0.8–1.5	8–22	Hepatic (UGT glucuronidation)	No	Renal (as conjugate)	Restoril®
Chlordiazepoxide (BZD)	~80–90	1–4	5–30	Hepatic (CYP3A4, CYP2C19)	Yes (desmethyl-chlordiazepoxide)	Renal (as metabolites)	Librium®
Nitrazepam (BZD)	~90–100	1–3	16–48	Hepatic (reduction + acetylation)	Yes (active metabolites)	Renal (as metabolites)	Mogadon®
Non-benzodiazepine Anxiolytics							
Buspirone (5-HT _{1A} partial agonist)	~4–8	0.5–1.5	2–3	Hepatic (CYP3A4)	No	Renal (as metabolites)	Buspar®
Hydroxyzine (antihistamine)	~70	2	7–20	Hepatic (CYP3A4/5)	No (inactive metabolites)	Renal (as metabolites)	Atarax® (Vistaril®)
Pregabalin (α _{2δ} ligand)	≥ 90	1	~6	Not significantly metabolized	No	Renal (unchanged)	Lyrica® (Alzain®)
Gabapentin (α _{2δ} ligand)	~60	2–3	5–7	Not significantly metabolized	No	Renal (unchanged)	Neurontin®
Propranolol (β-blocker, performance)	~25–30	1–2	3–6	Hepatic (CYP2D6, 1A2)	No	Renal (as metabolites)	Inderal®
Beta-blockers (other) (e.g. atenolol)	~50	2–4	6–7	Minimal metabolism	No	Renal (unchanged)	Tenormin® (atenolol)

Note: PK values are approximate ranges in healthy adults and may vary by source, formulation and patient factors.

Key Pharmacokinetic and Clinical Points

- **Benzodiazepines** are well absorbed orally; onset is rapid (except chlordiazepoxide and clobazam, which are slower).
- **Diazepam and chlordiazepoxide** have long half-lives and active metabolites → risk of accumulation, especially in elderly and hepatic impairment.
- **Lorazepam, oxazepam and temazepam (LOT)** undergo glucuronidation and are less dependent on hepatic oxidative metabolism → preferred in hepatic impairment or when drug interactions via CYP450 are a concern.
- **Buspirone** has low oral bioavailability, is metabolized by CYP3A4, and is not effective for acute anxiety relief (onset is gradual).
- **Pregabalin** is renally excreted unchanged; dose adjustment is required in renal impairment.
- **Hydroxyzine** is metabolized by CYP3A4/5; use with caution in elderly due to anticholinergic effects and potential QT prolongation.

Important Drug Interactions

- **CYP3A4 inhibitors** (e.g. macrolides, azole antifungals, grapefruit) ↑ levels of alprazolam, diazepam, clonazepam, chlordiazepoxide, clobazam, buspirone, hydroxyzine and pregabalin.
- **CYP3A4 inducers** (e.g. carbamazepine, phenytoin, rifampicin, St John's wort) ↓ levels of these drugs.
- **Additive CNS depression** with alcohol, opioids, antipsychotics, antihistamines and other sedatives.
- Caution with other QT-prolonging drugs (e.g. hydroxyzine).
- **Pregabalin/gabapentin:** additive CNS depression with opioids; increased risk of misuse.

Key Take-Home Messages

- 1 PK properties (onset, half-life, metabolism) help guide drug choice (e.g. long vs short half-life, hepatic vs renal impairment).
- 2 Lorazepam, oxazepam and temazepam are less dependent on hepatic oxidation (not mandatory for all elderly patients).
- 3 Buspirone is not effective for acute anxiety; onset is gradual (1–2 weeks).
- 4 Pregabalin can cause sedation and has abuse potential; adjust dose in renal impairment.
- 5 Review drug interactions, risk of dependence (especially BZDs), and plan for regular reassessment.

Based on: BNF (latest edition) | Maudsley 14th ed. (2021) | NICE CG113 (2011, updated 2020)

Benzodiazepines: Dependence, Withdrawal and Major Clinical Risks

Slide 13

Evidence-based approach to safe and effective use



Risk Factors for Dependence

- Higher doses and long duration of use (especially > 4 weeks)
- Short half-life agents (e.g. alprazolam, triazolam)
- History of substance use disorder (including alcohol)
- Comorbid psychiatric conditions (e.g. anxiety, depression, PTSD, personality disorders)
- Younger age
- Concomitant use of other CNS depressants (e.g. opioids, alcohol, gabapentinoids)
- Previous failed discontinuation attempts
- Psychological factors (e.g. trauma history, coping style)



Clinical Features of Dependence

- Tolerance (need for higher doses to achieve same effect)
- Loss of therapeutic effect over time
- Compulsive use or difficulty reducing dose
- Continued use despite adverse consequences
- Craving and drug-seeking behaviour
- Psychological and physical dependence
- Withdrawal symptoms on dose reduction or cessation



Strategies to Minimize Dependence

- Use the lowest effective dose for the shortest duration (ideally ≤ 2–4 weeks)
- Consider non-pharmacological treatments (e.g. CBT)
- Prefer longer half-life agents in patients at higher risk
- Regularly review the ongoing need for treatment
- Avoid co-prescribing with opioids or other CNS depressants
- Educate patients about risks of dependence and withdrawal
- Use alternative treatments for anxiety (e.g. SSRIs, SNRIs, pregabalin, psychological therapies)



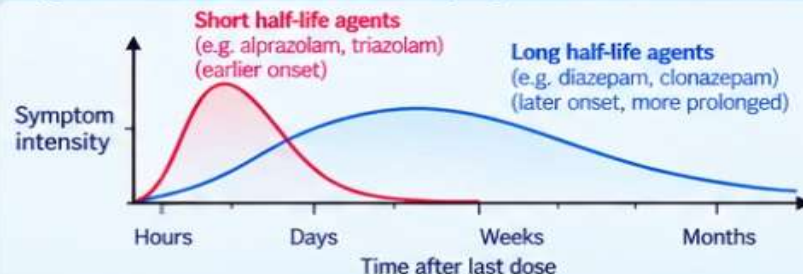
Withdrawal Syndrome

- Can occur after abrupt cessation, rapid dose reduction or missed doses, especially with regular use for > 2–4 weeks.
- Onset, duration and severity vary by agent (half-life), dose, duration of use and individual patient factors.
- Symptoms usually begin within days after last dose (short half-life agents: often earlier; long half-life agents: later) and may last from days to weeks (occasionally longer).

Common Withdrawal Symptoms

Mild	Anxiety, restlessness, irritability, insomnia, poor concentration, tremor, headache, sweating, palpitations, nausea, perceptual disturbances (e.g. heightened sensitivity to light/sound)
Moderate	Increased anxiety, panic attacks, muscle cramps, gastrointestinal upset, depersonalization/derealization
Severe	Confusion, agitation, severe insomnia, hallucinations, psychosis, seizures, delirium, autonomic instability (e.g. hypertension, tachycardia, hyperthermia)

Typical Course of Withdrawal Symptoms (Variable)



Key Take-Home Messages

- 1 Benzodiazepines can cause both psychological and physical dependence, especially with prolonged use.
- 2 Withdrawal can be serious and potentially life-threatening (e.g. seizures, delirium).
- 3 Onset and duration of withdrawal vary by agent, dose, duration of use and patient factors.
- 4 Use the lowest effective dose for the shortest duration and review regularly.
- 5 Taper gradually and individualize the plan (typically 5–10% every 2–4 weeks; not > 25% in 2 weeks).
- 6 Provide psychological support and consider specialist input for complex cases.



Major Clinical Risks

CNS effects	• Sedation, psychomotor impairment • Cognitive impairment (anterograde amnesia, reduced attention and processing speed) • Increased risk of falls and fractures (especially in older adults)
Paradoxical reactions	• Agitation, irritability, aggression, disinhibition (more common in children, older adults and those with psychiatric comorbidity)
Respiratory depression	• Especially when combined with opioids, alcohol or other CNS depressants • Can be life-threatening (FDA boxed warning)
Misuse and diversion	• Risk of non-medical use, dependence and diversion (higher with short half-life agents (e.g. alprazolam))
Increased mortality	• Higher risk of overdose and death, particularly when combined with opioids (FDA boxed warning)



Management of Withdrawal (Evidence-Based)

- Assess severity, risks (e.g. seizure history), comorbidities and social support.
- Consider transition to a longer-acting benzodiazepine (e.g. diazepam) in selected patients, especially those using short half-life agents.
- Gradual, individualized dose reduction: typically 5–10% every 2–4 weeks.
 - Do not reduce by more than 25% every 2 weeks.
 - Adjust the pace based on withdrawal symptoms and patient response.
- Provide psychological support (e.g. CBT) and address comorbid conditions (e.g. anxiety, insomnia, substance use).
- For severe withdrawal (e.g. seizures, delirium, significant medical instability), consider specialist input and close monitoring (inpatient management may be required).
- Avoid abrupt discontinuation or rapid dose reduction (risk of severe withdrawal and seizures).
- Consider adjunctive treatments for specific symptoms (e.g. insomnia, anxiety), but no medication is proven to prevent withdrawal.

Benzodiazepines: Dose Adjustment, Drug Interactions & Special Populations

Individualize therapy: start low, go slow, monitor and reassess



Selected Benzodiazepines: Typical Adult Dosing (Approximate)

Doses vary by indication, formulation, patient factors and local guidelines. Use the lowest effective dose.

Drug (class)	Common indications	Typical adult starting dose*	Typical maintenance range*	Key considerations
Diazepam (long-acting)	Anxiety, muscle spasm, alcohol withdrawal, seizure adjunct	2–5 mg 1–2 times daily	5–40 mg/day (divided)	Hepatic metabolism (CYP3A4, CYP2C19); active metabolites → accumulation risk (esp. elderly, hepatic impairment).
Lorazepam (intermediate)	Anxiety, insomnia, procedural sedation, seizure adjunct	0.5–1 mg 2–3 times daily	1–6 mg/day (divided)	Metabolized by glucuronidation (UGT); preferred in hepatic impairment and elderly.
Alprazolam (short-acting)	Anxiety, panic disorder	0.25–0.5 mg 2–3 times daily	0.5–4 mg/day (divided)	CYP3A4 substrate; higher risk of dependence and withdrawal (esp. short half-life).
Clonazepam (long-acting)	Anxiety, panic disorder, seizure disorders	0.25–0.5 mg 2 times daily	0.5–4 mg/day (divided)	Hepatic metabolism (CYP3A4); long half-life.
Midazolam	Procedural sedation, anesthesia (IV/IM/IN)	Not for routine anxiety treatment	Titrate to effect (e.g. 0.5–2 mg IV)	Short-acting; used in monitored settings only (e.g. procedural sedation).



General Dosing and Prescribing Principles

- Use the lowest effective dose for the shortest duration.
- Start low, go slow — especially in elderly, medically vulnerable patients and those with comorbidities.
- Individualize dose based on indication, severity, response and tolerability.
- Consider a longer-acting agent in selected patients (e.g. for withdrawal management or if frequent dosing is problematic).
- Plan a gradual, individualized taper when discontinuing (avoid abrupt cessation).
- Regularly review the ongoing need for treatment (e.g. every 1–4 weeks).
- Educate patients about risks of dependence, withdrawal and additive effects with alcohol or opioids.



Special Populations and Dose Adjustment

Older adults (≥ 65 years)

- Avoid benzodiazepines when possible.
- If clinically necessary, use lower starting doses and slower titration.
- Increased sensitivity to adverse effects (sedation, cognitive impairment, falls).
- Regularly reassess the ongoing need.

Hepatic impairment

- Benzodiazepines with hepatic oxidative metabolism (e.g. diazepam, chlordiazepoxide, clonazepam, alprazolam) may accumulate.
- Consider using agents less dependent on oxidation (e.g. lorazepam, oxazepam, temazepam).
- Use lower doses and/or longer dosing intervals based on the specific agent and severity of hepatic impairment.

Renal impairment

- Most benzodiazepines are hepatically metabolized.
- Lorazepam, oxazepam and temazepam are metabolized by glucuronidation; their metabolites can accumulate in severe renal impairment.
- Adjust dose and/or dosing interval based on the specific agent and clinical response.

Pregnancy and lactation

- Use only if clearly indicated and if potential benefits outweigh risks.
- Use the lowest effective dose for the shortest duration.
- Exposure near delivery may be associated with neonatal sedation, respiratory depression and withdrawal symptoms.
- Small amounts are excreted in breast milk; monitor the infant for sedation and poor feeding.

Respiratory disease / OSA

- Increased risk of respiratory depression.
- Use lower doses or avoid when possible.
- Use with caution in COPD, OSA and other conditions predisposing to hypoventilation.



Monitoring and Safety Considerations

- Assess efficacy, adverse effects and signs of misuse at each visit.
- Monitor for sedation, cognitive impairment, falls (especially in elderly).
- Be vigilant for signs of tolerance, dependence and drug-seeking behaviour.
- Consider periodic reassessment of liver and renal function in at-risk patients.
- Review all concomitant medications for potential interactions.
- Use prescription monitoring programs where available.
- Document indication, dose, duration, response and follow-up plan.



Important Drug Interactions

CNS depressants

- Additive sedative effects with alcohol, opioids, antihistamines, antipsychotics, TCAs, gabapentinoids (gabapentin, pregabalin) → increased risk of profound sedation, respiratory depression, coma and death.

CYP3A4 inhibitors (increase levels)

- Clinically relevant for: alprazolam, midazolam, triazolam (and to a lesser extent diazepam).
- Examples: azole antifungals (e.g. ketoconazole, itraconazole), macrolides (e.g. clarithromycin), protease inhibitors, grapefruit juice.
- May require dose reduction and closer monitoring.

CYP3A4 inducers (decrease levels)

- May reduce efficacy of: alprazolam, midazolam, triazolam.
- Examples: carbamazepine, phenytoin, phenobarbital, rifampicin, St John's wort.
- Monitor for reduced clinical effect; dose adjustment may be required.

Other interactions

- Valproate may increase levels of some BZDs (e.g. diazepam).
- Cimetidine may increase diazepam levels.
- No consistent evidence that smoking significantly affects benzodiazepine clearance.
- Consider additive CNS effects with other psychotropics.



Key Take-Home Messages

- 1 Dose adjustment depends on age, hepatic and renal function, indication and concomitant medications.
- 2 Be aware of clinically significant drug interactions, especially with CYP3A4 inhibitors/inducers and other CNS depressants.
- 3 Use lower doses and slower titration in older adults and medically vulnerable patients.
- 4 Avoid or use with caution in pregnancy, lactation and respiratory disease.
- 5 Use the lowest effective dose for the shortest duration, with regular reassessment.
- 6 Plan a gradual, individualized taper when discontinuing.

Abbreviations: BZD = benzodiazepine; COPD = chronic obstructive pulmonary disease; OSA = obstructive sleep apnoea; TCA = tricyclic antidepressant.

* Doses are approximate adult values for common indications and may vary by source, formulation and patient factors. Always refer to local guidelines and product information.

Based on: ASAM Benzodiazepine Tapering Guideline (2025) | NICE NG215 (2022) | FDA (2020) | BNF (2024)

Stimulants: Classification, Mechanism and Clinical Uses

Slide 15

Enhancing attention, executive function and wakefulness when used appropriately



Classification (by active ingredient)

Methylphenidate-based stimulants

(block dopamine and norepinephrine reuptake)

- Methylphenidate
- Dexmethylphenidate

Amphetamine-based stimulants

(increase release of dopamine and norepinephrine and inhibit reuptake)

- Amphetamine (racemic)
(specific formulations/products have different indications)
- Dextroamphetamine (d-isomer)
- Mixed amphetamine salts
(e.g. dextroamphetamine/amphetamine)
- Lisdexamfetamine (prodrug)
- Methamphetamine
(FDA-approved for ADHD; very limited clinical use due to high abuse potential)

Wake-promoting agents (non-amphetamine)

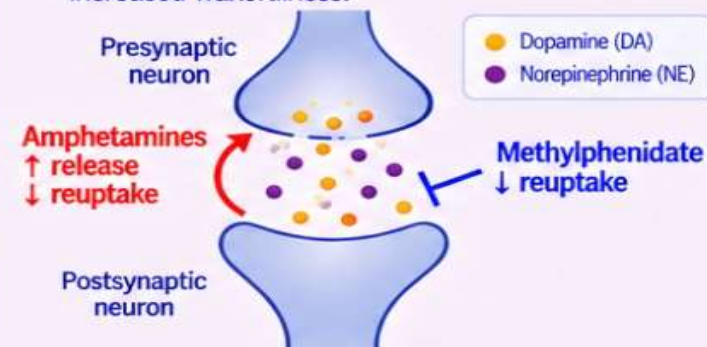
(mechanisms distinct from classic amphetamine stimulants)

- Modafinil
(enhances dopaminergic signalling via complex mechanisms)
- Armodafinil (R-enantiomer of modafinil)
- Solriamfetol (selective DAT and NET inhibitor)



Mechanism of Action

- Stimulants increase synaptic concentrations of dopamine (DA) and norepinephrine (NE), particularly in the prefrontal cortex.
- Methylphenidate primarily blocks reuptake of DA and NE via inhibition of DAT and NET.
- Amphetamines promote release of DA and NE from presynaptic terminals and also inhibit reuptake (reverse transport).
- Wake-promoting agents (modafinil/armodafinil and solriamfetol) act through mechanisms distinct from classic amphetamine stimulants: modafinil/armodafinil primarily enhance dopaminergic signalling via multiple pathways, while solriamfetol selectively inhibits DAT and NET.
- Net effect: improved attention, executive function, reduced impulsivity and, for some agents, increased wakefulness.



Clinical Uses (by drug/class)

Drug / Class	ADHD	Narcolepsy (excessive daytime sleepiness)		Binge-Eating Disorder (BED)
Methylphenidate	✓ (children, adolescents, adults)	✓ (some products)	—	—
Dexmethylphenidate	✓ (children, adolescents, adults)	—	—	—
Amphetamine (racemic)	✓ (adults; some children) (product-specific)	✓ (some products)	—	—
Dextroamphetamine	✓ (adults; some children)	✓ (some products)	—	—
Mixed amphetamine salts	✓ (adults; some children)	✓ (some products)	—	—
Lisdexamfetamine	✓ (children, adolescents, adults)	—	✓ (adults; moderate-severe) (FDA-approved)	—
Methamphetamine	✓ (adults; limited use)	—	—	—
Modafinil	—	✓	—	—
Armodafinil	—	✓	—	—
Solriamfetol	—	✓	—	—

✓ = FDA-approved indication (varies by product and region).

— = Not an approved indication.

Indications may vary by country and specific formulation; always consult local labeling.



Key Point

Stimulants and wake-promoting agents enhance dopaminergic and noradrenergic signalling, leading to improved attention, executive function and wakefulness, with drug- and patient-specific indications.



References

1. NICE. Attention deficit hyperactivity disorder: diagnosis and management (NG87). 2018 (updated 2019). <https://www.nice.org.uk/guidance/ng87>
2. British National Formulary (BNF). Central nervous system stimulants. Latest edition. <https://bnf.nice.org.uk>
3. Katzung BG, Trevor AJ. Basic & Clinical Pharmacology. 15th ed. McGraw Hill; 2021.

4. Stahl SM. Essential Psychopharmacology. 5th ed. Cambridge University Press; 2021.
5. FDA. Prescription stimulants: ADHD, narcolepsy and binge-eating disorder. <https://www.fda.gov/drugs>
6. UpToDate. Psychostimulant medications: pharmacology, clinical uses, and adverse effects. 2024.



Methylphenidate Products

Dopamine & norepinephrine reuptake inhibitor (DAT/NET)

Methylphenidate
(methylphenidate HCl)Ritalin®
IR (tablet)Concerta®
ER (OROS)Daytrana®
Transdermal patch

Formulations	IR (tablet), ER (OROS, LA, CD), chewable, transdermal patch
Common brands (examples)	Ritalin®, Concerta®, Metadate®, Daytrana®, Quillivant XR®
Key notes	- Multiple generic products available. - Transdermal patch (Daytrana) useful in patients who cannot swallow tablets.

Dexmethylphenidate

(dexmethylphenidate HCl; d-enantiomer)

Focalin®
IR (tablet)Focalin XR®
ER (capsule)Xelstrym®
Transdermal patch

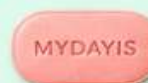
Formulations	IR (tablet), ER (capsule), transdermal patch
Common brands (examples)	Focalin®, Focalin XR®, Xelstrym®
Key notes	- Active d-enantiomer of methylphenidate. - Xelstrym® is a dexmethylphenidate transdermal system (FDA-approved).

Amphetamine Products

Increase synaptic dopamine & norepinephrine release and inhibit reuptake (DAT/NET)

Mixed Amphetamine Salts

(amphetamine aspartate, sulfate, dextroamphetamine sulfate, levoamphetamine sulfate)

Adderall®
IR (tablet)Adderall XR®
ER (capsule)Mydayis®
ER (capsule)Adzenys XR-ODT®
ER (orally disintegrating)

Formulations	IR (tablet), ER (capsule), chewable (ER), ODT (ER), oral solution (ER)
Common brands (examples)	Adderall®, Adderall XR®, Mydayis®, Adzenys XR-ODT®, Dyanavel XR® (liquid ER)
Key notes	- Racemic mixture (≈ 75% dextroamphetamine, 25% levoamphetamine). - Multiple generic products available.

Dextroamphetamine

(dextroamphetamine sulfate; d-amphetamine)

Dexedrine®
IR (tablet)Zenzedi®
ER (capsule)ProCentra®
Oral solution

Formulations	IR (tablet), ER (capsule), oral solution, spansule®
Common brands (examples)	Dexedrine®, Dexedrine Spansule®, Zenzedi®, ProCentra®
Key notes	- Single enantiomer (d-amphetamine). - Multiple generic products available.

Lisdexamfetamine

(lisdexamfetamine dimesylate; prodrug of d-amphetamine)



Vyvanse® (capsule)

Formulations	Capsule, chewable tablet
Common brands (examples)	Vyvanse® (and generics)
Key notes	- Inactive prodrug; converted to d-amphetamine after oral absorption. - Smoother onset/offset; lower abuse potential vs. IR.

Methamphetamine

(methamphetamine HCl)



Desoxyn® (tablet)

Formulations	IR (tablet)
Common brands (examples)	Desoxyn®
Key notes	- FDA-approved for ADHD; very limited clinical use due to higher abuse potential. - Schedule II controlled substance (U.S.).

Wake-Promoting Agents
(Non-amphetamine stimulants)

Enhance wakefulness via distinct mechanisms (not classic amphetamines)

Modafinil
(modafinil)

Formulations	Tablet (100 mg, 200 mg)
Common brands (examples)	Provigil® (and generics)
Key notes	- Mechanism: complex (↑ histamine, ↑ orexin, modulates dopamine). - Approved for narcolepsy, OSA, and shift work disorder (SWD) in adults. - Schedule IV (U.S.).

Armodafinil
(armodafinil;
R-enantiomer of
modafinil)

Formulations	Tablet (50 mg, 150 mg, 200 mg, 250 mg)
Common brands (examples)	Nuvigil® (and generics)
Key notes	- Longer half-life than modafinil. - Approved for narcolepsy, OSA, and SWD in adults. - Schedule IV (U.S.).

Solriamfetol
(solriamfetol)

Formulations	Tablet (37.5 mg, 75 mg, 150 mg)
Common brands (examples)	Sunosi® (and generics)
Key notes	- Selective dopamine and norepinephrine reuptake inhibitor (DAT/NET). - Approved for excessive daytime sleepiness (EDS) associated with narcolepsy or OSA in adults. - Schedule IV (U.S.).



- Brand names are examples of commonly used products; availability, formulations, and brand names vary by country and may change over time.
- This table is not exhaustive; it highlights the most clinically relevant agents and formulations.
- All listed medications are prescription-only and Schedule II-IV controlled substances in the U.S. (except modafinil/armodafinil/solriamfetol: Schedule IV).



Stimulant Pharmacokinetics (ADME), Dose Adjustment & Key Points

Slide 17

Pharmacokinetic properties, metabolism, elimination, and dosing considerations for commonly used stimulants and wake-promoting agents

Drug (Brand examples) & Image	Absorption (F, Tmax, Food)	Distribution (Vd, Protein binding)	Metabolism (Pathway)	Elimination (t½)	Dose Adjustment (Hepatic / Renal Impairment)
Methylphenidate (Ritalin®, Concerta®, Daytrana®) 	F ≈ 20–40% Tmax: 1–2 h (IR) 2–4 h (ER) Food: may ↓ rate	Vd ≈ 1.3–2.1 L/kg ~10–33% protein bound Good CNS penetration	Hepatic hydrolysis by CES1 to ritalinic acid (inactive)	~2–3 h (IR) ~3–4 h (ER)	Hepatic: Use with caution in severe hepatic impairment (limited data). Renal: No specific adjustment (ritalinic acid is renally excreted).
Dexmethylphenidate (Focalin®, Xelstrym® patch) 	F ≈ 20–40% Tmax: 1–2 h (IR) Food: may ↓ rate	Similar to methylphenidate ~10–33% protein bound	CES1 to inactive metabolite	~2–3 h	Hepatic: Use with caution in severe hepatic impairment. Renal: No specific adjustment.
Mixed amphetamine salts (Adderall®) 	F ≈ 75–100% Tmax: 3 h (IR) 7 h (XR) Food: minimal effect	Vd ≈ 3–4 L/kg ~15–40% protein bound Good CNS penetration	Hepatic (CYP2D6 and other pathways) to inactive metabolites	~9–14 h (pH-dependent)	Hepatic: Use with caution in severe hepatic impairment. Renal: Consider lower dose in severe RI (eGFR < 30; product-specific).
Dextroamphetamine (Dexedrine®, Zenzedi®) 	F ≈ 75–100% Tmax: 3 h Food: minimal effect	Vd ≈ 3–4 L/kg ~15–40% protein bound	Hepatic (CYP2D6 and other pathways)	~9–14 h (pH-dependent)	Hepatic: Use with caution in severe hepatic impairment. Renal: Consider lower dose in severe RI (eGFR < 30; product-specific).
Lisdexamfetamine (Vyvanse®) 	F ≈ 100% (prodrug) Tmax: ~3.5 h Food: minimal effect	Converted in blood to dextroamphetamine (not significantly protein bound)	Enzymatic hydrolysis in RBCs to dextroamphetamine (independent of CYP)	~10–13 h (d-amphetamine)	Hepatic: No adjustment in mild–moderate HI; not studied in severe HI. Renal: Severe RI (eGFR 15–<30): max 50 mg/day; ESRD: max 30 mg/day.
Methamphetamine (Desoxyn®) 	F ≈ 70–80% Tmax: 2–3 h Food: minimal effect	Vd ≈ 3–4 L/kg ~15–40% protein bound	Hepatic (CYP2D6 and other pathways)	~10–12 h (pH-dependent)	Hepatic: Use with caution in severe hepatic impairment. Renal: Consider lower dose in severe RI (product-specific).
Modafinil (Provigil®) 	F ≈ 80% Tmax: 2–4 h Food: minimal effect	Vd ≈ 0.9–1.4 L/kg ~60% protein bound	Hepatic (CYP3A4; induces CYP3A4; minor CYP2C19)	~12–15 h	Hepatic: Severe HI: reduce dose by 50% (max 100 mg/day). Renal: No specific adjustment (parent drug).
Armodafinil (Nuvigil®) 	F ≈ 80% Tmax: 2–3 h Food: minimal effect	Vd ≈ 0.9 L/kg ~60% protein bound	Hepatic (CYP3A4)	~15 h	Hepatic: Severe HI: reduce dose (max 150 mg/day). Renal: No specific adjustment (parent drug).
Solriamfetol (Sunosi®) 	F ≈ 90% Tmax: 2–4 h Food: minimal effect	Vd ≈ 0.6–0.9 L/kg ~16–21% protein bound	Minimal hepatic metabolism (< 5%); unchanged in urine	~7.1 h	Hepatic: No adjustment. Renal: eGFR 30–59: start 37.5 mg, max 75 mg/day; eGFR 15–29: max 37.5 mg/day; ESRD (eGFR < 15): not recommended.

▶ Key Clinical PK Pearls



Formulation matters: IR vs ER significantly affects Tmax, duration and potential for misuse.

Food effects: Generally minimal; may delay absorption of methylphenidate/dexmethylphenidate.

Lisdexamfetamine: Prodrug activated by enzymatic hydrolysis in RBCs (independent of CYP and less affected by drug interactions).

pH-dependent elimination: Amphetamines are weak bases; urinary acidification ↑ renal excretion (rarely used clinically).

Drug interactions: Modafinil/armodafinil induce CYP3A4 (↓ efficacy of CYP3A4 substrates, e.g., OCPs).

Renal/hepatic impairment, formulation, and drug interactions can substantially alter exposure for selected agents.

🔗 Solriamfetol – Renal Dosing Guide (Sunosi®)

eGFR (mL/min/1.73 m³)	Starting Dose	Maximum Dose
≥ 60	75 mg	150 mg
30 – 59	37.5 mg	75 mg
15 – 29	—	37.5 mg
< 15 (ESRD)	Not recommended	

🔗 Lisdexamfetamine – Renal Adjustment (Vyvanse®)

- Mild–moderate RI (eGFR 30–89): No adjustment.
- Severe RI (eGFR 15–<30): Max 50 mg/day.
- ESRD (eGFR < 15): Max 30 mg/day.
- Not studied in end-stage renal disease (use with caution).

🗨 Hepatic Considerations (Selected Agents)

- **Methylphenidate / Dexmethylphenidate / Amphetamines / Methamphetamine:** Use with caution in severe hepatic impairment (limited data).
- **Modafinil:** Reduce dose by 50% in severe hepatic impairment (max 100 mg/day).
- **Armodafinil:** Reduce dose in severe hepatic impairment (max 150 mg/day).
- **Lisdexamfetamine:** No adjustment in mild–moderate HI; not studied in severe HI.
- **Solriamfetol:** No adjustment required.

References: 1. FDA Prescribing Information: Ritalin®, Concerta®, Daytrana®, Focalin®, Xelstrym®, Adderall®, Dexedrine®, Zenzedi®, Vyvanse®, Desoxyn®, Provigil®, Nuvigil®, Sunosi® (latest labels, accessed 2024–2025).

2. Lexicomp. Stimulant Medications. UpToDate, 2024.

3. Katzung BG. Basic & Clinical Pharmacology, 15th ed. McGraw-Hill, 2021.

4. Stahl SM. Prescriber's Guide: Stimulants and Wake-Promoting Agents, 8th ed. 2023.

Note: Brand names and specific formulations are country- and product-specific. Always refer to local prescribing information.

Stimulant Adverse Effects & Safety Monitoring (Updated)

Slide 18

Clinical risks, monitoring strategies, and key precautions for stimulant and wake-promoting agents

Drug (Brand examples) & Image	Common Adverse Effects (≥5–10%)	Important / Serious Adverse Effects (less common)	Contraindications & Important Cautions (product-specific)	Monitoring Recommendations (baseline, follow-up)
Methylphenidate (Ritalin®, Concerta®, Daytrana®) 	- Decreased appetite - Insomnia - Headache - Nausea, abdominal pain	↑ BP & HR - Psychiatric symptoms (anxiety, agitation, psychosis, mania) - Growth suppression (children) - Misuse, dependence	- Hypersensitivity - Use caution in: severe CVD, uncontrolled hypertension, hyperthyroidism, glaucoma - Avoid with MAOIs (within 14 days)	- BP, HR (baseline, after dose changes, then periodically) - Weight (regularly), height (children, every 6 months) - Psychiatric symptoms, sleep, appetite - Assess for misuse/diversion - Same as methylphenidate
Dexmethylphenidate (Focalin®, Xelstrym®) 	Similar to methylphenidate (may have ↑ risk of insomnia and ↓ appetite)	Same as methylphenidate	- Hypersensitivity - Same precautions as methylphenidate - Avoid with MAOIs (within 14 days)	Same as methylphenidate
Mixed amphetamine salts (Adderall®) 	- Decreased appetite - Insomnia - Dry mouth - Nervousness, headache	↑ BP & HR - Psychiatric symptoms (anxiety, psychosis, mania) - Growth suppression (children) - Misuse, dependence - Rare: sudden death in structural heart disease	- Hypersensitivity - Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension - Glaucoma, hyperthyroidism - Avoid with MAOIs (within 14 days)	- BP, HR (baseline, after dose changes, then periodically) - Weight, height (children, every 6 months) - Psychiatric symptoms - Assess for misuse/diversion - ECG not routine; obtain if cardiac history/examination or concomitant drugs indicate risk - Same as amphetamines
Dextroamphetamine (Dexedrine®, Zenzedi®) 	Similar to mixed amphetamine salts	Same as mixed amphetamine salts	Same as amphetamines	Same as amphetamines
Lisdexamfetamine (Vyvanse®) 	- Decreased appetite - Insomnia - Dry mouth - Nausea	↑ BP & HR - Psychiatric symptoms - Growth suppression (children) - Misuse, dependence	- Hypersensitivity - Same precautions as amphetamines	Same as amphetamines
Methamphetamine (Desoxyn®) 	- Decreased appetite - Insomnia - Euphoria (higher risk) - Dry mouth	↑ BP & HR - Psychiatric symptoms - High abuse potential - Neurotoxicity (at high doses)	Same as amphetamines	Same as amphetamines
Modafinil (Provigil®) 	- Headache - Nausea - Nervousness - Insomnia	- Serious skin reactions (SJS/TEN, DRESS) - Psychiatric symptoms ↑ BP & HR - Hepatic injury (rare)	- Hypersensitivity - Severe hepatic impairment (reduce dose) - Use caution in CVD, psychiatric disorders	- BP, HR - Psychiatric symptoms - Skin reactions (especially early) - LFTs if symptoms of liver injury
Armodafinil (Nuvigil®) 	Similar to modafinil	Same as modafinil	Same as modafinil	Same as modafinil
Solriamfetol (Sunosi®) 	- Headache - Nausea - Decreased appetite - Anxiety	↑ BP & HR - Psychiatric symptoms - Use caution in patients with seizure disorders	- Hypersensitivity - End-stage renal disease (not recommended) - Use caution in uncontrolled hypertension and CVD	- BP, HR - Renal function (eGFR, periodically) - Psychiatric symptoms, sleep - Assess for misuse/diversion



Cardiovascular Safety

- Stimulants can increase BP and HR.
- Rare risk of serious cardiovascular events (e.g., MI, stroke, sudden death), especially in patients with underlying structural heart disease.
- Avoid in symptomatic cardiovascular disease and uncontrolled hypertension (product-specific).
- ECG is not routinely required; obtain when cardiac history/examination or concomitant drugs indicate risk.



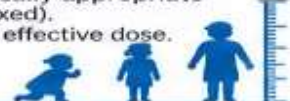
Psychiatric & Behavioral

- May cause or exacerbate anxiety, agitation, irritability, and insomnia.
- Can precipitate psychosis or mania, even in patients without prior history.
- Risk of misuse, abuse, and dependence (highest with amphetamines and methamphetamine).
- Use caution in patients with a history of substance use disorder.
- Monitor for mood and behavioral changes, especially after dose changes.



Growth in Children

- Stimulants may be associated with reduced weight gain and slower growth (height) with long-term use.
- Monitor weight and height regularly (height every 6 months).
- Consider drug holidays in selected patients if clinically appropriate (evidence is mixed).
- Use the lowest effective dose.



Other Important Safety Issues

- Dermatologic:** Serious skin reactions with modafinil/armodafinil (SJS/TEN, DRESS).
- Seizures:** Use caution in patients with seizure disorders (especially solriamfetol).
- Glaucoma:** Avoid in patients with glaucoma (methylphenidate/amphetamines).
- Hyperthyroidism:** Use with caution.
- Drug interactions:** Avoid concomitant MAOIs (within 14 days) with methylphenidate, amphetamines, and related agents.
- Pregnancy & lactation:** Use only if potential benefit justifies potential risk (limited data).
- Hepatic/Renal impairment:** See Slide 17 for dosing guidance.



Key Takeaway

Stimulants are generally well tolerated, but require careful patient selection, baseline assessment, and ongoing monitoring to minimize cardiovascular, psychiatric, growth-related, and misuse/diversion risks.

References:

- FDA Prescribing Information: Ritalin®, Concerta®, Daytrana®, Focalin®, Xelstrym®, Adderall®, Dexedrine®, Zenzedi®, Vyvanse®, Desoxyn®, Provigil®, Nuvigil®, Sunosi® (latest labels, 2023–2025).
- Lexicomp. Stimulant Medications. UpToDate. 2024.
- NICE Guideline NG87. Attention deficit hyperactivity disorder: diagnosis and management. 2018 (updated 2023).
- Katzung BG. Basic & Clinical Pharmacology. 15th ed. McGraw-Hill. 2021.
- Stahl SM. Prescriber's Guide: Stimulants and Wake-Promoting Agents. 8th ed. 2023.

Note: Incidence rates are approximate and may vary by population and source. Brand names and specific formulations are country- and product-specific. Always refer to local prescribing information.

1. Misuse, Abuse, Addiction & Dependence

- Stimulants (methylphenidate, amphetamines, modafinil/armodafinil, solriamfetol) have potential for misuse, abuse, addiction, and physical dependence.
- Higher risk in individuals with a history of substance use disorder (SUD), especially stimulant or cocaine use.
- Patterns of misuse: higher-than-prescribed doses, non-oral routes (insufflation, injection), use for cognitive enhancement, academic or occupational performance.
- Monitor for early refill requests, dose escalation, multiple prescribers ("doctor shopping"), lost prescriptions, or signs of diversion.
- Use long-acting formulations when possible and regular follow-up to reduce misuse risk.
- Educate patients and families about safe use, storage, and legal consequences of diversion.



Schedule II – US Controlled Substances

- Methylphenidate, amphetamines (including lisdexamfetamine) are Schedule II.
- Modafinil, armodafinil, and solriamfetol are Schedule IV in the US.

2. Key Drug Interactions (Drug-specific)

Interacting Drug/Class	Affected Stimulant(s)	Effect	Clinical Implication
MAOIs (e.g., phenelzine, tranylcypromine)	Amphetamines, lisdexamfetamine (± methylphenidate)	↑ Risk of hypertensive crisis, hyperthermia, serotonin syndrome	Contraindicated. Do not use within 14 days of MAOI or before starting MAOI.
Other sympathomimetics (e.g., decongestants, linezolid)	All stimulants	Additive ↑ BP, ↑ HR, ↑ risk of adverse cardiovascular effects	Use with caution. Avoid combination when possible.
SSRIs / SNRIs / TCAs (serotonergic drugs)	Amphetamines, lisdexamfetamine	Potential ↑ risk of serotonin syndrome (rare)	Use with caution. Monitor for serotonin syndrome.
CYP2D6 inhibitors (e.g., fluoxetine, paroxetine, bupropion, quinidine)	Amphetamines, lisdexamfetamine	↑ Amphetamine levels (reduced metabolism)	Consider lower doses and monitor for adverse effects.
CYP2D6 inducers (e.g., rifampin, carbamazepine)	Amphetamines, lisdexamfetamine	↓ Amphetamine levels (increased metabolism)	May reduce efficacy. Monitor clinical response.
Urinary alkalinizers (e.g., sodium bicarbonate)	Amphetamines (all)	↑ Amphetamine levels (reduced renal excretion)	May increase effects/toxicity. Use with caution.
Urinary acidifiers (e.g., ascorbic acid)	Amphetamines (all)	↓ Amphetamine levels (increased renal excretion)	May reduce efficacy.
CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin)	Modafinil, armodafinil	↓ Modafinil/armodafinil levels	May reduce efficacy. Monitor response.
CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin)	Modafinil, armodafinil	↑ Modafinil/armodafinil levels (magnitude varies)	Use with caution. Monitor for adverse effects.
Hormonal contraceptives (estrogen-containing)	Modafinil, armodafinil	↓ Contraceptive efficacy (↑ metabolism of ethinyl estradiol)	Use non-hormonal or additional contraceptive method during treatment and for 1 month after discontinuation.
Other CNS depressants (e.g., alcohol, benzodiazepines)	All stimulants	May mask impairment; increased risk-taking	Use with caution. Counsel on avoidance.

3. Overdose & Toxicity

- Clinical features:** agitation, confusion, hyperthermia, tachycardia, hypertension, arrhythmias, mydriasis, seizures, rhabdomyolysis, metabolic acidosis, psychosis, coma (severe).
- Management:**
 - Supportive care (airway, breathing, circulation).
 - Benzodiazepines may be used for severe agitation, seizures, or significant sympathomimetic toxicity.
 - Active cooling for hyperthermia.
 - Treat hypertension and arrhythmias as clinically indicated (e.g., short-acting agents).
 - Monitor for complications (rhabdomyolysis, renal failure, DIC).
- No specific antidote for most stimulants.
- Modafinil/armodafinil:** limited data; treat supportively.
- Solriamfetol:** limited data; supportive care.

4. Special Populations & Considerations

- History of SUD:** use with caution; consider non-stimulant alternatives first.
- Adolescents and young adults:** higher risk of misuse/diversion; close monitoring.
- Pregnancy & lactation:** use only if benefits outweigh risks (limited data).
- Older adults:** increased sensitivity to cardiovascular and CNS effects; start low, go slow.
- Renal or hepatic impairment:** adjust dose (drug-specific; see Slide 17).
- Comorbid psychiatric disorders:** monitor for anxiety, mood changes, or psychosis.

5. Strategies to Minimize Misuse & Diversion

- Careful patient selection and risk assessment (history of SUD, psychiatric comorbidity).
- Use long-acting formulations when possible (lower abuse potential).
- Regular follow-up and monitoring (efficacy, adverse effects, signs of misuse/diversion).
- Prescription monitoring programs (PMP).
- Educate patients about legal status, risks, and safe storage.
- Consider treatment agreements in high-risk patients.
- Pill counts or limited quantities if diversion is a concern.

6. Key Takeaways

- Stimulants are effective but carry risks of misuse, abuse, addiction, and drug interactions.
- Interactions are drug-specific – know the mechanism and clinical relevance.
- MAOIs are contraindicated with amphetamines (14-day washout).
- Use caution with serotonergic drugs, CYP modulators, and hormonal contraceptives (modafinil/armodafinil).
- Monitor cardiovascular, psychiatric, and misuse-related risks.
- Choose long-acting formulations and close follow-up.
- Patient education and prescription monitoring are essential.

References:

- FDA Prescribing Information: Ritalin®, Concerta®, Daytrana®, Focalin®, Xelstry®. Adderall®, Dexedrine®, Zenzedi®, Vyvanse®, Desoxyn®, Provigil®, Nuvigil®, Sunosi® (latest labels, 2023–2025).
- Lexicomp. Stimulant Medications. UpToDate. 2024.
- NICE Guideline NG87. Attention deficit hyperactivity disorder: diagnosis and management, 2018 (updated 2023).
- Katzung BG. Basic & Clinical Pharmacology. 15th ed. McGraw-Hill. 2021.
- Stahl SM. Prescriber's Guide: Stimulants and Wake-Promoting Agents. 8th ed. 2023.

Note: Recommendations may vary by country and product-specific labeling. Always refer to the most recent local prescribing information.

“Safe and effective use of stimulants requires awareness of their misuse potential, understanding of key drug interactions, and ongoing monitoring with a patient-centered approach.”

**Case 1 – Pediatric ADHD**

Growth and Appetite Concerns

Patient Profile

- 9-year-old boy
- ADHD, combined presentation
- No significant medical history
- Baseline: weight 28 kg (50th percentile), height 132 cm (50th percentile)
- Started on methylphenidate ER 18 mg daily

Follow-up at 3 Months

- Improved attention and school performance
- Decreased appetite
- Weight 26.5 kg (25th percentile)
- Height 133 cm (=50th percentile)
- No cardiovascular or psychiatric concerns

Clinical Questions

1. How would you manage the decreased appetite and weight loss?
2. What monitoring is recommended?
3. Would you continue the current dose?

Management Approach

- ✓ Continue treatment (efficacy maintained).
- ✓ Provide nutritional counseling (high-calorie meals, snacks, consider meal timing).
- ✓ Consider dose adjustment, drug holidays, or switch to an alternative formulation if needed.
- ✓ Monitor weight regularly (more frequently in younger children) and height every 6 months (per NICE).
- ✓ Reassess growth trajectory and consider catch-up growth.

Key Learning Points

- Appetite suppression and weight loss are common.
- Monitor weight regularly and height every 6 months in children (NICE).
- Consider behavioral and nutritional strategies before discontinuation.
- Balance efficacy with growth and nutritional status.

**Overall Takeaways**

- ✓ Stimulants are effective but require careful patient selection, monitoring, and individualized treatment.
- ✓ Consider efficacy, safety, comorbidities, drug interactions, and patient preferences.
- ✓ Regular follow-up and patient education are essential.
- ✓ Use the lowest effective dose and monitor for adverse effects and misuse/diversion.
- ✓ Apply guideline recommendations to real-world clinical scenarios.

**Case 2 – Adult ADHD with Cardiovascular Risk**

Treatment Initiation and Monitoring

Patient Profile

- 34-year-old man
- ADHD, predominantly inattentive presentation
- History: **controlled hypertension** (on lisinopril)
- No other significant medical history
- Baseline: BP 138/88 mmHg, HR 82 bpm, BMI 27 kg/m²
- Considering lisdexamfetamine 30 mg daily

Clinical Question

Is it safe to start a stimulant in this patient?
What baseline assessment and monitoring are needed?

Management Approach

- ✓ Stimulants can be used with **caution** in patients with **controlled hypertension**, after a comprehensive cardiovascular assessment (history, examination, and review of concomitant drugs).
- ✓ Optimize BP control before initiation.
- ✓ Baseline assessment: BP, HR, cardiovascular history (including personal and family history of CVD), and concomitant medications.
- ✓ ECG is **not routinely** required; obtain if cardiac history/examination or concomitant drugs indicate risk (NICE).
- ✓ Start low dose and monitor BP and HR after initiation and after dose changes, then periodically.
- ✓ Advise on lifestyle measures (diet, exercise, sleep, limit caffeine).
- ✓ Reassess efficacy, BP/HR, and adverse effects at each visit.

Key Learning Points

- Stimulants can increase BP and HR.
- Use caution in patients with cardiovascular risk factors or uncontrolled hypertension.
- Routine ECG is not recommended unless indicated (NICE).
- Monitor BP and HR at baseline, after dose changes, and periodically.
- Individualize risk-benefit assessment.

**Case 3 – Narcolepsy**

Drug Interactions and Special Considerations

Patient Profile

- 28-year-old woman
- Narcolepsy with excessive daytime sleepiness
- On combined oral contraceptive (ethinyl estradiol/levonorgestrel)
- No other medical history
- Considering modafinil 200 mg daily

Clinical Questions

1. What counseling and monitoring are needed?
2. Are there important drug interactions?
3. What alternative options can be considered?

Management Approach

- ✓ Modafinil can reduce the efficacy of hormonal contraceptives (induces CYP3A4).
- ✓ Advise using a non-hormonal contraceptive method (e.g., copper IUD, barrier method) or an additional contraceptive method during treatment and for 1 month after discontinuation (FDA).
- ✓ Counsel about common adverse effects (headache, nausea, insomnia) and serious skin reactions (SJS/TEN, DRESS).
- ✓ Monitor BP and HR as clinically appropriate (usually less pronounced than amphetamine stimulants).
- ✓ Assess liver function if clinically indicated (rare hepatic reactions).
- ✓ Educate about potential for misuse and safe storage.

Key Learning Points

- Modafinil/armodafinil can reduce hormonal contraceptive efficacy during treatment and for 1 month after discontinuation.
- Use non-hormonal or additional contraceptive methods.
- Monitor for serious skin reactions (SJS/TEN, DRESS).
- Monitor BP and HR as clinically appropriate.
- Consider hepatic monitoring if indicated.
- Counsel about misuse/diversion and safe storage.

**Discussion Questions**

- 1 How would your approach change in a patient with SUD?
- 2 When would you consider non-stimulant options?
- 3 What additional monitoring might be needed in complex patients?
- 4 How do you counsel patients about risks of misuse/diversion?
- 5 What factors influence your choice of stimulant vs. alternative therapy?

“Evidence guides our choices,
but it is the individual patient
who defines the best treatment
plan.”

Clinical Case:

Antipsychotic + Benzodiazepine in the Hospitalized Patient

Acute Agitation in the Context of Psychosis, Medical Illness and Delirium Risk

From Evidence
to Safer Practice
in Psychopharmacology



Case Presentation

- 45-year-old man with schizophrenia, brought to the ED with severe agitation, paranoia and verbal aggression.
- Fever, cough and hypoxia → diagnosed with pneumonia (admitted to medical ward).
- Past history: non-adherence to antipsychotic treatment.
- No known substance use. No known prolonged QT.



Key Clinical Questions

- 1 How to manage acute agitation safely?
- 2 How to differentiate delirium from psychosis-related agitation?
- 3 What is the appropriate role (and limitation) of benzodiazepines?
- 4 How to monitor for adverse effects?
- 5 How to plan ongoing treatment and discharge?



Clinical Goals

- ✓ Ensure safety (patient, staff, others)
- ✓ Identify and treat underlying causes (e.g. infection, delirium, pain, hypoxia)
- ✓ Use the right medication, at the right time
- ✓ Minimize adverse effects (sedation, respiratory depression, EPS, QT prolongation, falls)
- ✓ Plan ongoing antipsychotic treatment and relapse prevention



1 Initial Assessment

- Assess and manage immediate risks (violence, self-harm).
- Look for reversible causes (delirium): infection, hypoxia, pain, metabolic abnormalities, substance intoxication/withdrawal, medications.
- Mental state, physical exam, vital signs, investigations (e.g. CBC, electrolytes, ECG if indicated).
- Use the least restrictive, trauma-informed approach.



2 Non-Pharmacological Management

- Use de-escalation techniques (calm environment, clear communication, reduce sensory stimulation).
- Address basic needs (pain, hydration, oxygen, toileting).
- Consider 1:1 observation if risk persists.
- Use physical restraint only if necessary and according to local policy, with regular review.



3 Pharmacological Management (Acute Agitation)

- **NICE NG10 – Rapid tranquillisation (adults)**
 - First-line options:
 - IM lorazepam alone (e.g. 2 mg, repeat as needed)
 - OR
 - IM haloperidol + IM promethazine (e.g. haloperidol 5 mg + promethazine 25–50 mg)
 - If cardiovascular disease, prolonged QT or ECG not available → consider IM lorazepam alone.
 - Avoid IM olanzapine with parenteral benzodiazepine (within at least 1 hour) due to risk of excessive sedation and cardiorespiratory depression.^{1,2}



4 Ongoing Inpatient Management

- Treat underlying medical illness (e.g. pneumonia).
- Reassess regularly for delirium vs. psychosis.
- Continue antipsychotic treatment for psychosis (e.g. oral risperidone, olanzapine or other appropriate agent; consider long-acting injectable (LAI) if non-adherence is a concern).
- Use benzodiazepines only short-term and reassess daily: avoid prolonged use.
- Monitor for adverse effects (see below).



5 Monitoring and Safety

- **Vital signs:** pulse, BP, respiratory rate, temperature, oxygen saturation, level of consciousness (post-rapid tranquillisation).¹
- **Cardiac:** baseline and follow-up ECG if risk factors for QT prolongation or using antipsychotics with higher QT risk.³
- **Sedation/respiratory status:** especially with benzodiazepines or combination therapy.²
- **Neurological:** EPS (with antipsychotics), falls, delirium (especially in medically ill patients).
- **Metabolic:** weight, glucose, lipids (ongoing antipsychotic treatment).
- **Other:** assess for drug interactions, hepatic/renal impairment, and additive CNS depressant effects (e.g. opioids, alcohol).³



6 Discharge Planning and Follow-up

- Ensure clinical stability and resolution of acute agitation.
- Establish a clear antipsychotic treatment plan (consider LAI if non-adherence).⁴
- Address psychosocial needs and follow-up with community mental health services.
- Provide education to patient and family about medication adherence, warning signs and relapse prevention.
- Review and limit benzodiazepine use; plan taper if used for more than a few days.
- Ensure communication with primary care and outpatient psychiatry.



Key Take-Home Points

- ✓ De-escalation and treatment of underlying causes first.
- ✓ Use benzodiazepines short-term and indication-specific.
- ✓ Avoid IM olanzapine + parenteral benzodiazepine.
- ✓ Monitor closely for sedation, respiratory depression, QT prolongation, EPS and falls.
- ✓ Plan long-term treatment and relapse prevention (consider LAI when appropriate).



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Evidence-based care
for safer outcomes

Final Clinical Pearls & Take-Home Messages

Evidence-Based, Patient-Centred, Safer Practice

Integrating
Evidence, Safety
and Clinical Judgment
for Better Outcomes



Antipsychotics

Use the right drug, monitor, and stay alert to risks

- 1 Choose based on indication, efficacy, side-effect profile (EPS, metabolic burden, QT), and patient comorbidities.
- 2 Baseline and ongoing monitoring: weight/BMI, waist circumference, BP, fasting glucose and lipids; assess EPS and prolactin when indicated.
- 3 Clozapine: highest efficacy but requires monitoring for agranulocytosis, myocarditis/cardiomyopathy, seizures and metabolic effects.
- 4 Be vigilant for red flags: neuroleptic malignant syndrome (NMS), acute dystonia, severe QT prolongation, and anticholinergic toxicity.
- 5 Consider long-acting injectable (LAI) formulations for non-adherence in appropriate patients (e.g. schizophrenia).



Key Message

Maximise benefit, minimise harm, monitor consistently.



Anxiolytics

Effective, but use with caution

- 1 For chronic anxiety disorders (e.g. GAD, panic disorder), SSRIs/SNRIs are usually first-line pharmacotherapy (with psychological interventions).
- 2 Benzodiazepines: short-term and indication-specific use (e.g. acute severe anxiety, panic, catatonia, seizures, specific procedural use).
- 3 Risks: tolerance, dependence, withdrawal, cognitive impairment, falls (especially older adults).
- 4 Avoid or use extreme caution with opioids and other CNS depressants due to risk of profound sedation and respiratory depression.
- 5 If discontinuing, taper gradually; avoid abrupt cessation.



Key Message

Use the lowest effective dose for the shortest duration, with a clear plan.



Stimulants

Effective, with important safety considerations

- 1 Evidence-based pharmacologic options for ADHD; first-line choice varies by age and guideline (e.g. methylphenidate in children/adolescents; methylphenidate or lisdexamfetamine in adults).
- 2 Monitor BP/HR, appetite/weight (and growth in children), sleep, and psychiatric symptoms.
- 3 Assess risk of misuse, abuse, addiction and diversion; use prescription monitoring and prefer long-acting formulations in higher-risk patients.
- 4 Be aware of drug-specific interactions (e.g. CYP2D6 inhibitors with amphetamine products; reduced efficacy of hormonal contraceptives with modafinil/armodafinil).
- 5 Consider cardiovascular risk and overall clinical assessment before initiation; ECG not routine unless clinically indicated.



Key Message

Effective when used appropriately, with careful patient selection, monitoring and risk mitigation.



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Thank You for Your Attention!

Questions, Discussion & Collaboration

Better Science
Brighter Practice
Healthier Lives



*Evidence informs our decisions,
but it is our clinical judgment and humanity
that make the difference."*

— In the service of better mental health



Questions?

Let's discuss.



Ideas?

Let's share.



Collaboration?

Let's build
a better future together.

Thank you

for being part of this journey.

