Central nervous system stimulants: basic pharmacology and relevance to anaesthesia and critical care

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Abstract

Central nervous system stimulants provoke cortical, brainstem and spinal cord excitation. They have a wide range of clinical uses and a strong potential for abuse. Central nervous system stimulants can be divided into three categories: psychomotor stimulants; psychotomimetic stimulants.

Psychomotor stimulants produce excitement and euphoria, increase motor activity and reduce fatigue. Psychotomimetic stimulants alter mental function and affect perception and cognition. Respiratory stimulants and convulsants increase activity in the spinal cord and brainstem, leading to hyperreflexia, activation of the respiratory and vasomotor centres and promotion of seizure activity.

Keywords Amphetamine; analeptic; convulsant; methylxanthine; psychomotor; psychotomimetic; stimulant; sympathomimetic

Royal College of Anaesthetists CPD Skills Framework: Scientific principles

Learning objectives

After reading this article, you should be able to:

- classify central nervous system (CNS) stimulants according to their effects
- explain the mechanism of action of common CNS stimulants
- discuss the effects of acute and chronic use of CNS stimulants
- propose appropriate clinical uses for CNS stimulants

Introduction

Central nervous system (CNS) stimulants ('analeptics') provoke cortical, brainstem and spinal cord excitation. This allows for a wide range of clinical uses in the settings of anaesthesia, pain medicine, intensive care, psychiatry and respiratory medicine. However, their dissociative and euphoric effects lead to a strong potential for abuse so they are also clinically encountered in the context of acute intoxication or chronic adverse effects.

CNS stimulants are generally divided into three categories: psychomotor stimulants, psychotomimetics (hallucinogens) and respiratory stimulants (convulsants). Psychomotor stimulants produce excitement and euphoria, increase motor activity and reduce fatigue. Psychotomimetics alter mental function affecting perception and cognition, mimicking some elements of psychosis. Respiratory stimulants and convulsants increase neuronal activity in the spinal cord and brainstem resulting in hyperreflexia and activation of the respiratory and vasomotor centres, potentially causing seizure activity.

Psychomotor stimulants

Psychomotor stimulants are a group of drugs which act as sympathomimetic and dopaminergic agents. They can therefore produce combinations of alertness, excitement, euphoria, chronotropy, inotropy, vasoconstriction, bronchodilation, appetite suppression, motor activity and tremor. They have a wide range of clinical uses including countering the hypotensive effects of general anaesthesia, managing bronchospasm, reducing blood loss during surgery and aiding management of behavioural disorders. They are also utilized as stimulants, performance enhancers and recreational drugs.

Their mechanisms of action (Figure 1) involve both direct and indirect effects including:

- direct receptor activation, e.g. ephedrine
- competitive antagonism of inhibitory receptors, e.g. atropine
- promotion of ligand release, e.g. ephedrine, amphetamines
- inhibition of ligand reuptake, e.g. cocaine, methylphenidate
- reversal of ligand reuptake, e.g. amphetamines
- inhibition of second messenger degradation, e.g. methylxanthines.

These effects commonly act to increase the amount of postsynaptic cyclic adenosine monophosphate (cAMP), which in turn activates protein kinase A (PKA). However, this is complicated by interacting pathways (Figure 2). Dopamine D2 receptors activate $\alpha_{i/o}$ G-protein-coupled receptors (GPCRs), decreasing adenylate cyclase activity and thereby reducing cAMP levels in a similar way to $M_{2/4}$ muscarinic acetylcholine receptors (AChRs) and α_2 adrenergic receptors (ARs). Dopamine D1:D2 receptor dimers activate $\alpha_{q/11}$ GPCRs, as do $M_{1/3/5}$ AChRs and α_1 ARs, producing many downstream effects including calcium ion (Ca^{2+}) release and activation of protein phosphatase 1 (PP1) and protein kinase C (PKC).

The tableau of interacting effects created by each of the psychomotor stimulant drugs, as well as their different pharmacokinetics, allows for their range of different clinical uses and pharmacodynamic actions.

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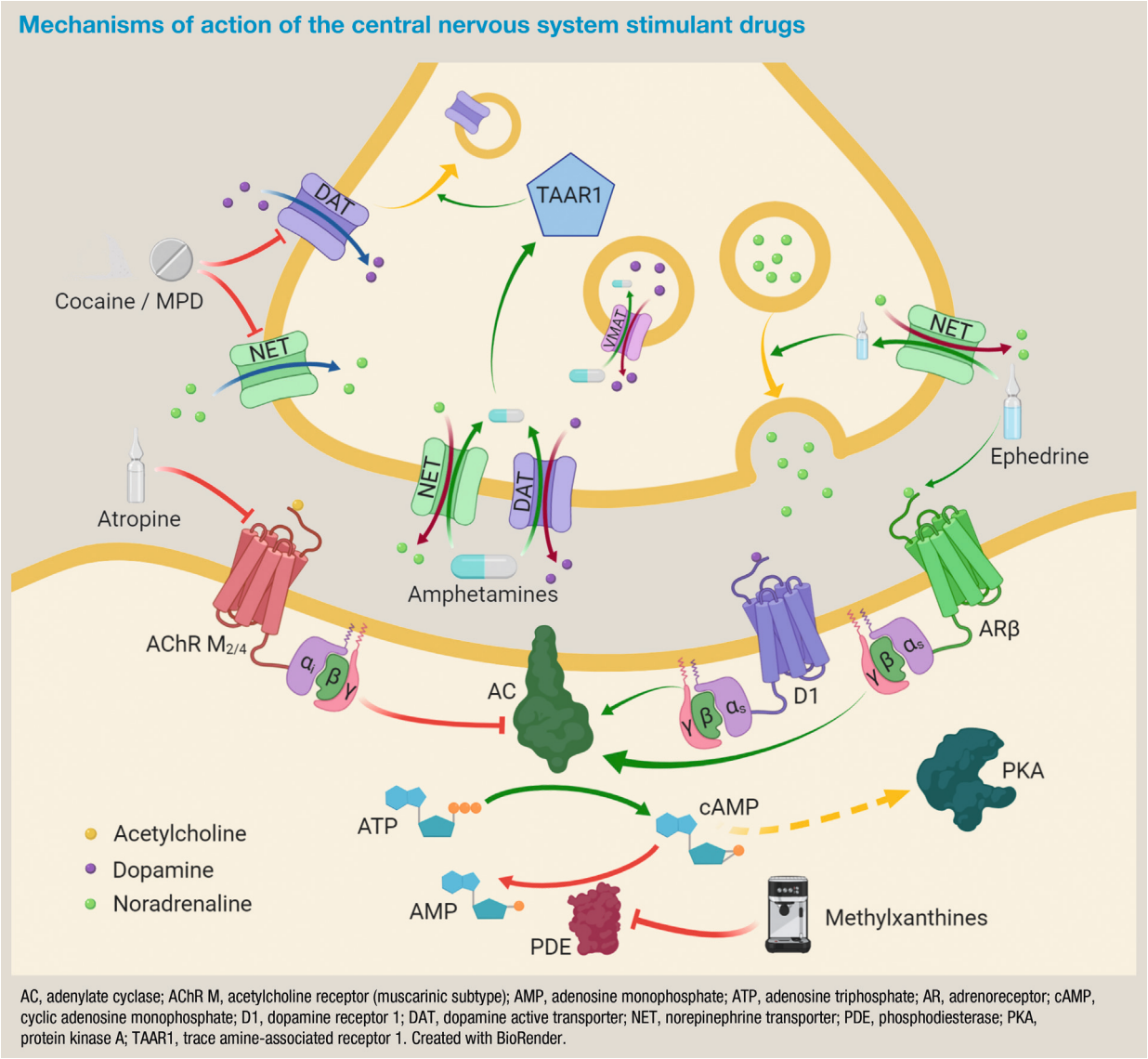


AC, adenylate cyclase; AChR M, acetylcholine receptor (muscarinic subtype); AMP, adenosine monophosphate; ATP, adenosine triphosphate; AR, adrenoreceptor; cAMP, cyclic adenosine monophosphate; D1, dopamine receptor 1; DAT, dopamine active transporter; NET, norepinephrine transporter; PDE, phosphodiesterase; PKA, protein kinase A; TAAR1, trace amine-associated receptor 1. Created with BioRender.

Figure 1

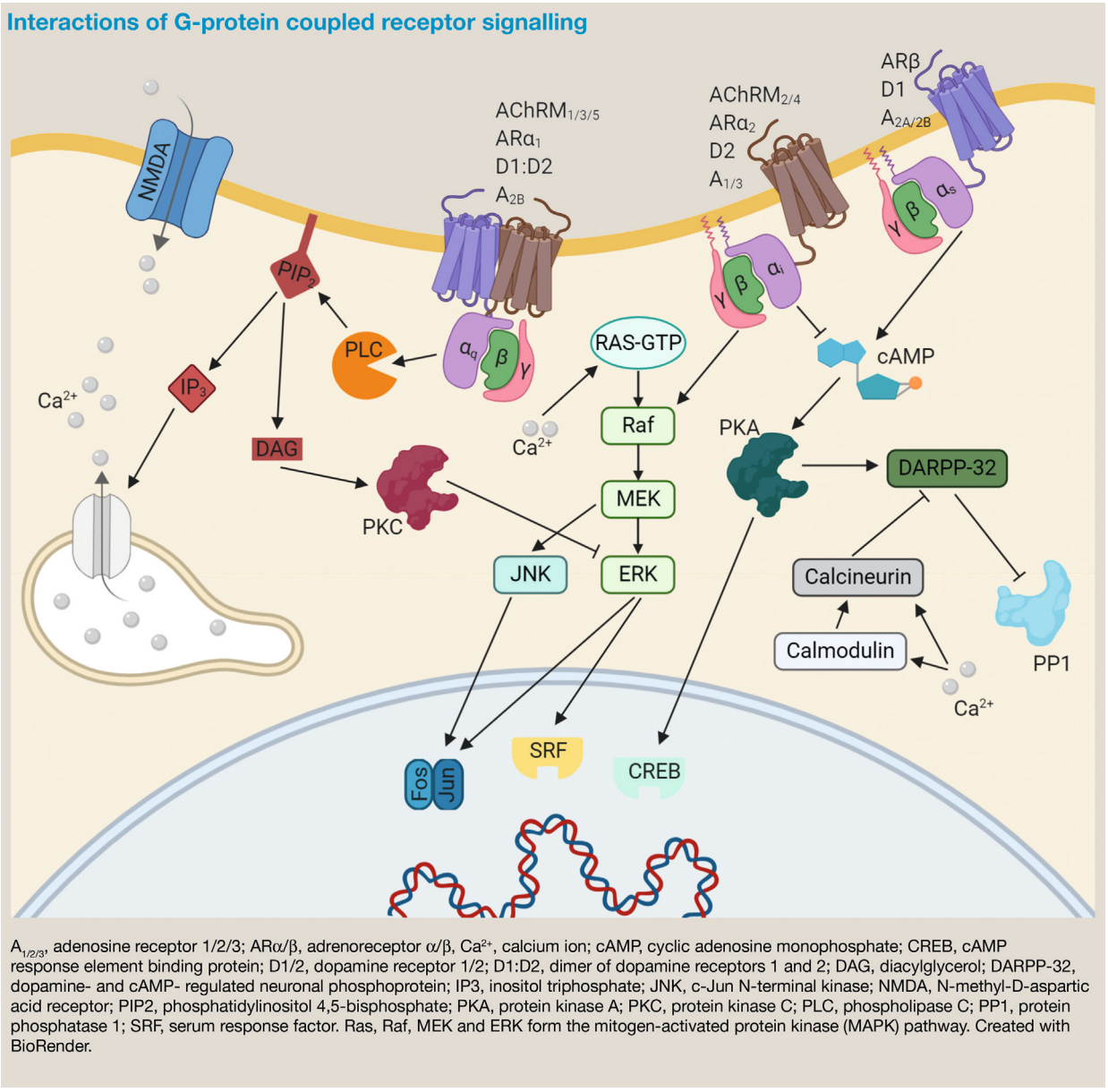
Promotion of ligand release

Ephedrine (Table 1) is a naturally occurring amine from plants of the *Ephedra* genus, such as *Ephedra sinica*. It is presented as a mixture of four isomers of which the levisomer is active. Its main action is to promote release of noradrenaline by displacement from storage vesicles, though it also has minor actions as a direct adrenergic agonist and as a noradrenaline reuptake inhibitor, potentially also reversing the action of norepinephrine transporter (NET). This has the effect of increasing neurotransmitter signal transmission raising post-synaptic cAMP. Tachyphylaxis occurs due to presynaptic noradrenaline depletion, requiring further noradrenaline synthesis to occur before it regains its full efficacy. It is used to treat hypotension under anaesthesia, and uncommonly for the management of bronchospasm and asthma.

One stereoisomer of ephedrine, pseudoephedrine, was commonly used as a nasal decongestant due to its properties as a mucosal vasoconstrictor and reduced CNS effects. However, pseudoephedrine can readily be reduced into methamphetamine, so it is now more common to find phenylephrine in over-the-counter preparations.

Amphetamines are a group of synthetic methylphenethylamine derivates. They include amphetamine, methamphetamine ('crystal meth'), and 3,4-methylenedioxymethamphetaine (MDMA, 'ecstasy'). Amphetamines act by inhibiting reuptake of mono-amines by NET and dopamine active transporter (DAT), reversing their action to promote ligand release. They also displace neuro-transmitters from vesicles and promote internalization of DAT. In addition, MDMA has weak agonist activity at 5-$HT_{1/2}$ receptors, potentially accounting for its hallucinogenic properties. Amphetamines cause wakefulness, increased concentration, tachycardia and euphoria. Toxic effects include formication ('meth mites'), gastrointestinal dysfunction, urinary retention, convulsions, coma, myocardial infarction and stroke.

Clinically, racemic amphetamine and enantiopure dextroamphetamine are used in the management of attention deficit hyper-



$A_{1/2/3}$, adenosine receptor 1/2/3; ARα/β, adrenoreceptor α/β, Ca^{2+}, calcium ion; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element binding protein; D1/2, dopamine receptor 1/2; D1:D2, dimer of dopamine receptors 1 and 2; DAG, diacylglycerol; DARPP-32, dopamine- and cAMP- regulated neuronal phosphoprotein; IP3, inositol triphosphate; JNK, c-Jun N-terminal kinase; NMDA, N-methyl-D-aspartic acid receptor; PIP2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PP1, protein phosphatase 1; SRF, serum response factor. Ras, Raf, MEK and ERK form the mitogen-activated protein kinase (MAPK) pathway. Created with BioRender.

Figure 2

activity disorder (ADHD) and narcolepsy. Amphetamines are also commonly misused as cognitive and physical performance enhancers and as recreational drugs. They have significant risk of dependence and addiction, with tolerance developing rapidly. Withdrawal symptoms, which can last for up to 4 weeks, include anxiety, fatigue, and cognitive and physical depression.

Cathinone is a monoamine alkaloid naturally occurring in *Catha edulis* (khat) shrubs. It promotes dopamine release as well as inhibiting noradrenaline and serotonin reuptake. While illicit in many countries, it is a common recreational drug in the Arabian.

Peninsula and East Africa with over 20 million daily users. It produces a euphoric effect followed by a depressive stage associated with irritability, anorexia and insomnia.

Substituted cathinones (bath salts) constitute a wide array of synthetic variants of cathinone developed as 'legal highs'. The Advisory Council on the Misuse of Drugs implemented a structure-based ban on this class of drugs in 2010, however they remain widely available through online retailers. Two commonly encountered molecules are 4-methylmethcathinone (mephedrone, 'meow meow') and methylendioxypyrovaleron (MDPV). They can be ingested, injected, and are water soluble so may be dissolved in drinks. They produce a feeling of euphoria, mood enhancement, stimulation and hallucination, with side effects of tachycardia, vasoconstriction and agitation.

Antimuscarinic activity

Atropine (Table 1) is a naturally occurring tertiary amine ester from plants of the Solanaceae family, famously from *Atropa belladonna*. It is presented as a racemic mixture of which the levenantiomer is active. It acts as a reversible antagonist of muscarinic acetylcholine receptors, preventing inhibition of

Properties of a selection of more frequently clinically used central nervous system stimulant drugs

		Atropine	Ephedrine	Aminophylline	Cocaine	Ketamine	Doxapram
Chemical		Tertiary amine ester derived from *Atropa belladonna*; racemic mixture of D- and L-hyoscyamine (L- is active)	Sympathomimetic amine; four isomers (L- is active)	Ethylenediamine salt of theophylline (methylxanthine derivative)	Benzoic acid ester from *Erythroxylum coca*	Phencyclidine derivative; racemic mixture of S- and R-ketamine (S- 4x affinity for NMDA receptors, R- greater bronchodilation effect); pH 3.5—5.5, pKa 7.5	Monohydrated pyrrolidinone derivative
Uses		Counter bradycardia, dry secretions, OP poisoning, tetanus, cycloplegia	Hypotension, asthma, nasal decongestion	Asthma, COPD	Topical vasoconstrictor	Induction of anaesthesia, sedation, analgesia, bronchodilation, chronic pain	Respiratory stimulation, laryngospasm, blind nasal intubation, postoperative shivering
Action		Competitive antagonist at mAChRs	Indirect: promotes nt release, inhibits uptake-1; direct: α & β AR agonist	PDEi, inhibits Ca^{2+} influx, stabilizes mast cells	Na^{+} channel blockade, inhibits uptake-1	NMDA receptor antagonist, inhibits glutamate release, opioid receptor interaction, AChR antagonist, Na^{+} channel blockade	Peripheral chemoreceptor activation, direct action on respiratory centre
Presentation		Clear colourless solution of 0.3—0.6 mg/ml; also 0.6 mg tablets and eye drops	Clear colourless solution of 30 mg/ml; also 3 mg/ml elixir, 15—60 mg tablets, 0.5—1% nasal drops	Clear colourless solution of 25 mg/ml; also 100—350 mg tablets and 180—360 mg suppositories	1—4% solution, paste, Moffett's solution (10% cocaine, adrenaline and $NaHCO_3$)	Clear colourless solution of 10—100 mg/ml racemic, or 5—25 mg/ml S-ketamine	Clear colourless solution of 2—20 mg/ml
Dose and route		20 mcg/kg IV or IM (0.6 mg per dose, max 3 g)	3—9 mg IV (max 30 mg), 30 mg PO TDS, 1—2 drops nasally 4 hourly	5 mg/kg IV loading over 10—15 minutes, maintenance 0.5 mg/kg/hour (therapeutic range 10—20 mcg/ml)	Topical (max 3 mg/kg)	Induction 0.5—3 mg/kg IV, 4—10 mg/kg IM, maintenance 10—50 mcg/kg/minute (for sedation divide by 3)	1 mg/kg IV bolus, 1.5—4 mg/minute
Effects	**CNS**	Excitation or depression, antiemesis, antiparkinsonism	Increased CBF		Biphasic effect - excitation (euphoria) followed by inhibition (drowsiness)	Dissociative anaesthesia, increased CBF/CMR/ICP, theta pattern with alpha rhythm loss on EEG	Increased CBF

	CVS	Increased HR/CO	Positive inotropy/ chronotropy, myocardial irritability, increased coronary flow, vasoconstriction	Positive inotropy and chronotropy, decreased SVR	HTN, tachycardia, vasoconstriction	Increased CVP/HR/CO	Increased SV/CO
	Respiratory	Bronchodilation, reduced secretions, increased RR	Respiratory stimulant, bronchodilation	Bronchodilation, increased VC, increased brainstem sensitivity to CO_2, inhibition of HPV	Central increase in ventilation	Respiratory stimulant, preserved airway reflexes, bronchodilation	Increased V_t/MV, increased RR, increased sensitivity to CO_2
	GI	Reduced secretions, reduced tone and peristalsis, antispasmodic	Muscle relaxation, splanchnic vasoconstriction		Increased motility, nausea and vomiting	Increased secretions	Increased salivation and motility
	GU	Reduced tone and peristalsis	Decreased RBF/GFR, urinary retention, decreased uterine tone	Increased RBF/GFR, decreased Na^+ reabsorption, diuresis		Increased ureteric tone	Increased motility/UO
	Other	Cycloplegia, mydriasis, increased IOP, reduced sweating, increased BMR, reduced ADH release	Mydriasis, increased glycogenolysis/BMR/ thermogenesis	Hypokalaemia, LFT derangement, inappropriate ADH secretion	Hyperreflexia, mydriasis, increased IOP	Increased IOP, mydriasis, nystagmus, hypertonus, increased catecholamine levels, leukocyte inhibition	Increased catecholamine/steroid secretion, increased BMR
Toxicity		Central anticholinergic syndrome, transient bradycardia via the Bezold-Jarisch reflex, dysrhythmias, urinary retention	Insomnia, anxiety, tremor, headache, dysrhythmias, N&V, chest pain; hypertensive crisis with MAOi	Agitation, convulsions, dysrhythmias	MI, VF, hyperthermia, cerebral haemorrhage, hallucinations, convulsions, coma, DIC, pulmonary oedema, respiratory arrest, bowel infarction, rhabdomyolysis.	N&V, rash, delirium, hallucinations; bladder dysfunction with chronic use	Restlessness, hallucinations, sweating, dizziness, increased O_2 consumption
Pharmacokinetics	**Absorption**	20% oral bioavailability	100% oral bioavailability	90% oral bioavailability	0.5% intranasal bioavailability	25% oral bioavailability; 40% nasal bioavailability	
	Distribution	50% protein bound, V_D 3 litres/kg, crosses placenta/BBB	V_D 3 litres/kg, crosses placenta and BBB, excreted in breast milk	50% protein bound, V_D 0.5 litres/kg	98% protein bound, V_D 2 litres/kg	35% protein bound, V_D 3 litres/kg	V_D 1.5 litres/kg
	Metabolism	Hydrolysed (liver and tissues)	Hepatic to norephedrine (active) and other inactive metabolites	Hepatic; saturation leads to zero-order kinetics	Plasma esterase degradation	Hepatic to norketamine (30% activity) and other inactive metabolites	

(*continued on next page*)

Table 1 (*continued*)

	Atropine	Ephedrine	Aminophylline	Cocaine	Ketamine	Doxapram
Excretion	Urinary excretion, Cl 17 ml/minute/kg, $t_{1/2}$elim 2.5 hours	Urinary excretion (enhanced with low urine pH), Cl 7 ml/minute/kg, $t_{1/2}$elim 6.3 hours	Urinary excretion, Cl 1 ml/minute/kg, $t_{1/2}$elim 8 hours (saturable becoming zero-order kinetics)	Urinary excretion, Cl 35 ml/minute/kg, $t_{1/2}$elim 45 minutes	Urinary excretion, Cl 17 ml/minute/kg, $t_{1/2}$elim 2.5 hours	Urinary excretion, Cl 5 ml/minute/kg, $t_{1/2}$elim 3 hours

AChR, acetylcholine receptor; ADH, antidiuretic hormone; AR, adrenoreceptor, BBB, blood–brain barrier; BMR, basal metabolic rate; CBF, cerebral blood flow; Cl, clearance; CMR, cerebral metabolic rate; CNS, central nervous system; CO, cardiac output; CO_2, carbon dioxide; COPD, chronic obstructive pulmonary disease; CVP, central venous pressure; CVS, cardiovascular system; DAN, diabetic autonomic neuropathy; DIC, disseminated intravascular coagulation; EEG, electroencephalogram; GFR, glomerular filtration rate; GI, gastrointestinal; GU, genito-urinary; HF, heart failure; HPV, hypoxic pulmonary vasoconstriction; HR, heart rate; HTN, hypertension; ICP, intracranial pressure; IOP, intraocular pressure; IM, intramuscular; IV, intravenous; LFT, liver function tests; mAChR, muscarinic acetylcholine receptor; MAOi, monoamine oxidase inhibitor; mcg, micrograms; MI, myocardial infarction; MV, minute volume; N&V, nausea and vomiting; Na, sodium; $NaHCO_3$, sodium bicarbonate; NMDA, N-methyl-D-aspartate; nt, neurotransmitter; O_2, oxygen; OP, organophosphate; PDEi, phosphodiesterase inhibitor; RBF, renal blood flow; RR, respiratory rate; SV, stroke volume; SVR, systemic vascular resistance; $t_{1/2elim}$, elimination half-life; UO, urine output; VC, vital capacity; VD, volume of distribution; VF, ventricular fibrillation; Vt, tidal volume.

Table 1

adenylate cyclase to have the net effect of increasing post-synaptic cAMP. This counteracts the parasympathetic nervous system, causing tachycardia, mydriasis, cycloplegia and reduction of oral secretions. It is used to treat bradycardia, dry secretions, manage organophosphate poisoning and as an aide for ophthalmic examination.

Atropine (unlike glycopyrrolate) crosses the blood–brain barrier causing CNS excitation, though it may also cause depression. Toxic effects include the anticholinergic toxidrome, memorable by the mneumonic 'hot as a hare, blind as a bat, dry as a bone, red as a beet and mad as a hatter'. This is the combination of anhidrosis, mydriasis, urinary retention, flushing and altered mental status. Central anticholinergic syndrome manifests as agitation or somnolence, hallucinations, confusion, dysarthria and ataxia. Atropine can also cause a transient bradycardia (particularly in small doses) which is hypothesized to be centrally mediated or be a result of chemoreceptor activation triggering the Bezold–Jarisch reflex.

Phosphodiesterase inhibition

Methylated xanthine alkaloids are a group of drugs including theophylline, caffeine and theobromine. They act as antagonists at adenosine receptors and as phosphodiesterase inhibitors (PDEi). Inhibition of phosphodiesterase allows accumulation of cAMP in the post-synaptic nerve terminal. Action at adenosine receptors has variable effects (Figure 2). A_1 and A_3 adenosine receptors activate $\alpha_{i/o}$ G-proteins decreasing cAMP production, A_{2A} and A_{2B} activate a_s G-proteins increasing cAMP production and A_{2B} can also activate $\alpha_{q/11}$ G-proteins activating phospholipase C (PLC). Increasing cAMP in the CNS is often excitatory, acting in glutamatergic pathways. However, *decreasing* cAMP can also be excitatory by reducing transmission at γ-aminobutyric acid (GABA)-ergic and glycinergic inhibitory pathways.

Theophylline is used for the management of asthma and chronic obstructive pulmonary disease (COPD) due to its role as a bronchodilator. It acts as both a PDEi and a non-selective adenosine receptor antagonist. The parenteral preparation is an ethylenediamine salt of theophylline, aminophylline (Table 1), given as a 5 mg/kg bolus followed by a 0.3–1.0 mg/kg/hour infusion for acute asthma or bronchospasm. Theophylline acts by relaxing bronchial smooth muscle, increasing cardiac inotropy and chronotropy, modulating the inflammatory response, and acting as a respiratory stimulant. It has a narrow therapeutic range of 10–20 micrograms/ml, with toxic levels resulting in agitation, cardiac dysrhythmias and seizures.

Caffeine is naturally occurring in *Coffea* plant seeds (coffee beans), *Camellia sinesis* (tea) leaves and the kola nut. Chemically it is methyltheobromine, theobromine being another methylated xanthine alkaloid naturally occurring in cocoa, kola nuts and *C. sinesis*. The main action of caffeine is as an antagonist of A_{2A} adenosine receptors, though it also antagonizes other adenosine receptor subtypes and inhibits PDE.

Caffeine is used clinically to reduce the incidence of apnoea of prematurity in neonates, improving pulmonary outcomes though with no effect on long-term neurological outcomes.[1] It has also been used for symptomatic relief of post-dural puncture headache via the proposed mechanism of cerebral vasoconstriction.

However, there is limited evidence to support its use and caffeine does not change the proportion of patients requiring epidural blood patch.[2] Caffeine is the most widely consumed psychoactive drug, reducing fatigue and improving concentration. Tolerance to its effects is demonstrable, and psychological and physical withdrawal symptoms can manifest on abstinence in chronic users.

Reuptake inhibition

Cocaine (Table 1) is a naturally occurring benzoic acid ester from the leaves of *Erythroxylon coca*. It acts as a reuptake inhibitor of dopamine, noradrenaline and serotonin, and at high concentrations inhibits voltage-gated sodium and potassium channels. It therefore acts as a stimulant, as well as having vasoconstrictor and local anaesthetic properties. Effects on the CNS occur in a biphasic pattern, with euphoria, perception disturbance including formication ('snow bugs'), and convulsions due to inhibitory pathway blockade, developing into confusion, somnolence and coma due to excitatory pathway blockade.

Cocaine is used as a topical vasoconstrictor for nasal procedures, often presented as Moffett's solution (a mixture of 10% cocaine, adrenaline and sodium bicarbonate). Maximum dose should not exceed 3 mg/kg, with toxic effects including coronary vasospasm, arterial dissection, myocardial infarction, prolonged QTc, ventricular fibrillation, hyperthermia, cerebral haemorrhage, pulmonary oedema, disseminated intravascular coagulation, bowel infarction and rhabdomyolysis. It is a common drug of misuse in a variety of forms, with substantial associated morbidity and mortality. Users develop psychological dependence, and withdrawal symptoms include emotional and motivational depression.

Cocaine-associated chest pain accounts for around 40% of cocaine-associated accident and emergency visits, though only around 6% of these develop a myocardial infarction.[3] In addition to routine emergency assessment, patients presenting with severe cocaine toxicity should have continuous cardiac monitoring, and temperature and pH monitoring. Echocardiography, coronary angiography or other specialized cardiac imaging should be considered as indicated. Management includes anxiolysis with incremental doses of benzodiazepines (e.g. 1–2 mg midazolam; 5–10 mg diazepam), and treatment of hypertensive emergencies using glyceryl trinitrate (10–200 micrograms/minute – maximum 400 micrograms/minute), sodium nitroprusside (0.5–1.5 micrograms/kg/minute), or phentolamine (5 mg bolus repeated at 10 minutes intervals). There has been significant debate around the use of β-blockers in the context of cocaine toxicity due to concern over unopposed alpha stimulation worsening coronary vasospasm. However, in light of recent evidence failing to demonstrate adverse outcomes from β-blocker use, a mixed β/α-blocker such as labetalol could be considered for cautious use (5–10 mg boluses or 0.5–1 mg/minute infusion to be discontinued when target blood pressure is reached).[4,5]

Methylphenidate (Ritalin, Concerta) is a synthetic piperidine derivative. It acts as a dopamine and noradrenaline reuptake inhibitor, increasing their duration of effect in synapses. It increases attention span and wakefulness, with clinical uses including management of ADHD and narcolepsy. It can have significant side effects, including psychosis, anxiety, insomnia, palpitations and mydriasis, with delirium, hyperthermia, arrhythmias, convulsions, coma and rhabdomyolysis in overdose. It carries risk of dependence similar to amphetamines and has been investigated as a replacement therapy for treating cocaine addiction. Pipradrol is a diphenylmethane which has historically been used as a treatment for obesity, narcolepsy, ADHD and depression. It acts as a noradrenaline and dopamine reuptake inhibitor, though only has mild CNS stimulant effects. Multiple variants including desoxypipradrol (2-DPMP), diphenylprolinol (D2PM) and diphenylmethylpyrrolidine (desoxy D2PM) emerged as designer drugs and can still be encountered as drugs of misuse. Clinical signs typically mimic amphetamines.

Methiopropamine ('blow') is a structural analogue of methamphetamine, though it differs functionally primarily acting as a noradrenaline and dopamine reuptake inhibitor. It was produced as a 'legal high' though was made a class B controlled drug in 2017. Acute toxicity can cause psychosis alongside cardiovascular and gastrointestinal symptoms.

Interactions

Monoamine oxidase inhibitors (and **catechol-O-methyltransferase inhibitors**) reduce degradation of monoamines such as dopamine and noradrenaline, though are not traditionally classed as psychomotor stimulants. Importantly however, they interact with medications that increase monoamine concentrations, including ephedrine, amphetamines, cocaine and methylphenidate causing hypertensive crisis or serotonin syndrome. Hypertensive crisis can lead to encephalopathy, arterial dissection, myocardial infarction, pulmonary oedema and stroke. It should be managed in a high dependency area with antihypertensives including nitrates, calcium channel blockers, β-blockers and α_2 agonists. Serotonin syndrome (which may result from amphetamines or cocaine use alone) presents as akathisia, hyperthermia, hypertonicity, hyperreflexia and clonus. Management is supportive and involves stopping the precipitating agent, though may require ventilation and active cooling in severe cases.

Psychotomimetics

Psychotomimetics (hallucinogens) alter mental function affecting perception and cognition, potentially mimicking elements of psychosis. They can be broadly split into two groups: N-methyl-D-aspartate (NMDA) antagonists and serotonin antagonists. Ketamine, an NMDA antagonist, is commonly used clinically for induction of anaesthesia. Few others have medical uses, though are common drugs of misuse encountered in presentations of acute intoxication and overdose. A working understanding of the underlying pharmacology can help guide treatment in these cases.

NMDA antagonism

The NMDA receptor is a specific type of ionotropic glutamate receptor that allows calcium into the cell, which then acts as a second messenger (Figure 2).

Ketamine (Table 1, Figure 3) is a synthetic phencyclidine derivative first developed in 1962. It was used extensively as an anaesthetic agent during the Vietnam War owing to its

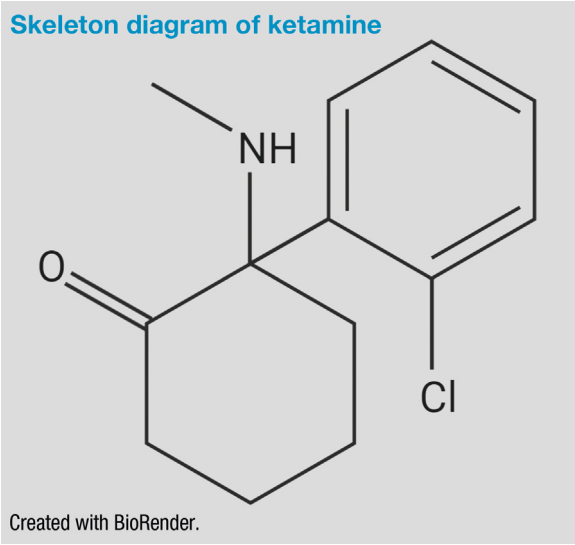


Figure 3

favourable safety profile. In contemporary medical practice, ketamine has a broad range of clinical applications. It is commonly employed for the induction and maintenance of anaesthesia in haemodynamically compromised patients, for pre-hospital anaesthesia in trauma casualties, and for the management of the agitated, non-capacitous patient, where intramuscular administration offers practical advantages.

The safety and versatility of ketamine were notably demonstrated during the 2018 Tham Luang cave rescue in Thailand, where it was used to induce deep sedation in members of a trapped youth football team, enabling specialist cave divers to safely extricate them through a flooded and hazardous cave system.

In procedural sedation, ketamine may be used in combination with propofol to form 'ketofol', which enhances both the safety and analgesic profile compared with propofol alone, particularly for highly stimulating procedures such as burns dressing changes. At sub-anaesthetic doses, ketamine is an effective analgesic in both acute and chronic pain management. In the acute inpatient setting, it is frequently employed when surgical procedures are not amenable to regional anaesthesia, such as scoliosis surgery in both paediatric and adult populations.

Ketamine also possesses bronchodilatory properties and is used in the management of severe, refractory asthma and bronchospasm. Although not licensed for this indication in the UK, ketamine has demonstrated rapid antidepressant effects, including reduction of suicidal ideation in patients with severe depression.[6] It is also a drug of misuse; effects from both acute and chronic intoxication can be observed.

Ketamine acts as a non-competitive antagonist of the NDMA receptor and inhibits presynaptic glutamate release. It has interactions with many other receptors including δ, μ and κ opioid receptor agonism and partial agonism, serotonin 5-HT_3 receptor antagonism, dopamine D_2 receptor agonism, and antimuscarinic action at acetylcholine AChR $M_{1,2,3}$ receptors (Figures 1, 2). Ketamine is presented as a clear colourless solution in a variety of concentrations. It is commonly a racemic mixture of S and R isomers, though an S enantiopure preparation is also available. The S isomer has double the anaesthetic potency and four times the binding avidity for the NMDA receptor compared to the R isomer, alongside fewer side effects. However, it should be noted that the R isomer has a greater bronchodilatory effect.

Ketamine stimulates the sympathetic nervous system, increasing blood pressure, heart rate and bronchodilation. It does also have direct myocardial depressant effects, seen more with the R isomer, though this is usually countered by the sympathomimetic activity. It causes a dissociative anaesthesia by thalamo-neocortical limbic separation with a typical theta delta electroencephalogram (EEG). It does not have a definitive end point and has a wide range of induction doses (0.5–3 mg/kg IV), so should be used with caution in inexperienced hands. It is relatively contraindicated for intubation in those who have already taken an overdose of a psychomotor stimulant such as MDMA or amphetamines, or for those who are already hypertensive and tachycardic.

Traditionally, ketamine has been avoided in anaesthesia of traumatic brain-injured patients due to the theory that it increases intracranial pressure (ICP). This belief stems from a series of case reports of patients with cerebrospinal fluid obstruction in 1972. Ketamine has now been demonstrated not to increase ICP in traumatic brain injury, with Oxford level 2b (GRADE C) evidence, and is becoming the anaesthetic of choice in the acute setting due to its relative cardiostability and preservation of respiratory drive.[7]

Ketamine can increase intraocular pressure, so should be avoided in patients with penetrating eye injuries or raised intraocular pressure. It is also considered to be porphyrinogenic so should be avoided in acute porphyria. Prolonged ketamine use is associated with a form of interstitial cystitis colloquially termed 'ketamine bladder' (alternately called ketamine-induced vesicopathy or ketamine-induced ulcerative cystitis), a syndrome including decreased bladder volume, increased urinary frequency, urge incontinence, detrusor overactivity, haematuria, urinary tract obstruction with bilateral hydronephrosis and renal papillary necrosis.

Phencyclidine (PCP) or 'angel dust' is the synthetic drug from which ketamine was derived. It was developed in 1926 and started being used as an anaesthetic medication in the 1950s, however because of its severe side effects (postoperative psychosis, severe anxiety and dysphoria) its use was discontinued by 1965. It continued to be produced for veterinary use only until it was disallowed in 1978 and largely replaced by ketamine. PCP and many of its derivatives are now purely used recreationally. It has a dose-dependent effect, with low doses causing unsteady gait and slurred speech, moderate doses causing analgesia and anaesthesia and high doses producing seizure activity. Its primary action is as an NMDA receptor antagonist via the PCP binding site, though also has actions on many other pathways including dopamine D_2R receptor agonism, nicotinic acetylcholine receptor antagonism, and dopamine reuptake inhibition.

Nitrous oxide (N_2O) is not typically classed as a CNS stimulant, however is another drug routinely used in clinical practice that has NMDA antagonist activity. The antagonism of NMDA receptor in dopaminergic neurons causes dopamine release leading

to its euphoric effect and its colloquial name of 'laughing gas' (with associated recreational use). N_2O also acts on potassium TREK1 channels, supraspinal opioid receptors, GABAergic interneuron $GABA_A$ receptors in the periaqueductal grey matter and noradrenergic neurones in the locus coeruleus.

Serotonin (5-HT) agonism

Lysergic acid diethylamide (LSD) is an ergoline alkaloid first synthesized in 1938 from lysergic acid, a chemical found in the fungus ergot. It currently has no medical uses, though is used recreationally as a hallucinogen ('acid'). LSD affects the serotonin 5-$HT_{1A/2A/2B/2C/5A/6}$ receptors; it does not bind to 5-$HT_{3/4}$. The psychedelic properties are attributed to 5-HT_{2A} which acts through a complex signalling web including phospholipase C, the ERK signalling cascade (Figure 2), phospholipase D, and through arachidonic acid formation via phospholipase A2. LSD has also been shown to activate the DARPP-32 pathway and has some affinity as an agonist at dopamine D_2 receptors (Figure 2).

Psilocybin is a tryptamine, a naturally occurring substance found in over 200 species of mushrooms, so called 'magic mushrooms', which are consumed recreationally for their hallucinogenic properties. Psilocybin is a prodrug and readily converted to psilocin by dephosphorylation. Psilocin is a partial agonist of serotonin receptors, with a high affinity for 5-HT_{2A} and a lower affinity for 5-HT_1 subtypes. It also has histamine H_1 receptor antagonist activity.

Respiratory stimulants/convulsants

Respiratory stimulants (also termed convulsants due to their side effect of promoting seizure activity) are a group of drugs historically used to promote anaesthetic emergence and lighten narcosis. Their mechanisms of action are poorly understood, though include inhibition of GABA, chloride channels and glycine antagonism.

Unclear mechanism of action

Doxapram (Table 1) is the only respiratory stimulant commonly available clinically due to its low risk of convulsions, though in modern practice it is rarely used. It is a monohydrated pyrrolidinone derivative which appears to act both centrally, at brain-stem respiratory centres, and peripherally, at the chemoreceptors in the carotid bodies and aortic arch. A proposed molecular mechanism of action is by inhibition of the K_{2P} family of potassium channels, specifically subtypes TASK-1 and TASK-3 (TWIK-related acid-sensitive K^+ channel). These are pH-regulated channels expressed in the brainstem and carotid bodies.[8]

Doxapram was used to promote emergence from anaesthesia at a bolus dose of 1 mg/kg IV, or to stimulate ventilation in acute respiratory insufficiency as an IV infusion of 1.5—4 mg/minute. It has also been used to reduce laryngospasm, reduce postoperative shivering and assist blind nasal intubation, all with variable efficacy. It causes an increased minute volume (primarily by increasing tidal volume) and sensitivity to CO_2, with side effects including increased salivation and hallucinations.

Pentylenetetrazol is a tetrazol derivative that has historically been used as an antitussive and to induce seizures for convulsive therapy prior to the development of electroconvulsive therapy in 1939. Its mechanism is poorly understood, though it appears to be predominantly active as a $GABA_A$ antagonist. It is still used as a research tool for studying seizure activity.

γ-aminobutyric acid receptor A ($GABA_A$) antagonism

Bicuculline is a phthalide-isoquinoline compound from plants of the subfamily *Fumarioideae*. It acts as a competitive antagonist of $GABA_A$ channels and appears to block calcium-gated potassium channels. It is used experimentally to study GABA-mediated neuronal transmission.

Picrotoxin (cocculin) is an equimolar mixture of picrotoxinin and picrotin found in the fruit of *Anamirta cocculus*. It acts as a non-competitive antagonist of $GABA_A$ channels. It was historically used as a respiratory stimulant and to reverse benzodiazepine overdose, however it is no longer used due to its toxic effects of convulsions, respiratory paralysis and cardiac dysrhythmias.

Glycine and acetylcholine antagonism

Strychnine is a crystalline alkaloid from plants of the genus *Strychnos*, notably *Strychnos nux-vomica* tree seeds. It acts as an antagonist of glycine and acetylcholine receptors. It was used as an athletic performance enhancer and as a medical respiratory stimulant until the early 20th century, when it was abandoned due to its toxic effects of convulsions, generalized muscle spasms with opisthotonos, respiratory failure, hyperthermia, rhabdomyolysis and renal failure. It is still used as a rodenticide, and strychnine poisoning is still sometimes seen as it has been found as an adulterant in street preparations of recreational drugs such as diamorphine (heroin). Treatment is mainly supportive, though may include activated charcoal (or rarely gastric lavage with an oxidizing agent such as tannic acid or potassium permanganate) in cases with recent ingestion. Renal replacement therapy may be utilized to manage ensuing renal failure, though it has not been demonstrated to remove strychnine. Benzodiazepines, barbiturates or propofol can be used to manage seizures though benzodiazepines may not be effective in all cases.

Other

Nicotine is a naturally occurring parasympathomimetic alkaloid from *Nicotiana tabacum* (tobacco) leaves, and other plants in the family Solanaceae. Its main action is as a nicotinic acetylcholine receptor agonist (though it acts as an antagonist at subtypes α_9 and α_{10}), leading to increased dopaminergic transmission in the CNS. It also binds to ganglionic nicotinic receptors increasing adrenaline and noradrenaline release from the adrenal medulla and may promote endogenous opioid release. It is used medically as an aide for smoking cessation. It was previously used as a pesticide, and it is commonly misused as a recreational drug in tobacco products and vapes, and as a cognition-enhancing drug. Nicotine increases alertness and causes anxiolysis and tachycardia. The apparent dichotomy of causing heightened arousal and reduced stress is known as the Nesbitt's Paradox, after the physician who described it in 1969. Nicotine is extremely addictive and the anxiolysis may simply be relief of irritability secondary to craving, though it may also result from endogenous

opioid release. Adverse effects include paraesthesia, headache, insomnia, restlessness, and physical and psychological dependence, with withdrawal causing stress, depression, anxiety and reduced concentration.

Modafinil is a synthetic benzhydryl sulfinyl compound which has an unclear mechanism of action. It appears to inhibit DAT, thereby increasing dopamine neurotransmission, however it also binds to norepinephrine and serotonin transporters, promotes release of orexin and histamine, and has partial agonist effects at D_2 receptors. It causes wakefulness and is used medically to manage narcolepsy and daytime sleepiness disorders, as well as being used to manage sleep deprivation by the military. Unlike many CNS stimulants that alter dopamine transmission, it has low liability for dependence and minimal potential for abuse. Adverse effects include headache, anxiety, insomnia and cutaneous reactions.

Piperazines are a broad class of chemical compounds based on the historic anthelmintic piperazine. Alongside the many clinically utilized drugs (from cyclizine to sildenafil), there are a multitude of recreational drugs. Sold as 'herbal ecstasy' or 'legal E', these drugs have the intended effects of euphoria, stimulation and sometimes hallucination, however have a range of mechanisms of action and unpredictable, potentially serious, side effects.

Some medications are not CNS stimulants but can exhibit CNS stimulant-like effects by blocking or reversing the effects of depressant drugs. Naloxone is a synthetic morphinan derivative which acts as a competitive opioid receptor antagonist, thereby reversing the CNS depression and respiratory suppression caused by opioids. It has few side effects if opioids are not present. Flumazenil is an imidazobenzodiazepine derivative which competitively inhibits $GABA_A$:benzodiazepine receptor complexes, potentially with inverse agonist activity. It reverses the CNS depression caused by benzodiazepines, however lowers the seizure threshold and can cause refractory status epilepticus. ◆

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