

CNS stimulants and ADHD agents

Controlled stimulants that raise noradrenergic and dopaminergic signalling, together with the non-stimulant agents used for the same indication, grouped here because the division between scheduled and unscheduled drugs governs almost every practical decision about them.

Online guide: <https://www.medguideglobal.com/pharmacology/central-nervous-system/cns-stimulants-and-adhd-agents>

Content updated: 2026-08-23

Quick revision

One Liner: Stimulants act on the noradrenaline and dopamine transporters and act fast, but every one of them is a Schedule II controlled substance whose label demands attention to the heart, to growth and to mental state.

1. Methylphenidate blocks the reuptake of noradrenaline and dopamine into the presynaptic neuron and increases the release of these monoamines into the extraneuronal space. [1]
2. Even so, the same label is explicit that the mode of therapeutic action in ADHD and narcolepsy is not known, so the transporter effect is a description rather than an explanation. [1]
3. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity, and their labels state the exact mode of therapeutic action in ADHD is not known either. [4]
4. Every stimulant here is a Schedule II controlled substance carrying a boxed warning headed abuse, misuse, and addiction. [3][5]
5. As a class these drugs raise blood pressure by a mean of roughly 2 to 4 mmHg and heart rate by roughly 3 to 6 beats per minute. [1]
6. Sudden death has been reported in patients with structural cardiac abnormalities or other serious cardiac disease treated with CNS stimulants at recommended ADHD dosages. [4]
7. Children given methylphenidate on seven days a week through the year had a temporary slowing of growth rate, averaging about 2 cm less height and 2.7 kg less weight over three years. [1]
8. At recommended dosage stimulants may cause psychotic or manic symptoms in patients with no prior history of psychotic illness or mania. [3]
9. Lisdexamfetamine is a prodrug of dextroamphetamine, converted to dextroamphetamine and l-lysine primarily in blood by the hydrolytic activity of red blood cells. [3]
10. Atomoxetine is not a controlled substance, but it carries its own boxed warning for suicidal thoughts and behaviours in paediatric patients aged six and over. [6]
11. Guanfacine and clonidine are central alpha-2 adrenergic agonists and are not central nervous system stimulants; sedation and falling blood pressure are the trade-off. [7][8]

Overview

1. The medicines used for attention deficit hyperactivity disorder divide into two groups that are easier to learn apart than together. The stimulants act on monoamine transporters, work quickly, and are scheduled controlled drugs. The non-stimulants act elsewhere, are not scheduled, and buy their lower abuse liability with sedation, hypotension or a different warning altogether. Methylphenidate is licensed for ADHD in paediatric patients six years and older and in adults, and also for narcolepsy. [1][7]
2. What the stimulant labels actually claim is narrower than most textbooks suggest. Methylphenidate blocks monoamine reuptake and increases monoamine release into the extraneuronal space, and amphetamines are described the same way, yet both labels then say the therapeutic mechanism in ADHD is not known. The dextroamphetamine label goes further, stating there is neither specific evidence which clearly establishes the mechanism whereby amphetamines produce mental and behavioural effects in children, nor conclusive evidence about

how those effects relate to the state of the central nervous system. [1][4][5]

3. Four safety themes run through every stimulant label and are the reason this class is monitored rather than simply prescribed: abuse and dependence, a modest but real pressor effect set against a warning about pre-existing cardiac disease, slowing of growth in children, and the emergence or worsening of psychiatric symptoms. UK regulators translate those themes into practice by advising baseline cardiovascular assessment and a family history of sudden cardiac death, then recording blood pressure and pulse on a centile chart at every dose adjustment and at least every six months. [1][10]

Classification and drug examples

Intro: Grouped by molecular target, because that is what determines whether an agent is a controlled substance, how fast it acts, and which organ system needs watching. The first two groups are the scheduled stimulants; the remaining three are the alternatives reached for when a stimulant is unsuitable, ineffective or unwanted.

1. Name: Methylphenidate-type reuptake blockers

1. Note: Piperidine stimulants that act at the noradrenaline and dopamine transporters without the release-promoting reputation of the amphetamines, though their labels credit them with both actions.

1. Name: Methylphenidate

1. Ritalin

2. Concerta

1. Route: Oral

1. Note: First approved in the United States in 1955 and still the reference stimulant. Its warnings section is a checklist of the class problems: abuse, risk in serious cardiac disease, raised blood pressure and heart rate, psychiatric reactions, priapism, peripheral vasculopathy, growth suppression, glaucoma and tics. [1]

2. Name: Dexmethylphenidate

Focalin

2. Route: Oral

2. Note: The pharmacologically active d-threo enantiomer of racemic methylphenidate. It carries the identical boxed warning and the same growth-rate figures, so choosing it over the racemate changes exposure, not the warning set. [2][1][2]

2. Name: Amphetamine-type stimulants

2. Note: Sympathomimetic amines whose labels describe both transporter blockade and increased monoamine release. Peripheral sympathomimetic actions are part of the pharmacology, not an off-target surprise.

1. Name: Lisdexamfetamine

1. Vyvanse

2. Elvanse

1. Route: Oral

1. Note: A prodrug of dextroamphetamine. Unconverted parent drug is present at low and transient concentrations, generally becoming non-quantifiable within eight hours, which is why the profile a patient experiences is essentially that of dextroamphetamine arriving slowly. [3]

2. Name: Dextroamphetamine

1. Dexamfetamine

2. Xelstrym transdermal system

2. Route: Oral and transdermal

2. Note: Has no medicine page on this site yet. Licensed for narcolepsy and for attention deficit disorder with hyperactivity, and contraindicated during or within fourteen days of a monoamine oxidase inhibitor because hypertensive crises may result. [5][4] [4][5]

3. Name: Selective noradrenaline reuptake inhibitors

3. Note: The non-stimulant that stays within monoamine pharmacology. No dopamine transporter action is claimed, and

no controlled-substance schedule applies.

Name: Atomoxetine

Strattera

Route: Oral

Note: Has no medicine page on this site yet. Its label states the precise mechanism is unknown but is thought to be related to selective inhibition of the pre-synaptic noradrenaline transporter, and that atomoxetine is not a controlled substance. [6] [6]

4. Name: Central alpha-2 adrenergic agonists

4. Note: Antihypertensives repurposed for ADHD, licensed both alone and alongside a stimulant. Their cardiovascular effect runs in the opposite direction to the stimulants, which is the whole point and also the whole problem.

1. Name: Guanfacine

Intuniv

1. Route: Oral, extended release

1. Note: A central alpha-2A adrenergic receptor agonist whose mechanism in ADHD its label says is not known. The label states plainly that it is not a controlled substance and has no known potential for abuse or dependence. [7]

2. Name: Clonidine

Kapvay

2. Route: Oral, extended release

2. Note: Stimulates alpha-2 adrenergic receptors in the brain and is not a central nervous system stimulant. The extended-release ADHD label warns that abrupt discontinuation can cause rebound hypertension. [8] [7][8]

5. Name: Wakefulness-promoting agents

5. Note: Not ADHD drugs, but they sit in this family because they share a stimulant-adjacent pharmacology and a controlled-substance schedule, and students meet them alongside narcolepsy.

Name: Modafinil

Provigil

Route: Oral

Note: Has no medicine page on this site yet. A Schedule IV controlled substance whose wakefulness mechanism is unknown; in vitro it binds the dopamine transporter and inhibits dopamine reuptake, associated in vivo with raised extracellular dopamine in some brain regions. [9] [9]

Mechanism of action

Summary: Two stimulant mechanisms and three alternatives. Methylphenidate and the amphetamines both act at the noradrenaline and dopamine transporters, blocking reuptake and increasing release into the extraneuronal space, while their labels decline to say that this is why they help ADHD. Atomoxetine narrows the target to the noradrenaline transporter alone, the alpha-2 agonists leave monoamine transport entirely, and modafinil's wakefulness mechanism remains unexplained.

Target: The noradrenaline and dopamine transporters, the pre-synaptic noradrenaline transporter alone, and central alpha-2 adrenergic receptors

Cidal Static: Symptom-suppressing while present, not disease-modifying

Kill Kinetics: Effect tracks plasma concentration, which is why formulation and duration of action dominate practical choice

1. Step: 1

1. Title: Transporter blockade by methylphenidate

1. Detail: The label's pharmacodynamic section credits methylphenidate with blocking noradrenaline and dopamine reuptake into the presynaptic neuron while increasing the amount of those monoamines released into the extraneuronal space. It separates that description from any therapeutic claim, stating in the same document that the mode of therapeutic action in ADHD and narcolepsy is not known. [1]

2. Step: 2

2. Title: The same action described for the amphetamines

2. Detail: Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity, and are likewise described as blocking monoamine reuptake into the presynaptic neuron and increasing release of those monoamines into the extraneuronal space. Peripheral consequences follow directly: elevation of systolic and diastolic blood pressure, and weak bronchodilator and respiratory stimulant action. [4][5]

3. Step: 3

3. Title: Enzymatic unmasking of a prodrug

3. Detail: Lisdexamfetamine is dextroamphetamine covalently bound to the amino acid L-lysine. It is converted to dextroamphetamine and L-lysine primarily in blood, by the hydrolytic activity of red blood cells, and the unconverted parent is present only at low and transient concentrations. Because the active drug has to be liberated enzymatically rather than absorbed as such, the intention was to make the molecule less rewarding to swallow in bulk, snort or inject. [3]

4. Step: 4

4. Title: Selective inhibition of the noradrenaline transporter

4. Detail: Atomoxetine's label states that the precise mechanism by which it produces its therapeutic effects in ADHD is unknown, but is thought to be related to selective inhibition of the pre-synaptic noradrenaline transporter. Leaving the dopamine transporter alone is the pharmacological difference that tracks with its lack of a controlled-substance schedule. [6]

5. Step: 5

5. Title: Post-synaptic alpha-2 adrenergic agonism

5. Detail: Guanfacine is a central alpha-2A adrenergic receptor agonist and clonidine stimulates alpha-2 adrenergic receptors in the brain. Both labels state that the drug is not a central nervous system stimulant and that its mechanism in ADHD is not known. The receptor these agents occupy is the same one that lowers sympathetic outflow, which is why sedation and reduced blood pressure arrive with the therapeutic effect rather than instead of it. [7][8]

6. Step: 6

6. Title: An unexplained wakefulness effect

6. Detail: The mechanism through which modafinil promotes wakefulness is unknown. In vitro it binds the dopamine transporter and inhibits dopamine reuptake, an action associated in vivo with increased extracellular dopamine in some brain regions, which is the pharmacological reason it is scheduled at all. [9]

Major clinical uses

1. Drug: Methylphenidate

1. Organism: Not applicable

1. Indication: ADHD in paediatric patients six years and older and in adults, and narcolepsy

1. Line: first-line stimulant

1. Note: The narcolepsy indication is worth remembering because it explains why a controlled stimulant appears on a sleep-medicine list as well as a paediatric psychiatry one. [1]

2. Drug: Dexmethylphenidate

2. Organism: Not applicable

2. Indication: ADHD

2. Line: alternative to racemic methylphenidate

2. Note: In paediatric trials the reactions reported at a rate of at least 5% and at twice the placebo rate were abdominal pain, fever, nausea and anorexia. [2]

3. Drug: Lisdexamfetamine

3. Organism: Not applicable

3. Indication: ADHD in adults and paediatric patients six years and older, and moderate to severe binge eating disorder

in adults

3. Line: first-line stimulant

3. Note: The binge eating disorder indication is specific to this molecule among the drugs on this page, and is limited to adults with moderate to severe disease. [3]

4. Drug: Dextroamphetamine

4. Organism: Not applicable

4. Indication: Narcolepsy, and attention deficit disorder with hyperactivity

4. Line: established stimulant

4. Note: Named without a link because it has no medicine page here. The transdermal system carries the same boxed warning and the same Schedule II status as the oral tablets. [5][4]

5. Drug: Atomoxetine

5. Organism: Not applicable

5. Indication: ADHD

5. Line: non-stimulant alternative

5. Note: Chosen where a controlled substance is unsuitable, unwanted or has failed. The trade is a slower onset and a boxed warning of its own rather than a scheduling problem. [6]

6. Drug: Guanfacine

6. Organism: Not applicable

6. Indication: ADHD, as monotherapy and as adjunctive therapy to stimulant medicines

6. Line: non-stimulant alternative or add-on

6. Note: The adjunctive licence matters: these agents are not only a fallback but a recognised addition when a stimulant alone is insufficient. [7]

7. Drug: Clonidine

7. Organism: Not applicable

7. Indication: ADHD, either alone or added to a stimulant

7. Line: non-stimulant alternative or add-on

7. Note: The extended-release preparation is the one licensed for ADHD; the drug's older identity as a centrally acting antihypertensive is what shapes its warning set. [8]

8. Drug: Modafinil

8. Organism: Not applicable

8. Indication: Improving wakefulness in adults with excessive sleepiness associated with narcolepsy, obstructive sleep apnoea or shift work disorder

8. Line: wakefulness-promoting agent

8. Note: In obstructive sleep apnoea it is indicated to treat the excessive sleepiness and not as treatment for the underlying obstruction, and the label states it does not take the place of getting enough sleep. [9]

Pharmacokinetics

1. Drug: Lisdexamfetamine

1. Route: Oral

1. Absorption: Peak parent-drug concentration around one hour after a dose, with dextroamphetamine peaking around three and a half hours in children with ADHD

1. Csf Penetration: Not applicable

1. Metabolism: Hydrolysed to dextroamphetamine and l-lysine primarily in blood by red blood cells

1. Elimination: Predominantly urinary; about 96% of an oral radiolabelled dose was recovered in urine and only 0.3% in faeces

1. Half Life: Under one hour for the parent prodrug; roughly 8.6 to 9.5 hours for dextroamphetamine in children aged six to twelve and 10 to 11.3 hours in healthy adults

1. Dose Adjust: Neither a high-fat meal, yoghurt nor orange juice altered dextroamphetamine exposure in healthy adults [3]
2. Drug: Atomoxetine
2. Route: Oral
2. Absorption: Absolute bioavailability around 63%, rising to about 94% in CYP2D6 poor metabolisers
2. Csf Penetration: Not applicable
2. Metabolism: CYP2D6, an enzyme whose gene carries variants that alter metabolic function
2. Elimination: More than 80% of a dose leaves as 4-hydroxyatomoxetine-O-glucuronide and less than 3% as unchanged drug
2. Half Life: About 5.2 hours in extensive metabolisers against about 21.6 hours in poor metabolisers
2. Dose Adjust: Paroxetine or fluoxetine raised plasma atomoxetine exposure six- to eight-fold, so a CYP2D6 inhibitor turns an ordinary patient into a slow metaboliser [6]
3. Drug: Guanfacine
3. Route: Oral, extended release
3. Absorption: Exposure rises markedly with a high-fat meal, so the label directs against administering it with one
3. Csf Penetration: Not applicable
3. Metabolism: Primarily CYP3A4, with plasma concentrations significantly affected by inhibitors and inducers of that enzyme
3. Elimination: Hepatic metabolism with a renal contribution
3. Half Life: Mean of approximately 18 hours in adults
3. Dose Adjust: The label caps exposure with a strong CYP3A4 inhibitor and allows upward titration with a strong inducer such as rifampicin; the figures are prescribing decisions and are deliberately not reproduced here [7]
1. No dose regimens appear on this page. Choice of agent, formulation, titration and monitoring are decisions for the treating clinician working from a current prescribing reference and the individual patient in front of them.
2. Formulation is the dominant pharmacokinetic variable for the stimulants, because duration of action rather than any difference in receptor pharmacology is usually what separates one methylphenidate product from another. [1][2]
3. Two enzymes are worth memorising for the non-stimulants: CYP2D6 for atomoxetine and CYP3A4 for guanfacine, since each converts an ordinary drug interaction into a several-fold change in exposure. [6][7]

Adverse effects

1. Effect: Appetite suppression, weight loss and insomnia
1. Detail: The reactions reported most often with lisdexamfetamine in ADHD trials were anorexia, anxiety, decreased appetite, decreased weight, diarrhoea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain and vomiting. Methylphenidate's own list runs along the same lines, with insomnia, decreased appetite, weight loss, dry mouth, anxiety and hyperhidrosis. [3][1]
2. Effect: Tachycardia and palpitations
2. Detail: Reported commonly with methylphenidate alongside headache. These are the symptomatic face of the same pressor and chronotropic effect that shows up as a small mean rise in blood pressure and pulse across a treated population. [1]
3. Effect: Somnolence and sedation with the alpha-2 agonists
3. Detail: Somnolence and sedation were commonly reported in the clinical studies of both guanfacine and clonidine, with fatigue, hypotension and lethargy among the other frequent reactions. The direction of travel is the exact opposite of the stimulants. [7][8]
1. Effect: Abuse, misuse and addiction
1. Detail: The stimulant boxed warning is uniform across the class. The lisdexamfetamine version reads that the drug has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction, that misuse and abuse of CNS stimulants can result in overdose and death, and that this risk is increased

with higher doses or unapproved methods of administration, such as snorting or injection.

1. Action: The label directs that each patient's risk is assessed before prescribing, that patients and families are educated about storage and disposal, and that risk is reassessed with frequent monitoring for signs of abuse throughout treatment. [3]

2. Effect: Risk in patients with serious cardiac disease

2. Detail: The reports of sudden death that shape this warning came from patients who already had a structural cardiac abnormality or other serious cardiac disease and were taking a CNS stimulant at a recommended ADHD dosage. The labels frame this as a risk concentrated in that group rather than as a general expectation, and separately record that the drugs raise blood pressure by a mean of about 2 to 4 mmHg and heart rate by about 3 to 6 beats per minute.

2. Action: Methylphenidate labelling advises avoiding use in patients with known serious structural cardiac disease, cardiomyopathy, serious arrhythmias or coronary artery disease; whether an individual falls into that group is a clinical judgement, not a page-level one. [4][1]

3. Effect: Psychiatric adverse reactions

3. Detail: At the recommended dosage these drugs may cause psychotic or manic symptoms such as hallucinations, delusional thinking or mania in patients with no prior history of psychotic illness or mania. They may also exacerbate symptoms of behaviour disturbance and thought disorder in patients with a pre-existing psychotic disorder, and may induce a manic or mixed mood episode.

3. Action: Screening for a personal or family history of bipolar disorder before treatment, and treating new psychosis or mania as a reason for urgent clinical reassessment rather than dose adjustment by the patient. [3][1]

4. Effect: Long-term suppression of growth in children

4. Detail: CNS stimulants have been associated with weight loss and slowing of growth rate in paediatric patients. Children medicated on seven days a week throughout the year showed a temporary slowing of growth rate amounting on average to about 2 cm less height and 2.7 kg less weight over three years.

4. Action: Labels direct close monitoring of weight and height, with treatment interruption considered for a child who is not growing or gaining as expected. UK guidance operationalises this as recording height, weight and appetite on a growth chart at least every six months. [1][10]

5. Effect: Suicidal thoughts and behaviours with atomoxetine

5. Detail: Atomoxetine increased the risk of suicidal ideation in paediatric patients aged six and over with ADHD in short-term studies. Across twelve studies of more than 2,200 children, the mean incidence of suicidal ideation was 0.4%, five of 1,357 treated patients, against 0% of 851 given placebo. No suicides occurred in those studies.

5. Action: Its boxed warning directs that all treated paediatric patients aged six and over are monitored and observed closely for suicidal thoughts and behaviour, clinical worsening, or unusual changes in behaviour. [6]

6. Effect: Hepatic injury with atomoxetine

6. Detail: Rare cases of liver failure, including cases progressing to transplantation, have been reported after marketing. Jaundice or laboratory evidence of liver injury is treated as an end point rather than a monitoring finding.

6. Action: The label directs that the drug is discontinued and not restarted in patients with jaundice or laboratory evidence of liver injury. [6]

7. Effect: Peripheral vasculopathy including Raynaud's phenomenon

7. Detail: Signs and symptoms are usually intermittent and mild, but sequelae have included digital ulceration and soft tissue breakdown. Patients may report numbness, coolness, pain or colour change in fingers and toes.

7. Action: Careful observation for digital changes is advised during treatment, with further evaluation such as rheumatology referral where signs of peripheral vasculopathy develop. [2][3]

8. Effect: Serious rash with modafinil

8. Detail: Rare cases of serious or life-threatening rash, including Stevens-Johnson syndrome, toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms, have been reported in adults and children.

8. Action: A rash on modafinil is a reason for prompt medical assessment rather than watchful waiting, and the decision about continuing rests with the prescriber. [9]

1. Drug: Methylphenidate

1. Effect: Priapism. Prolonged and painful erections, sometimes requiring surgical intervention, have been reported, and the label directs that sustained painful erection prompts immediate medical attention. [1]

2. Drug: Methylphenidate

2. Effect: Motor and verbal tics, and worsening of Tourette's syndrome, appear as a named warning; the amphetamine labelling records the same association with onset or exacerbation of tics. [1][5]

3. Drug: Lisdexamfetamine

3. Effect: Serotonin syndrome, a potentially life-threatening reaction, may occur when amphetamines are combined with other drugs affecting serotonergic neurotransmitter systems. [3]

4. Drug: Atomoxetine

4. Effect: Clinically important rises in pulse and blood pressure in a minority of patients, which is why heart rate and blood pressure are measured at baseline, after each increase and periodically thereafter. [6]

5. Drug: Guanfacine

5. Effect: Dose-dependent falls in blood pressure and heart rate, with orthostatic hypotension and syncope reported. [7]

6. Drug: Clonidine

6. Effect: Dose-related decreases in blood pressure and heart rate, together with nightmare, irritability, constipation and dry mouth among the commonly reported reactions. [8]

7. Drug: Modafinil

7. Effect: Psychiatric reactions reported after marketing include mania, delusions, hallucinations, suicidal ideation and aggression, and caution is advised in patients with a history of psychosis, depression or mania. [9]

Contraindications, precautions and interactions

1. Concomitant use of methylphenidate with a monoamine oxidase inhibitor, or within fourteen days of stopping one, is contraindicated because of the risk of hypertensive crisis with potentially fatal outcome. [1]

2. The amphetamine labels state the same exclusion in their own words: during or within fourteen days following administration of a monoamine oxidase inhibitor, because hypertensive crises may result. [5][4]

3. Atomoxetine is contraindicated with monoamine oxidase inhibitors, including linezolid and intravenous methylene blue, or within fourteen days of stopping one, and also in narrow angle glaucoma and in pheochromocytoma or a history of it. [6]

1. Stimulants are to be avoided in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease or other serious cardiac disease, which is the population in whom sudden deaths have been reported. [3]

2. Atomoxetine is contraindicated in severe cardiac or vascular disorders whose condition would be expected to deteriorate with a clinically important rise in heart rate or blood pressure, so the non-stimulant is not automatically the cardiac-safe option. [6]

3. Before a stimulant is started, UK guidance advises assessing baseline cardiovascular status including blood pressure and heart rate, and documenting any family history of sudden cardiac death, unexplained death or malignant arrhythmia. [10]

4. Abrupt discontinuation of extended-release clonidine can cause rebound hypertension, so the label directs gradual reduction in small decrements over several days rather than simply stopping. [8]

5. Guanfacine behaves less dramatically on withdrawal: infrequent, transient elevations of blood pressure above the original baseline have been reported after abrupt discontinuation, and tapering is advised to minimise them. [7]

6. Because the alpha-2 agonists sedate, the labels advise considering additive effects with other central nervous system depressants and alcohol, and warn against driving or operating heavy machinery until the individual response is known. [7][8]

1. With: Monoamine oxidase inhibitors

1. Effect: The defining interaction of the class. Blocking monoamine breakdown while a stimulant drives monoamine

release risks hypertensive crisis, and a fourteen-day washout after the inhibitor is the standard requirement across stimulant and non-stimulant labels alike. [1][6]

2. With: Strong CYP2D6 inhibitors such as paroxetine and fluoxetine

2. Effect: Six- to eight-fold increases in plasma atomoxetine exposure. Since both drugs are antidepressants, this is a plausible real-world combination rather than a theoretical one. [6]

3. With: CYP3A4 inhibitors and inducers

3. Effect: Guanfacine is primarily metabolised by CYP3A4 and its plasma concentrations can be affected significantly in either direction, with ketoconazole raising exposure and rifampicin lowering it. [7]

4. With: Serotonergic drugs

4. Effect: Amphetamines combined with drugs affecting serotonergic neurotransmission may precipitate serotonin syndrome, a potentially life-threatening reaction. [3]

5. With: Steroidal contraceptives

5. Effect: Their effectiveness may be reduced during modafinil treatment and for one month after it stops, so alternative or additional contraception is recommended. [9]

6. With: Other central nervous system depressants and alcohol

6. Effect: Additive sedation with guanfacine, which is the practical reason the alpha-2 agonists are often given at a time of day chosen around the sedation rather than around the symptoms. [7]

Comparison tables

Title: Stimulant against non-stimulant: what actually differs

Caption: Scheduling, speed and the shape of the warning set separate these agents far more than efficacy claims do. Which one suits a given patient is a decision for the treating clinician.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: target

2. Label: Molecular target

3. Key: schedule

3. Label: Controlled status

4. Key: signature

4. Label: Signature warning

1. Drug: Methylphenidate

1. Target: Noradrenaline and dopamine transporters

1. Schedule: Schedule II

1. Signature: Abuse and addiction; growth slowing; priapism and tics [1]

2. Drug: Dexmethylphenidate

2. Target: Noradrenaline and dopamine transporters, as the active enantiomer

2. Schedule: Schedule II

2. Signature: Identical stimulant warning set to the racemate [2]

3. Drug: Lisdexamfetamine

3. Target: Amphetamine pharmacology, released by hydrolysis of a prodrug

3. Schedule: Schedule II

3. Signature: Abuse and addiction despite the prodrug design; serotonin syndrome with serotonergic drugs [3]

4. Drug: Dextroamphetamine

4. Target: Noradrenaline and dopamine transporters, with increased monoamine release

4. Schedule: Schedule II

4. Signature: Hypertensive crisis with a monoamine oxidase inhibitor [4][5]

5. Drug: Atomoxetine
5. Target: Pre-synaptic noradrenaline transporter only
5. Schedule: Not a controlled substance
5. Signature: Suicidal thoughts and behaviours in paediatric patients; hepatic injury [6]
6. Drug: Guanfacine
6. Target: Central alpha-2A adrenergic receptor
6. Schedule: Not a controlled substance, with no known abuse potential
6. Signature: Hypotension, bradycardia, syncope and somnolence [7]
7. Drug: Clonidine
7. Target: Central alpha-2 adrenergic receptors
7. Schedule: Not a controlled substance
7. Signature: Rebound hypertension after abrupt withdrawal [8]
8. Drug: Modafinil
8. Target: Unknown; binds the dopamine transporter in vitro
8. Schedule: Schedule IV
8. Signature: Serious rash, and reduced steroidal contraceptive effectiveness [9]

High-yield exam pearls

1. Pearl: Every stimulant on this page is Schedule II; modafinil is Schedule IV; atomoxetine, guanfacine and clonidine are not controlled substances at all.
1. Why: Scheduling is the fastest way to sort the class in an examination question, and it maps directly onto the boxed warning each drug carries. [3][9][6][7]
2. Pearl: The label figure for the stimulant pressor effect is a mean rise of roughly 2 to 4 mmHg in blood pressure and 3 to 6 beats per minute in heart rate.
2. Why: It is small enough to be missed on a single reading and large enough to matter in someone already at cardiovascular risk, which is precisely why monitoring is scheduled rather than symptom-driven. [1]
3. Pearl: Lisdexamfetamine must be hydrolysed by red blood cells to dextroamphetamine before it does anything, and the parent drug becomes non-quantifiable within about eight hours.
3. Why: The conversion step is the examinable feature of the molecule, and the reason its onset is smoother than an equivalent immediate-release amphetamine. [3]
4. Pearl: Atomoxetine's boxed warning is for suicidal ideation in children and adolescents, not for abuse.
4. Why: Candidates who assume every ADHD drug carries the same boxed warning get this backwards; the non-stimulant swaps one warning for another rather than escaping warnings. [6]
5. Pearl: Clonidine's label warns of rebound hypertension on abrupt discontinuation, while guanfacine's describes infrequent, transient elevations above the original baseline.
5. Why: Two alpha-2 agonists with the same broad mechanism carry differently worded withdrawal warnings, and reproducing each label's own wording is what a well-set question rewards. [8][7]
6. Pearl: Atomoxetine is a CYP2D6 substrate whose half-life stretches from about 5.2 hours in extensive metabolisers to about 21.6 hours in poor metabolisers.
6. Why: It is a clean pharmacogenomic example, and it explains why adding paroxetine or fluoxetine multiplies exposure several-fold. [6]

Common exam traps

1. Trap: Stating that stimulants cause sudden cardiac death.
1. Correction: The labels report sudden death in patients with structural cardiac abnormalities or other serious cardiac disease treated at recommended ADHD dosages, and direct avoidance in that group. That is a restriction in a defined population, not a general claim about healthy patients. [4][3]

2. Trap: Saying methylphenidate blocks reuptake while amphetamines only promote release.
2. Correction: Both label families describe blockade of noradrenaline and dopamine reuptake into the presynaptic neuron together with increased release of those monoamines into the extraneuronal space. The clean textbook split is not what the regulatory text says. [1][4]
3. Trap: Treating the prodrug design of lisdexamfetamine as a solution to abuse liability.
3. Correction: It remains a Schedule II drug carrying the full boxed warning on abuse, misuse and addiction, with an explicit statement that risk rises with higher doses or unapproved routes such as snorting or injection. [3]
4. Trap: Assuming a non-stimulant is the safe choice in cardiac disease.
4. Correction: Atomoxetine is contraindicated in severe cardiac or vascular disorders that would be expected to deteriorate with a clinically important rise in heart rate or blood pressure, and it raises pulse and blood pressure in a minority of patients. [6]
5. Trap: Claiming the mechanism of ADHD treatment is settled.
5. Correction: Methylphenidate, amphetamine, atomoxetine, guanfacine, clonidine and modafinil labels all say in one form or another that the therapeutic mechanism is not known. Transporter pharmacology describes what the drug does, not why the symptoms improve. [1][6][7][9]
6. Trap: Forgetting that modafinil interferes with hormonal contraception.
6. Correction: Steroidal contraceptive effectiveness may be reduced during modafinil treatment and for a month after it is stopped, so alternative or concomitant methods are recommended. [9]

Self-test questions

1. Question: A methylphenidate label describes the drug's action on monoamine transporters. Which statement matches the label's own position on mechanism?
 1. It blocks reuptake of noradrenaline and dopamine and increases their release, yet the mode of therapeutic action in ADHD is not known
 2. It is a selective dopamine receptor agonist with a proven mechanism in ADHD
 3. It irreversibly inhibits monoamine oxidase in the presynaptic terminal
 4. It acts entirely through the alpha-2A adrenergic receptor
1. Explanation: The label pairs a pharmacodynamic description of reuptake blockade and increased monoamine release in the extraneuronal space with an explicit statement that the mode of therapeutic action in ADHD and narcolepsy is not known. [1]
2. Question: Which ADHD medicine carries a boxed warning for suicidal ideation in paediatric patients rather than for abuse and addiction?
 1. Atomoxetine
 2. Lisdexamfetamine
 3. Dexmethylphenidate
 4. Dextroamphetamine
2. Explanation: Atomoxetine's boxed warning concerns suicidal thoughts and behaviours in paediatric patients aged six and over, with an incidence of 0.4% against 0% on placebo across twelve short-term studies. It is not a controlled substance. [6]
3. Question: How is lisdexamfetamine converted to its active moiety?
 1. Hydrolysis primarily in blood by red blood cells, yielding dextroamphetamine and l-lysine
 2. First-pass N-demethylation in the liver by CYP3A4
 3. Hydrolysis by gastric acid before absorption
 4. Renal tubular cleavage during excretion
3. Explanation: Its label states that lisdexamfetamine is converted to dextroamphetamine and l-lysine primarily in blood due to the hydrolytic activity of red blood cells, and that unconverted parent drug circulates only at low and transient concentrations. [3]

4. Question: A child treated with a stimulant every day for three years is likely to show which growth effect according to the labelling?

1. A temporary slowing of growth rate, on average about 2 cm less height and 2.7 kg less weight
2. Permanent loss of about 10 cm of final adult height
3. Accelerated growth with early epiphyseal closure
4. No measurable effect on height or weight at any point

4. Explanation: Labelling reports that paediatric patients medicated on seven days a week throughout the year had a temporary slowing in growth rate averaging about 2 cm less growth in height and 2.7 kg less growth in weight over three years, with close monitoring advised. [1]

5. Question: Which agent's label specifically warns that abrupt discontinuation can cause rebound hypertension?

1. Clonidine
2. Atomoxetine
3. Modafinil
4. Dexamethylphenidate

5. Explanation: The extended-release clonidine ADHD label states that abrupt discontinuation can cause rebound hypertension and directs gradual reduction in small decrements over several days rather than stopping outright. [8]

6. Question: A patient stabilised on atomoxetine is started on fluoxetine for depression. What is the expected pharmacokinetic consequence?

1. A six- to eight-fold increase in plasma atomoxetine exposure through CYP2D6 inhibition
2. A halving of atomoxetine exposure through CYP3A4 induction
3. No interaction, because atomoxetine is renally cleared unchanged
4. Accelerated conversion of atomoxetine to an active metabolite

6. Explanation: Atomoxetine is metabolised by CYP2D6, and its label records that concomitant paroxetine or fluoxetine produced six- to eight-fold increases in plasma atomoxetine exposure, effectively converting the patient into a poor metaboliser. [6]

7. Question: Which class of drug must be avoided for fourteen days before a stimulant is started, because of the risk of hypertensive crisis?

1. Monoamine oxidase inhibitors
2. Proton pump inhibitors
3. Beta-lactam antibiotics
4. Thiazide diuretics

7. Explanation: Stimulant and non-stimulant labels alike exclude use during or within fourteen days of a monoamine oxidase inhibitor, because hypertensive crises with potentially fatal outcome may result. [1][5]

8. Question: Which statement about modafinil matches its labelling?

1. It is a Schedule IV controlled substance whose wakefulness mechanism is unknown
2. It is not a controlled substance and acts through proven histamine H3 antagonism
3. It is Schedule II and treats the underlying airway obstruction in sleep apnoea
4. It has no interaction with hormonal contraception

8. Explanation: Modafinil is a Schedule IV controlled substance, the mechanism through which it promotes wakefulness is unknown, and in obstructive sleep apnoea it is indicated for the excessive sleepiness and not as treatment for the underlying obstruction. [9]

Frequently asked questions

1. Question: Why are stimulants controlled substances when they are given to children?

1. Answer: Because the same monoamine pharmacology that improves attention also carries reinforcing potential. The boxed warning states that these drugs have a high potential for abuse and misuse leading to substance use disorder including addiction, and that misuse can result in overdose and death, with risk rising at higher doses or by routes such

as snorting or injection. Scheduling is the regulatory response to that pharmacology, not a comment on the children who are prescribed them. [3]

2. Question: Does a stimulant damage the heart?

2. Answer: The labels are careful here and the page follows them. Across treated populations these medicines produce a mean rise in blood pressure of roughly 2 to 4 mmHg and in heart rate of roughly 3 to 6 beats per minute. Separately, sudden death has been reported in patients who had structural cardiac abnormalities or other serious cardiac disease, and the labelling advises avoiding stimulants in that group. Assessment of an individual's cardiac risk and any change of treatment rest with the treating clinician. [1][4]

3. Question: Why does the prodrug design of lisdexamfetamine matter?

3. Answer: The molecule is dextroamphetamine bound to l-lysine, and it has to be hydrolysed by red blood cells before any amphetamine is available. That enzymatic step was intended to blunt the reward from taking the drug by unapproved routes. It did not remove the liability: the product remains Schedule II with the full class boxed warning on abuse, misuse and addiction. [3]

4. Question: What is lost by choosing a non-stimulant?

4. Answer: Different things depending on which one. Atomoxetine avoids controlled-substance status but carries a boxed warning for suicidal thoughts and behaviours in children and adolescents, needs a CYP2D6-aware eye on interactions, and is stopped permanently if liver injury appears. Guanfacine and clonidine avoid abuse liability altogether but sedate and lower blood pressure, and clonidine's label adds a rebound hypertension warning if it is stopped abruptly. [6][7][8]

5. Question: What monitoring does a child on a stimulant need?

5. Answer: UK regulators advise baseline cardiovascular assessment with a history covering family sudden cardiac death, then blood pressure and pulse recorded on a centile chart at every dose adjustment and at least every six months, height, weight and appetite recorded on a growth chart at least every six months, and review for new or worsening psychiatric symptoms at the same intervals and at every visit. The schedule itself is set by the prescribing team. [10]

6. Question: Are appetite loss and insomnia avoidable?

6. Answer: They are among the most frequently reported reactions rather than rare events: decreased appetite, decreased weight and insomnia appear in the common adverse reaction lists for both methylphenidate and lisdexamfetamine. They also connect to the growth warning, since reduced intake is part of why growth rate slows, which is why appetite is recorded alongside height and weight. [1][3][10]

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