

3.1 General anesthetics

General anesthesia is a controlled, reversible state of unconsciousness, amnesia, analgesia, immobility and suppression of reflexes. The classical Guedel stages, seen with ether, remain the vocabulary: Stage I analgesia, Stage II excitement (delirium, irregular breathing, the dangerous stage modern induction passes through quickly), Stage III surgical anesthesia in four planes (deepening depression of reflexes), and Stage IV medullary paralysis (respiratory and vasomotor failure: overdose).

Potency is measured by **MAC, the minimum alveolar concentration** preventing movement in response to a surgical stimulus in 50 percent of patients; MAC falls with age and with adjuvant drugs, which is why anesthetics are combined in "balanced anesthesia". Speed of induction and recovery is governed by blood solubility: agents with a low blood to gas partition coefficient (desflurane, sevoflurane, nitrous oxide) equilibrate fast and wear off fast, while soluble agents such as halothane are slow in both directions. The old Meyer-Overton rule, that potency tracks lipid solubility, pointed at membranes, but modern evidence favours specific protein targets: most intravenous and inhaled agents enhance GABA-A inhibition and many also block NMDA excitation (ketamine, nitrous oxide, xenon).

Agent	Key properties	Main problems
Halothane (inhaled, older)	Smooth induction, bronchodilator	Sensitises the heart to catecholamine arrhythmias; immune hepatitis on repeat exposure
Isoflurane, sevoflurane, desflurane	Modern maintenance agents, faster and cleaner	Desflurane is pungent and sympathetic stimulating; sevoflurane is the smooth paediatric induction agent
Nitrous oxide	Weak (MAC above 100 percent), rapid, analgesic	Expands closed gas spaces; inactivates vitamin B12 pathways with prolonged use; always a carrier, never a sole agent
Propofol (intravenous)	Rapid, smooth, antiemetic; the standard induction agent	Pain on injection, dose dependent respiratory and cardiac depression, rare infusion syndrome in prolonged ICU use
Etomidate	Hemodynamically the gentlest induction agent	Adrenal suppression after even single doses in the critically ill; myoclonus
Ketamine	Dissociative anesthesia, analgesia, bronchodilation, sympathetic stimulation	Emergence delirium and hallucinations; raised intracranial pressure debated; valued in shock and field anesthesia
Thiopentone (barbiturate)	Ultra short by redistribution, anticonvulsant	Accumulates with infusion; severe hypotension in hypovolaemia

Premedication, neuromuscular blockers (Unit 2), opioids and antiemetics complete the anesthetic system; the anesthesiologist's skill is dose titration across all of them at once.

3.2 Local anesthetics

Local anesthetics block voltage gated **sodium channels** from the inside of the nerve membrane, in their ionised form, preferentially when the channel is open or inactivated (**use dependent block**). Small, myelinated and rapidly firing fibres (pain, temperature, autonomic) are blocked before large motor fibres, which is why a spinal anesthetic abolishes pain while the patient can still move early on. Chemistry divides the class into esters (**procaine, benzocaine, tetracaine**, hydrolysed by plasma cholinesterase, with allergy

prone PABA metabolites) and amides (**lidocaine, bupivacaine, ropivacaine, prilocaine**, hepatic metabolism, safer allergy profile). Onset tracks pKa (more unionised drug at tissue pH means faster entry), duration tracks protein binding, and potency tracks lipid solubility. Adrenaline added to the injection constricts local vessels, prolongs the block and lowers peak blood levels.

Systemic toxicity is the class danger: rising plasma levels produce circumoral numbness, tinnitus and convulsions (CNS excitation as inhibitory circuits fail first) and then cardiac arrhythmias and collapse, bupivacaine being the most cardiotoxic; intravenous lipid emulsion is the specific rescue. Prilocaine and benzocaine add methemoglobinaemia to the list. Techniques span surface, infiltration, nerve block, intravenous regional, spinal and epidural anesthesia.

3.3 Sedatives and hypnotics

Sleep drugs act on the GABA-A receptor chloride channel, the brain's main inhibitory switch, but at different sites and with different ceilings:

- **Benzodiazepines** (diazepam, lorazepam, temazepam, midazolam, chlordiazepoxide) bind the benzodiazepine site and increase the **frequency** of channel opening in response to GABA. They require GABA to be present, giving them a relative ceiling and a wide safety margin alone; their effects span anxiolysis, sedation, hypnosis, anticonvulsant action, muscle relaxation and amnesia. The antagonist **flumazenil** reverses them, used cautiously because it can precipitate seizures in dependent patients.
- **Barbiturates** (phenobarbitone, thiopentone) increase the **duration** of channel opening and at high concentrations open the channel directly. No ceiling: the dose response runs from sedation through anesthesia to fatal medullary depression, which, with enzyme induction and dependence, has retired them from routine hypnotic use.
- **Z drugs** (zolpidem, zopiclone, zaleplon) bind the same benzodiazepine site with alpha1 subunit preference, giving hypnosis with less anxiolytic and anticonvulsant baggage, though dependence and complex sleep behaviours still occur.
- **Newer mechanisms:** melatonin receptor agonists (ramelteon, and melatonin itself) reset the sleep clock rather than forcing inhibition; **suvorexant** blocks orexin, the wakefulness peptide; sedating antihistamines and low dose sedative antidepressants fill gaps off label.

All GABAergic hypnotics distort sleep architecture (suppressing REM and deep sleep), produce tolerance and dependence, and combine dangerously with alcohol and opioids, the interaction behind many overdose deaths.

3.4 Drugs used to treat anxiety

Anxiety disorders were historically treated with the same sedatives; modern practice separates acute from chronic control. **Benzodiazepines** act within the hour and remain unmatched for acute anxiety, panic and alcohol withdrawal (where long acting chlordiazepoxide or diazepam cover the withdrawal syndrome), but dependence limits them to short courses. **SSRIs and SNRIs** are first line for generalised anxiety, panic disorder, social anxiety and PTSD, taking weeks to work. **Buspirone**, a 5-HT_{1A} partial agonist, treats generalised anxiety without sedation or dependence but with a slow onset and no cross tolerance with benzodiazepines, so it cannot rescue a benzodiazepine dependent patient. **Pregabalin** (binding the alpha2delta calcium channel subunit, reducing excitatory transmitter release) is licensed for generalised anxiety in many countries; beta blockers blunt the peripheral symptoms of performance anxiety. Hydroxyzine and other sedating antihistamines persist as mild options.

3.5 Depression and antidepressant drugs

The monoamine hypothesis, that depression reflects deficient serotonin, noradrenaline and dopamine signalling, organised fifty years of drug design; the modern reading adds neuroplasticity, since all effective antidepressants take weeks to work while their transporter effects are immediate, and the benefit tracks slower adaptive changes including BDNF signalling. The classes, in the order an examiner expects:

Class	Mechanism	Examples	Signature problems
SSRIs	Block the serotonin transporter (SERT)	Fluoxetine, sertraline, escitalopram, paroxetine	First line. GI upset, sexual dysfunction, hyponatraemia in the elderly, discontinuation syndrome (worst with paroxetine), serotonin syndrome with MAOIs
SNRIs	Block SERT and the noradrenaline transporter	Venlafaxine, duloxetine	Hypertension at higher doses; duloxetine also used in neuropathic pain
Tricyclics (TCAs)	Block SERT and NET plus muscarinic, H1 and alpha1 receptors	Amitriptyline, imipramine, nortriptyline	The side effect profile is the receptor profile: dry mouth, sedation, postural hypotension, cardiac conduction block; lethal in overdose
MAO inhibitors	Block monoamine oxidase A and/or B	Phenelzine, tranylcypromine (irreversible); moclobemide (reversible A)	Tyramine cheese reaction, serotonin syndrome; dietary and drug interaction discipline required. Selegiline (MAO-B) belongs to Parkinson therapy
Atypical agents	Mixed mechanisms	Mirtazapine (alpha2, 5-HT2 and 5-HT3 blockade; sedating, weight gain), bupropion (NET and dopamine transporter; activating, lowers seizure threshold), trazodone, vortioxetine, agomelatine (melatonin agonist)	Each trades the SSRI profile for its own
Rapid acting	NMDA antagonism	Esketamine (nasal, for resistant depression under supervision)	Dissociation and abuse potential; important as proof that non monoamine routes work

The **serotonin syndrome**, agitation, clonus, hyperreflexia, sweating and hyperthermia from excess serotonergic transmission (classically an SSRI combined with an MAOI, tramadol, linezolid or triptans), is the toxicology of this table and is treated by stopping the agents, sedation and cooling, with cyproheptadine as a 5-HT2 antagonist adjunct.

3.6 Psychosis and antipsychotic drugs

The dopamine hypothesis of schizophrenia holds that positive symptoms (delusions, hallucinations) reflect excess dopamine transmission in mesolimbic pathways, while negative and cognitive symptoms involve cortical dopamine deficiency, which is why simple dopamine blockade treats the first group and not the second. All antipsychotics block **D2 receptors**; antipsychotic effect appears when roughly two thirds of striatal D2 receptors are occupied, and extrapyramidal effects climb steeply above about four fifths, a narrow mechanistic window.

Typical (first generation) agents such as haloperidol and chlorpromazine are fairly pure D2 blockers, potent against positive symptoms, at the price of extrapyramidal side effects: acute dystonia, akathisia, drug induced parkinsonism and, with time, **tardive dyskinesia**, plus hyperprolactinaemia (blocking the tuberoinfundibular brake on prolactin) and, for low potency agents, heavy anticholinergic, antihistamine and alpha blocking loads. **Atypical (second generation) agents** add **5-HT2A antagonism** and looser or faster D2 binding: risperidone, olanzapine, quetiapine, amisulpride, aripiprazole (a D2 partial agonist, the

mechanistic bridge to Unit 1) and **clozapine**, the most effective drug for treatment resistant schizophrenia, reserved by its risks of agranulocytosis (mandatory blood monitoring), myocarditis, seizures and severe metabolic effects. The atypical class trades extrapyramidal burden for **metabolic syndrome**: weight gain, diabetes and dyslipidaemia, worst with olanzapine and clozapine. The class emergency is **neuroleptic malignant syndrome**: rigidity, hyperthermia, autonomic instability and raised creatine kinase, treated by stopping the drug, cooling, and dantrolene or bromocriptine.

3.7 Mania and mood stabilisers

Bipolar mania is treated acutely with antipsychotics and benzodiazepines, and prevented with mood stabilisers, of which **lithium** remains the standard. Lithium's mechanism is honestly plural: it modulates inositol signalling (depleting IP3 recycling), inhibits GSK-3 beta, and alters serotonergic and dopaminergic transmission. Its pharmacology is a lesson in narrow indices: a small volume of distribution, no metabolism, renal excretion competing with sodium, and a therapeutic range close to toxicity, so plasma levels, renal function and thyroid function are monitored; thiazides, NSAIDs and dehydration raise lithium levels by increasing its proximal reabsorption. Toxicity progresses from tremor, polyuria (nephrogenic diabetes insipidus) and hypothyroidism to confusion, convulsions and coma. Alternatives and partners include **valproate, carbamazepine and lamotrigine** (borrowed from epilepsy, lamotrigine favouring the depressive pole), and several atypical antipsychotics with maintenance licences.

3.8 Epilepsy and antiepileptic drugs

A seizure is a paroxysm of abnormal, synchronised neuronal firing; epilepsy is its recurrence. Antiepileptic drugs suppress firing by four main mechanisms:

- **Use dependent sodium channel blockade:** phenytoin, carbamazepine, lamotrigine, lacosamide. First line for focal seizures; carbamazepine and phenytoin are notably ineffective, indeed aggravating, in absence seizures.
- **GABA enhancement:** benzodiazepines and phenobarbitone (GABA-A), vigabatrin (irreversible GABA transaminase inhibition, at the cost of visual field defects), tiagabine (GABA uptake blockade).
- **Calcium channel effects:** ethosuximide blocks T type channels in the thalamus, the absence seizure mechanism; gabapentin and pregabalin bind the $\alpha_2\delta$ subunit of voltage gated calcium channels.
- **Mixed and other mechanisms:** valproate (several of the above, the broadest spectrum agent), levetiracetam (binds the synaptic vesicle protein SV2A), topiramate, perampanel (AMPA antagonism).

Choice follows seizure type first, then patient factors: valproate is teratogenic (neural tube defects and developmental effects) and is restricted in women of childbearing potential; enzyme inducers (carbamazepine, phenytoin) compromise contraception and other drugs (Unit 1); lamotrigine carries a serious rash risk including Stevens-Johnson syndrome and is titrated slowly. **Status epilepticus** is a time critical emergency run on a protocol: intravenous lorazepam first, then a loaded second line agent (levetiracetam, phenytoin or valproate), then anesthetic infusion in intensive care.

3.9 Neurodegenerative diseases: Parkinson and Alzheimer

Parkinson disease is the loss of dopaminergic neurons of the substantia nigra, leaving the striatum short of dopamine and relatively overactive in cholinergic terms. Treatment restores the balance: **levodopa** with a peripheral decarboxylase inhibitor (carbidopa or benserazide) remains the most effective drug, its long term cost being motor fluctuations and dyskinesias as the buffering capacity of the dying terminals is lost; **dopamine agonists** (ropinirole, pramipexole, rotigotine) serve younger patients but cause impulse control disorders and sleep attacks; **MAO-B inhibitors** (selegiline, rasagiline, safinamide) and **COMT inhibitors**

(entacapone) prolong dopamine and levodopa respectively; **amantadine** helps dyskinesia; and anticholinergics (trihexyphenidyl) help tremor in the young at a cognitive price. Blocking dopamine carelessly, with metoclopramide or typical antipsychotics, worsens the disease, and levodopa must never be stopped abruptly.

Alzheimer disease adds cortical cholinergic loss to amyloid and tau pathology. The licensed symptomatic drugs are the **cholinesterase inhibitors** donepezil, rivastigmine and galantamine (Unit 2) and **memantine**, a use dependent NMDA blocker that dampens glutamate excitotoxicity while sparing normal transmission. Newer anti amyloid monoclonal antibodies (such as lecanemab) modestly slow decline in early disease at the cost of amyloid related imaging abnormalities (brain swelling and microbleeds), and represent the first disease modifying, rather than symptomatic, approach.

3.10 Narcotic analgesics: opioid drugs

Opioids act on the mu, kappa and delta **opioid receptors** (Gi/o coupled: less cAMP, more potassium outflow, less calcium entry, so less transmitter release from pain fibres and less postsynaptic excitability). Mu receptor activation gives analgesia, euphoria, respiratory depression, miosis, constipation and physical dependence in one package, because the same receptor serves all those circuits. The class ladder:

- **Pure agonists:** morphine (the standard), codeine (a CYP2D6 prodrug of morphine), tramadol (weak mu agonism plus serotonin and noradrenaline reuptake blockade, with seizure and serotonin syndrome risks), fentanyl and its analogues (very potent, lipophilic, the anesthetic opioids), pethidine (whose metabolite norpethidine accumulates and causes seizures), methadone (long and variable half life, NMDA antagonism, used in pain and in opioid substitution), oxycodone, hydromorphone, diamorphine.
- **Agonist antagonists and partial agonists:** buprenorphine (partial mu agonist with a ceiling on respiratory depression, used in substitution therapy and as a patch), pentazocine (kappa agonist, dysphoric), nalbuphine.
- **Antagonists:** **naloxone**, short acting, the overdose antidote, dosed to restore breathing without precipitating full withdrawal where avoidable; naltrexone, oral and long acting, for relapse prevention in opioid and alcohol dependence; methylnaltrexone and naloxegol, peripherally restricted antagonists for opioid induced constipation.

Opioid poisoning is the classic triad of coma, pinpoint pupils and respiratory depression. Tolerance develops to most effects but strikingly not to constipation and miosis. Dependence management (methadone and buprenorphine substitution, supervised withdrawal) and the rule never to give an antagonist casually to a dependent patient complete the clinical picture.

3.11 Non-narcotic analgesics: NSAIDs and paracetamol

Non steroidal anti-inflammatory drugs inhibit **cyclo-oxygenase**, blocking prostaglandin synthesis (the autocoid chemistry is Unit 5). COX-1 is the housekeeping enzyme of gastric mucosa, platelets and kidney; COX-2 is induced at inflammation sites, though it is also constitutive in kidney and endothelium. Non selective agents (aspirin, ibuprofen, diclofenac, naproxen, indomethacin) give analgesia, antipyresis and anti-inflammatory action with a shared adverse triad: gastric ulceration and bleeding, renal impairment (prostaglandins defend renal blood flow when perfusion is threatened) and antiplatelet effects. **Aspirin** is unique in irreversibly acetylating COX, so its antiplatelet effect lasts the life of the platelet (Unit 4 doses it accordingly). **COX-2 selective agents** (celecoxib, etoricoxib) spare the stomach but tilt the prostacyclin to thromboxane balance toward clotting, the lesson of rofecoxib's withdrawal for cardiovascular events.

Paracetamol is analgesic and antipyretic with negligible peripheral anti-inflammatory action and no gastric or platelet penalty, acting centrally by mechanisms still argued over; its danger is entirely hepatic, the

NAPQI metabolite of section 1.4 overwhelming glutathione in overdose, reversed by N-acetylcysteine. NSAIDs also close the ductus arteriosus (indomethacin therapeutically), precipitate asthma in aspirin sensitive patients (leukotriene shunting), and blunt antihypertensive and diuretic action, interactions all readable from the prostaglandin physiology of Unit 5.

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