Revision

## Affective Disorders

"Monoamine hypothesis" → Depression is caused by a functional deficit of NA, 5-HT and possibly DA (dopamine) in the brain. Proved by the following 1. and 2.

1. Reserpine → depleting neuronal stores of monoamines. (a proportion of patients taking this drug suffer from severe depression)

2. Iproniazid → Inducing euphoria 欣快感 (sometimes) by preventing monoamine oxidase (MAO)

The hypothesis leads to a corollary 推论: Augmentation of prolongation of the actions of monoaminergic transmission in the brain → therapeutic effects of antidepressants.

### Augmentation:

Phenelzine, moclobemide → MAO inhibitors, increasing transmitter release.
Phenelzine is non-selective (MAO-A/B) and irreversible: Risk of interaction with tyramine (tyramine diffuses into circulation without being metabolized) in the diet, especially for those who take sympathomimetics e.g. ephedrine.
Moclobemide is MAO-A selective and reversible inhibitor (RIMA – Reversible inhibitors of MAO-A). MAO-A breaks down NA and 5-HT
Selegiline is MAO-B selective inhibitor: of small value in treating depression, but useful as an adjunct in the treatment of Parkinson's.

Tricyclics, selective uptake blockers → preventing transmitter reuptake from the synapse.

### Adverse effects of MAO inhibitors:

Hepatotoxicity, CNS effects (insomnia 失眠, agitation, convulsion 抽搐), Postural hypotension (Probably by potentiating the effects of DA in autonomic ganglia), sympathetic effects (e.g. dry mouth, sweating, gastro-intestinal, sexual & visual disturbances)

### Prolongation (+ augmentation?):

Imipramine → Uptake inhibitor
Tricyclic antidepressants such as imipramine and clomipramine (Tertiary amines), desipramine (secondary amine), and iprindole (Atypical tricyclic) are structurally related phenothiazines. (Detailed structures in Note).
**In vitro**: these drugs block neuronal uptake of NA and 5-HT.
**In vivo**: due to metabolism (e.g. imipramine → desmethylimipramine), most of the drugs (metabolites) inhibit the uptake of NA.

**Exception**: clomipramine retains any appreciable selectivity against 5-HT reuptake in vivo.
Iprindole is a tricyclic antidepressant but does not block the uptake of monoamines.

Adverse effects:
Most of the side effects of tricyclic antidepressants are all by their antagonism of a1-adrenoceptors, muscarinic receptors, and histamine (H1) receptors.

Antimuscarinic: Sedation, dry mouth (decreased secretion), blurred vision (mydriasis 瞳孔散大), constipation.
Postural hypotension (probably central action), Cardiac dysrhythmias, including ventricular fibrillation. Convulsion (epileptogenic), Confusion (particularly in the elderly.)

Selective uptake blockers → NA uptake blockers (e.g. maprotiline), and selective serotonin (5-HT) reuptake inhibitors (SSRI, e.g. fluoxetine)
These selective blockers have fewer side effects than the tricyclics (especially to avoid antimuscarinic and cardiotoxic effects): they might be safer in overdose.

Serotonin noradrenaline reuptake inhibitors (SNRIs) → non-selective inhibitors such as venlafaxine. Differ from tricyclic agents in vivo in two respects: 1. No appreciable antimuscarinic side effects. 2. The 5-HT uptake inhibition is maintained in vivo.

Prolongation/Augmentation 没细说:

Iprindole & mianserin → Atypical antidepressants: No effect on monoamine reuptake.
Therapeutic mechanisms of iprindole are unknown.
Mianserin is an a2-adrenoceptor (mostly presynaptic) antagonist → Prevents feedback inhibition of NA release → Potentiate synaptic transmission. Mianserin also binds to 5-HT receptors ($5\text{-HT}_{1D}$, $_{2A}$, $_{2C}$ subtypes, all of therapeutic value) to elicit therapeutic effects.

Adverse effects (Mianserin & iprindole):
Resemble those of the tricyclics but particular problems include:
Epileptogenesis, extrapyramidal & skin reactions, Hepato- and renal toxicity (especially mianserin), Postural hypotension (especially mianserin), blood dyscrasias 恶液质 (especially mianserin).

Others
→ Benzodiazepines (alprazolam & adinazolam): Triazolo- and pyrazolo- derivatives have both anxiolytic and antidepressant actions. As with other benzodiazepines, the main adverse effect is sedation.

→ multiple-action drugs: Mirtazapine – NA reuptake inhibitor + a2 antagonist
Trazodone: 5-HT reuptake inhibitor + 5-HT2 receptor antagonist.

Uptake not acting as antidepressants (e.g. cocaine & amphetamine): amphetamine (ab)use is even noted for inducing depression.

Manic-depressive illness (bipolar depression) treatment (as well as mania) → treated with lithium (high plasma levels of drug are required – 1 mM) The therapeutic effects of lithium are unexplained but it has many actions affecting neuronal function. It accumulates intraneuronally and causes partial depolarisation and attenuation of transmitter release. It also disrupts cAMP synthesis and phosphatidyl inositol (PI) metabolism, preventing regeneration of PI and, possibly, IP3 formation. Like other antidepressants, lithium reduces the number of adrenoceptors in the brain but it is ineffective in the treatment of unipolar depression.

Adverse effects:

Nephrotoxicity, hypothyroidism 甲状腺功能减退症, CNS effects which can culminate in coma & death. High plasma levels of lithium are toxic and have a narrow therapeutic window.

## Anxiolytics And Hypnotics

Benzodiazepines → Frontline prescribed drugs for treating anxiety

Other properties: anxiolytic, sedative, hypnotic 催眠的, anti-convulsant, muscle relaxant and amnestic 健忘的. (Benzodiazepines of different types with different half-lives are used for different situations. See Note). There are numerous benzodiazepine derivatives and many have common active metabolites – All lipophilic and so cross the blood-brain barrier (BBB). Low plasma solubility is compensated by extensive binding to plasma proteins (>90%). Inactivation depends on the conjugation of drugs (unmetabolized drugs or active metabolites) with glucuronic acid in the liver.

Benzodiazepines bind to a specific site on $GABA_A$ receptors at the interface between the alpha and gamma subunits.

Drugs like diazepam: positive allosteric modulators for GABA→ increasing GABA potency causing inhibition.

Drugs like β-carboline (another benzodiazepine) → negative allosteric modulator, antagonizes GABA action

A third class: benzodiazepine antagonist (e.g. flumazenil) → prevents the binding of positive and negative allosteric modulators to $GABA_A$. Hence does not affect the GABA function.

Benzodiazepines are used in different conditions based on their pharmacokinetic profiles:

Diazepam, clonazepam → treating epilepsy.

Temazepam, lorazepam → anxiolytic and hypnotic.

Advantages: Don't cause respiratory depression (safer in higher doses unless combined with large alcohol consumption)

Unwanted aspects:

Exhibit tolerance in chronic use and individual develop drug dependency (although craving is much less compared to what experienced with opioids)

Details of clinical use are in Note: duration of action and metabolic fate determine the clinical applications.

Zolpidem, zopiclone (Z-drugs) → also act at the benzodiazepine site on $GABA_A$ receptors.

Barbiturates → these are derivatives of urea and malonic acid which were first introduced for the treatment of epilepsy.

Phenobarbitone → relieving anxiety, anticonvulsant
Thiopentone → rapid induction of general anesthesia
Amylobaritone → severe intractable insomnia 失眠

Barbiturates potentiate the action of GABA at the $GABA_A$ receptor (via increasing the duration for which Cl- channel is open, compared to benzodiazepines which increase the frequency of Cl- channel opening). They can directly open Cl- channels without GABA as well. (As a result: potentiated inhibition)

Adverse effects: Barbiturates are not used or recommended for treating anxiety because:
1. Anxiolytic effects are apparent at sedative dose only. 2. Drug dependence and abuse is a notable problem. 3. Barbiturates are dangerous in overdose (fatal, e.g. respiratory depression) 4. Have additive effects with other CNS depressants presenting significant risk of accidental overdose.

Anxiolytic drugs affecting monoaminergic neurotransmission

Buspirone → Binds to $5\text{-}HT_{1A}$ autoreceptors on the cell bodies and dendrites in the raphe nuclei: auto-inhibition at first (leading to less postsynaptic inhibition and exacerbating anxiety), then desensitize the receptors and lead to enhanced release of 5-HT (increased inhibition)
Buspirone has no additive effects with alcohol and does not induce drug dependence.

Propanolol → β-antagonist. This is likely to involve a reversal of increased peripheral sympathetic autonomic effects rather than acting centrally. Only used in situational anxiety (e.g., public speaking).

Other drugs affecting anxiety:

Histamine (H1) receptor blockers → exert a brief respite 喘息 from anxiety and promote sleep, though tolerance occurs rapidly.
Plant extracts such as Valerian with its active ingredient valerenic acid relieving anxiety by potentiating $GABA_A$ receptor function.

## Antiepileptic drugs

Phenytoin (A hydantoin derivative) and Carbamazepine (Dibenzazepines) → are anti-epileptics inhibiting Na+ channels in hyperexcitable cells without affecting normal electrical activity. Recently developed drugs such as lamotrigine and topiramate also have this action.

Ethosuximide dampens the excitability by an action on voltage-gated channels (Na+ and/or Ca2+ disputed!!) in the thalamus: Explaining its effectiveness against absence seizures generated by thalamic oscillations.

Phenobarbitone (Barbiturates) → Act to inhibit neurons (via hyperpolarization) by directly increasing Cl- influx. The action is not restricted to the area of epileptic focus, so this drug can induce general sedation.

Recently introduced anticonvulsant tiagabine → prolongs the action of GABA transmitters by blocking the membrane transporters responsible for GABA uptake.

Sodium valproate (Na valproate, fatty acids) → inhibits GABA metabolism (by inhibiting GABA transaminase). It is also capable of inhibiting voltage-gated Na channels and T-type calcium channels, which may explain why it has some action in most forms of epilepsy. Vigabatrin is a more selective GABA transaminase inhibitor and is more active in partial than generalized epilepsy and may exacerbate absence seizures.

Gabapentin → developed as a GABA agonist but does not bind to GABA receptors. However, it is still an anti-epileptic effective in partial and generalized seizures (possibly by modifying Na+ channels).

Diazepam and clonazepam (benzodiazepines) as well as barbiturates → increase postsynaptic GABA efficacy by acting as positive allosteric modulators (binding to the modulatory sites on $GABA_AR$). Topiramate may have a similar action. Benzodiazepines are given intravenously (i.v.) in emergency situations (e.g. status epilepticus), though tolerance will be resulted in.

All anti-epileptics display side effects. Frequent among these are sedation and ataxia: (without coordination: loss of muscle control in arms and legs).

The table of mechanisms of action is in Note.

Drug use for different seizures:
Partial → Carbamazepine, Valproate, Phenytoine, etc. (in Note Table)
Generalized Tonic-clonic → Valproate, Carbamazepine, etc.
Generalized absence → Ethosuximide, etc.
Status Epilepticus → Clonazepam

Toxicity of anti-epileptics drugs (AEDs) in women of childbearing potential:

Pharmacological effects on oral contraceptive metabolism due to enzyme induction.
(Phenytoin, phenobarbital, carbamazepine)
Developmental toxicity: All established AEDs show some teratogenicity 致畸性, major congenital malformations increase in possibility. Particular concern over valproate – in women of childbearing potential lamotrigine is used instead.

## General anesthesia

Propofol, etomidate, thiopentone → intravenous agents, enhancement of $GABA_A$ receptor activity, potent: enhance the $GABA_A$ activity at relatively low concentrations. Super-clinical doses would cause death. Etomidate-induced enhancement of $GABA_A$ activity is stereoselective (+ (more potent) and – isomers have different potencies.) Ortho-propofol: a photo-reactive analogue of propofol still binds $GABA_A$ receptor and enhances its activity (engineered, still active).

Halothane (low MAC, high solubility), enflurane, isoflurane → volatile agents, enhancement of $GABA_A$ and glycine (it appears most likely that they target more than one protein type) receptors at clinically relevant concentrations. At similar low concentrations, these drugs are able to open certain types of potassium channels (e.g. TREK-1, TASK-1, and TASK-3 channels), for anesthetics such as cyclopropane, the potassium channels such as TASK-3 (in the case of cyclopropane) are not activated.

Nitrous oxide ($N_2O$, high MAC, low solubility), cyclopropane, xenon (Xe) → gas, activate the potassium channel TREK-1 at clinically relevant concentrations without any activity on $GABA_A$ receptors. The inert gas: xenon: has low blood solubility (rapid onset of anesthesia), lacks vasodilatory effect, has protective effects on neurons against ischemic injury (cost and limited availability of this gas is probably one reason why it is not more widely used). Xenon, like $N_2O$, is not just a TASK-1 opener. These two agents both bind to the glycine binding site on NMDA receptors (inhibition), contributing to anesthesia.

Ketamine → produces profound analgesia and “dissociative anesthesia” (meaning that this drug causes profound sensory loss, amnesia, and paralysis without full loss of consciousness) by binding to NMDA receptor channel pores (A channel pore blocker, which may account for its neuroprotective effect). The inhibition can occur at a clinically relevant concentration and its isomer shows a lower potency (S(+)>R(-)).

MAC (minimal alveolar concentration) * partition coefficient (blood: air) = blood concentration of a gaseous anesthetic at equilibrium when n1 MAC is administered.

Methoxyflurane → another volatile and soluble anesthetic (Low MAC for anesthesia).

### Adverse effects:

Anesthetics → can decrease cardiac contractility. They can also give rise to respiratory depression (with the notable exceptions of xenon, $N_2O$, and ketamine).

Halothane and other halogenated anesthetics reduce blood pressure (caused by myocardial depression and vasodilation).
The therapeutic window is relatively low for general anesthetics (indicated by low therapeutic ratio/index). Use of a mixture of halogenated hydrocarbon and N2O may minimize vasomotor depression.
Toxicity → Serious side effects are rare, while cardiac dysrhythmias can be produced. Other side effects such as nausea are in Note, effects may be produced by metabolites.

Thiopentone → "ultra-short-acting" or "Quite-long-acting". After intravenous injection, the blood concentration of this drug reaches a peak rapidly. As it is lipophilic, it easily crosses the BBB and induces anesthesia (Other tissues with high blood supply also show an increase in thiopentone concentration). After the first administration, redistribution ensues. The less well-perfused tissues such as lean tissue and eventually body fat accumulate the anesthetic later after injection and reduce the blood and brain thiopentone concentrations: leading to the recovery of consciousness. Repeated administration of thiopentone enables the concentration to remain high. Due to the complications of intravenous anesthetics, they are normally used for induction. Inhaled anesthetics are used for long-period anesthesia since they allow control of the anesthesia level from moment to moment.

Thiopentone adverse effects → no analgesic prior to anesthesia and respiratory depression can be profound. Thiopentone solution is very alkaline: causes serious tissue damage if injection is not done properly.

Propofol and fospropofol (a prodrug that is converted into propofol in the body) → Propofol is metabolized rapidly (fast recovery), and increasingly used for short procedures without inhalational anesthetics, whereas pain is caused at the site of injection → fospropofol is thus produced.

## Analgesic drugs

Many mechanisms of opioids are to be remembered in Note.

### Opioid receptors and agonists/antagonists:

Mu: G protein opens K+ channel
Endogenous opioid: beta-endorphin, endomorphins.
Synthetic agonists: morphine, codeine, fentanyl, pethidine
Antagonist: naloxone, beta FNA

Delta: G protein opens K+ channel
Endogenous opioid: enkephalins
Synthetic agonists: DSTBULET
Antagonist: naloxone, naltrindole

Kappa: G protein closes Ca2+ channel
Endogenous opioid: dynorphins
Synthetic agonists: pentazocine
Antagonist: naloxone, norBNI

ORL 1: G protein opens K+ channel
Endogenous opioid: nociceptin
Synthetic agonists: --
Antagonist: Not naloxone

The opioid receptors in the spinal cord are mostly of the Mu and Delta type and are found in the C-terminal zone (substantia gelatinosa, in the superficial dorsal horn).

The opioid receptors located in the 5HT and noradrenergic nuclei of the brain stem and midbrain including raphe nuclei, the periaqueductal grey matter, and the locus coeruleus are of Mu, Delta, and Kappa type (Supraspinal opioid analgesia). Supraspinal morphine is thought to shift these controls to reduce the perception of pain. Antidepressants altering 5HT and NA levels are used for analgesia in neuropathic pains.

Cholecystokinin → its mobilization interferes with the action of opioids in the spinal cord.

Dextromethorphan is a non-opioid isomer of levorphanol and a cough suppressant.

Adverse effects: (Details see Note)
Peripheral such as constipation and nausea as well as bronchospasm
Central such as dependence

Opioid agonist:
Kappa agonist: Pentazocine
Mu opioids → weak opioid, orally effective Codeine; long duration, orally effective Methadone; highly potent, short duration Fentanyl. (These agonists differ only in potency and pharmacokinetics)

Heroin (diacetylmorphine) → highly lipophilic drug but has no affinity for opioid receptors. Penetrate BBB and metabolize to morphine (Mu agonist).

Tramadol → weak opioids, block the reuptake of NA and 5-HT (SNRI): Combined actions synergize to give a good analgesia that lacks some of the typical opioid side effects.

Opioid antagonists → Naloxone, reverse analgesia, and some opioid side effects such as respiratory depression.

Non-opioid drugs in the relief of pain:
NSAID and COX2 inhibitors.

Anti-epileptic agents including carbamazepine and gabapentin.

Local anesthetics

Sumatriptan, methysergide, and other 5-HT agents, acting on 5-HT1B/D receptors in scalp 头皮.

Ketamine – the NMDA channel blocker

## Non-medical use of drugs: Dependence

Several theories of drug abuse → See PPT or lecture recording: habit theory (goal-directed → habitual); incentive salience theory (Drug abuse incentivizes the learning of drug-related cues at the expense of non-drug-related cues); The withdrawal theory (drug dependence is to avoid the negative symptoms of drug withdrawal)
Pros and cons discussed in the PPT&Lecture.

Drug types of abuse: Depressants including alcohol. stimulants: (e.g.) cocaine, amphetamine. narcotics 毒品: morphine, diacetylmorphine – heroin. Psychotomimetics: LSD, cannabis.

Treatment: naltrexone (for alcohol), and Varenicline (for smoking) → Not target the dopamine system. Newer, alternative treatments (also not targeting the DA system) such as ketamine and psilocybin.

## Anti-obesity drugs

Body mass index: weight in kg/ height in meters$^2$), index > 30 = obese. Energy (food) intake > energy expenditure = weight gain.

Obesity-associated problems: coronary heart disease, Type II diabetes, certain forms of cancer, sexual impotence, osteoarthritis 骨关节炎.

### Orexigenic 开胃的 factors (factors that increase food intake):

Neuropeptide Y (NPY): released by neurons with nuclei located in the arcuate nucleus (ARC), which project to the paraventricular nucleus. Its release is triggered by a decline in fat stores and inhibited by the feedback inhibition provided by leptin and insulin. Their stimulation reduces the sympathetic outflow to the brown adipose tissues and so lowers the energy expenditure. Besides, lipogenesis is stimulated by their stimulation. Production of NPY may be inhibited by leptin and desensitization of NYP-releasing neurons may impair satiety (regulation of meal size).

Agouti-related peptide (AgRP): colocalizes with NPY and antagonizes the melanocortin system—disruption of its synthesis results in weight loss and increased energy expenditure without affecting food intake.

Endocannabinoids: Peripheral administration of anandamide 大麻素 increases food intake. The antagonization of CB1 receptor reduces food intake. Fasting leads to the accumulation of anandamide (to drive food intake).

Anorexigenic 厌食的 (Factors that reduce food intake):

Melanocortins (derived from POMC – pro-opiomelanocortin): This neuropeptide family (e.g. αMSH (α-melanocortin stimulating hormone)) potently reduces food intake and energy expenditure via acting on MC3 and MC4 receptors. These peptides are synthesized in ARC neurons and project to other areas of the hypothalamic areas.

CART (cocaine amphetamine-regulated transcript regulates food intake and still have several other roles.)

5-hydroxytryptamine (5-HT, serotonin): Reducing food intake via acting on 5-$HT_{2C}$ receptors. It is thought that the main anorexigenic action of 5-HT is at PVA (paraventricular nucleus) and possibly prevents the release of NPY. Dietary intake of carbohydrates can increase 5HT release in the brain through elevating the insulin level which promotes the uptake of serotonin precursors, tryptophan. This might augment the effects of 5HT on satiety

NA: reduces food intake. Its action is thought to be acting on α1 and β adrenoceptors in the hypothalamus.

DA: May increase food intake? Antagonism of both abnormal D1/2 receptors concurrently 同时 in rats reduces food intake.

Nicotine: Chronic administration reduces food intake.

Some key peripheral mediators:

Leptin: Produced by adipose tissue and regulated by energy balance. Increases in production as fat stores increase. It reduces fat deposition by acting in the “satiety center” of the hypothalamus. This is achieved by reducing food intake and increasing energy expenditure. Energy expenditure in this case is increased by activating sympathetic outflow. A decrease in fat stores reduces leptin production. Leptin resistance (insensitivity) may be a cause of obesity. Evidence also shows the importance of leptin in influencing synaptic number and activity, suggesting a role in hypothalamic plasticity. It may also involved in neuronal development.

Insulin: Its action resembles leptin and stimulates leptin release. It gains entry to the brain through specific transporters. It is thought to reduce NPY synthesis and stimulate POMC synthesis. Under some circumstances, it also increases food intake.

Peptide YY: (produced in the gut) inhibits feeding.

Cholecystokinin: Promotes satiety (cessation of feeding) and increases release of 5HT in the hypothalamus. CCK-B receptor is critically involved in mediating satiety and their antagonism increases food intake.

Glucocorticoids: Endogenous antagonists of leptin and insulin.

GLP-1: Incretin best known for its glucose-lowering effect. It is also antidiabetic and causes sustained weight loss. It is released from enteroendocrine cells in the gut postprandially.

Anti-obesity drugs:

d-amphetamine → potent inhibitors of NA uptake (but not serotonin). Anorexigenic but liable to induce dependence as it increases dopaminergic transmission.

Sibutramine → SNRI, originally developed as an antidepressant but body weight is reduced (so developed as an anti-obesity agent). Has two active metabolites that reduce food intake and increase energy expenditure (also by inhibition of reuptake). It promotes the activation of β3-adrenoceptors on adipose tissue.

d-Fenfluramine: A weak monoamine reuptake inhibitor. In addition, it can trigger impulse-independent release of 5-HT and NA (the latter, weakly) from neurons.

Phentermine → Actions resemble d-Fenfluramine but without the adverse reactions of Fenfluramine.

Phen-Fen: A formulation combining fenfluramine and phentermine (adverse effect shown in Note).

Orlistat: Inhibits pancreatic lipase so reduces fat absorption (by preventing fat from breaking down into glycerol and fatty acids)

Lorcaserin: 5-$HT_{2C}$ antagonist (orexigenic?) The main action is believed to be an increased melanocortin production from POMC neurons, thus stimulating satiety.

Liraglutide, Exenatide: GLP-1 analogues, Might suppress the metabolically food intake and reward-driven food intake.

Gastric bypass surgery: By far the most effective weight-loss treatment. Changes in GLP-1 system might underlie some of its beneficial effects.

Antidiabetic agents:

Insulin → It is a protein hormone consisting of 2 polypeptide chains with 30 and 21 amino acids.

The precursor of insulin (proinsulin) is a large molecular weight, biologically less active, and single-chain polypeptide. After the removal of the intermediate connecting peptide chain (C-peptide), the insulin molecule can form with two disulfide bridges connecting the 2 separated polypeptides. Species differences in insulin → mostly in the C-peptide. Therapeutic uses of insulin are bovine 牛的, porcine 猪的, or human. The non-human insulins are antigenic, whereas they rarely cause reactions of clinical significance.

Mechanisms of insulin action → Insulin receptor is a glycoprotein complex consisting of 2 alpha (extracellular) and 2 beta subunits (membrane-spanning). Following binding of insulin to the α subunits, tyrosine kinase (TK) activity is shown by the β subunits. The β subunits act upon themselves and cause autophosphorylation at several sites. After this step, the kinase action on other proteins is enhanced. One of the target proteins is the insulin receptor substrate-1 (IRS-1), which is phosphorylated on at least 5 tyrosine residues and becomes a link between the receptor and a group of signaling proteins manifesting protein kinase activity. The insulin receptor is also coupled to the activation of a specific PLC, catalyzing the hydrolysis of glycosyl-phosphoinositol molecules in the plasma membrane. A second messenger is produced as a consequence – inositol phosphate glycan. This product can then activate the serine-threonine phosphatases. The lipid and glucose metabolism are regulated afterward. Furthermore, insulin plays a role in the recruitment of glucose transporters, particularly GluT-4.

Effects of insulin (e.g. anabolic effects) are discussed in Note (e.g., decreased gluconeogenesis, increased glucose uptake).

Preparations (types) of insulin: (different pharmacokinetic profiles shown in Note):
Soluble insulin, Isophane insulin, Lente insulin, Ultralente IZS (Insulin zinc suspension). (Left to right → with increasing duration of action)

Oral hypoglycemic agents:

Sulphonylureas → The basic structure for hypoglycemic activity is the sulphonylurea radicals. Different derivatives differ in their pharmacokinetic properties.

Mechanism of action: Acting on β-cells in the islets of Langerhans to increase insulin release (but not synthesis like glucose). No effect on IDDM (juvenile-onset diabetes) and pancreatectomized animals and patients. The drug blocks the ATP-sensitive K+ channels which are controlled by glucose. The insulin release appears to be triggered by a reduced K+ movement through the channels (triggers depolarization) and increased calcium entry secondary to the membrane depolarization.

This drug can be used to treat NIDDM (maturity-onset diabetes), only when diet alone is not ineffective and the diagnosis of insulin-secreting cancer.

First generation: Tolbutamide, short-acting; Chlorpropamide, long-acting; Gliclazide, also promotes fibrinolysis and inhibits platelet aggregation.

Secondary generation: Glibenclamide, very potent and rapidly acting.

Adverse effects:
Hypoglycemia, antidiuretic activity, toxic and allergic reactions, etc. (see Note)

Biguanides:

Phenformin → a hypothesis for its mechanism of action is the increase in peripheral glucose utilization. Some evidence also suggests that it reduces the GI tract's glucose absorption and hepatic gluconeogenesis.

This drug can be used to treat NIDDM (maturity-onset diabetes), only when diet alone is not ineffective or by diet plus a sulphonylurea derivative. Biguanides may also help reducing insulin dose in insulin-treated patients.

Side effects: Lactic acidosis, GI side effects.

Other drugs:

Thiazolidinedione derivatives: (Ciglitazone, pioglitazone and englitazone, all undergoing trail)
Potentiate the action of insulin on target tissues. Of potential use in NIDDM

Gliptins (DPP-4 inhibitors)
Inhibits the enzyme that inactivates the incretin peptide GLP-1, thereby enhancing the glucose-lowering incretin effect of postprandially released GLP-1.

Minor adjuncts:
Acarbose: An α-glucose inhibitor, reduces postprandial glucose peaks.
Guar gum: Delays gastric emptying, reduces postprandial glucose level.
Both may cause flatulence 胀气 due to fermentation of unabsorbed sugar.

New injectable antidiabetic agents: Liraglutide, exenatide: Stable GLP-1 (glucagon-like peptide-1) receptor agonists. “incretin mimetic” for treatment of Type 2 diabetes.

## Pharmacology of reproductive hormones

Gonadotropin-releasing hormone (GnRH) → Secreted from hypothalamus and acts on anterior pituitary gland (via Gq-coupled GPCR) to control the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH): In pulsatile dosing, FSH and LH secretion is stimulated, while in continuous dosing, the secretion of the two gonadotrophins is inhibited. GnRH is a decapeptide and acts via a Gs-coupled receptor. Leuprorelin is a synthetic analogue of GnRH.

GnRH is used for treating infertility (pulsatile dosing) as well as malignant diseases such as androgen-dependent prostate cancer (continuous dosing, depressing endogenous FSH/LH release,

and reducing circulating androgen levels). GnRH antagonists (e.g. ganirelix) are also used to depress FSH/LH release.

Gonadotropins→FSH, LH and hCG (human chorionic gonadotropin). hCG is released by placenta and the 3 gonadotropins are coupled to Gs. Gonadotropins are used for the control of ovarian follicle development, ovulation, and production of estrogen and progesterone. In the male, FSH controls spermatogenesis and LH controls testosterone secretion.

Pharmacological preparation of gonadotropins: purified from the urine of postmenopausal women of recombinant.
Use:
Treating male infertility due to pituitary insufficiency.
With GnRH agonist/antagonist for controlled ovulation (in assisted reproductive technology, ART)
Pregnancy test detects hCG in urine.

Oestrogen (E; e.g. 17-β-Oestradiol, ethinyl-oestradiol) → synthesized from androgenic precursor mainly in ovary (secreted in small amounts from adrenal cortex and testis). Its synthesis is triggered by FSH receptor activation: the precursors are converted into oestrogen, which is catalyzed by aromatase enzymes (following FSH receptor activation). It has its actions on ERα and β receptors (intracellular, ligand-activating transcriptional factors). A third, recently discovered receptor (a GPCR) – GPER1 – influences both cAMP and intracellular Ca2+ signaling pathways.

Oestrogen physiological actions:
1. Control of ovary development and control of the development of secondary sex characteristics.
2. In control of menstrual cycle:
– Feedback inhibition of gonadotropin secretion in low concentration of E. In high concentration, gonadotropin secretion is facilitated.
– Promote endothelial proliferation (including increasing expression of progesterone receptors)
– Stimulates cervical mucous glands (high volume section, low viscosity, sperm-friendly secretion)
3. Maintain vascular function (reduce vascular fragility, preserve vasodilator function)
4. Metabolic effects: Water and salt retention; anabolic.
5. reduced bone resorption.
6. Cardiovascular function: increase blood coagulation, increase HDL and lower LDL and cholesterol.

Pharmacological preparations: e.g. ethinyloestradiol: active orally.
Uses: contraception, combined with progestogen. Replacement therapy: Alone (e.g. Raloxifene) or combination with a progestogen.

Oestrogen modulators:

Clomiphene→It acts as an antagonist of oestrogen receptors in pituitary and hypothalamus, preventing the negative feedback on GnRH and gonadotropin release. It can be used for treating infertility by inducing ovulation.

Tamoxifen→It is a selective oestrogen receptor modulator (SERM) that acts differently in different tissues: Antagonist in breast, partial agonist in bone, liver (site of synthesis and control blood lipids), and uterus. This drug can be used to treat oestrogen-induced breast cancer, but increases risk of endometrial cancer and thromboembolic disease.

Anastrozole→It is an inhibitor of aromatase enzyme which converts androgenic precursor to oestrogen. Also, it is used to treat and prevent breast cancer.

Raloxifene→this is another SERM: an antagonist in breast and uterus, a partial agonist in bone and liver. Used to prevent osteoporosis in postmenopausal women at high risk.

Progestogens (P):
The natural hormone is the steroid progesterone. Its receptor is a ligand-activated transcriptional factor. Corpus luteum starts secreting it upon luteinizing hormone (LH) receptor activation. Placenta during pregnancy also secretes a large amount of progesterone.

Physiological action of progesterone:
1. In control of menstrual cycle:
– Promotes the secretory phase of endometrial development in the second half of the menstrual cycle (vascularization and differentiation to produce nutrient-rich secretion that favors implantation), withdrawal results in endometrial shedding (menstruation)
– Modulate the activity of the cervical mucous glands → Secreting low-volume, highly viscous secretion)
– Negative feedback inhibition of GnRH (reduced frequency of pulses) and FSH/LH release.
2. Action of progesterone in pregnancy: acting on the uterus and breast.

Pharmacological preparations:
Norethisterone, medroxyprogesterone acetate: oral use or depot injection. Used in contraception and replacement therapy.
Mifepristone: Is a progesterone antagonist and it is used for early abortion (administered along with prostaglandin). It acts on uterus and triggers endometrial breakdown and prostaglandin sensitization.

Contraceptives and Menopausal Hormone Therapy details in Note.

## Chemotherapy: Anti-bacterial and anti-fungal drugs

### Exploitable difference: Transpeptidase that recognizes D-stereoisomers.

Penicillins→β-lactam antibiotics (β-lactam mimics a D-alanyl-D-alanine peptide bond→Cleaved by a transpeptidase cross-linking the circular polymers). It is specific to the transpeptidases in bacteria as the transpeptidases in humans D-stereoisomers of amino acids are absent. It binds to the bacterial transpeptidase and dissociates slowly, causing the restrain network around bacteria

to weaken (by preventing the formation of a strong 3-dimensional network), and under high osmotic pressure (in a low osmotic environment), bacteria will lyse (through extensive swelling). Penicillin is thus bactericidal.
Various variants from the archetype 原型 of penicillin have been constructed, all of which possess the β-lactam ring, varying in their susceptibility to a β-lactam degrading enzyme (β-lactamase).

Cephalosporins→Also β-lactam antibiotics. Act in the same way as penicillin (More resistant to β-lactamase and 3 generations of drugs with different spectrum of activity)

Vancomycin→binds to the D-alanyl-D-alanine of the pentapeptide tails of the circular glycopeptide polymers and hence prevents the crossing-linking. The consequence is the same as for the penicillins and cephalosporins. Use is limited by its adverse effects and blood level should be monitored.

Exploitable difference: The cell membrane/envelop.

Polymyxins→Target gram-negative bacteria only (narrow spectrum). It interacts with the phospholipids in the cell envelope (outer membrane) and/or cell membrane and subsequently destroys the barrier function (by inserting it into the membranes to make pores). The unwanted cations/anions get through the membranes. Besides, essential components of the bacteria are released. This detergent does not bind as efficiently to the phospholipids of the eukaryotic plasma membrane → selectivity. Polymyxin is often administrated topically to treat superficial infections.

Exploitable difference: DNA replication

Deoxynucleotides synthesis: P-aminobenzoic acid (+ 2-amino-4-hydroxy-6-methyl-pterin + glutamic acid) → Folate (via dihydropteroate synthase) → Dihydrofolate (via reduction) → tetrahydrofolate (via dihydrofolate reductase)

Sulphonamide → Targets dihydropteroate synthesis. It mimics the structure of P-aminobenzoic acid (pABA) without being able to be converted into folate. Humans can take up folate via their diet (bypass the first conversion), while bacteria have no such uptake mechanism.

Trimethoprim → Inhibits dihydrofolate reductase, and prevents the formation of tetrahydrofolate. The counterpart enzyme in humans is less sensitive (~100-fold) to trimethoprim.

Sulphonamide + Trimethoprim: Synergic therapeutic effect.

Quinolones → Target the topoisomerase II (also named DNA gyrase) in bacteria. This enzyme is important for DNA positioning, after which DNA polymerase can act on and copy the two strands. It is also involved in the subsequent supercoiling of DNA after replication. Inhibition of topoisomerase II in microorganisms is lethal. The human topoisomerase II is less sensitive to

quinolones (due to structural differences) and the transport of the drugs into human cells is less efficient (exploitable difference).

### Exploitable differences: Protein synthesis – Ribosomes

Metabolic freeze → Bacteriostatic (e.g., when protein synthesis is inhibited). Intact immune system is required to eliminate the non-growing bacteria.

Tetracyclines → Bind to the 30S subunit and prevent tRNA from binding to mRNA and consequently prevent translation of genetic codes.

Aminoglycosides → Bind to 30S subunit and alter codon-anticodon recognition (genetic codes on mRNA are not translated properly): Nonsense proteins are formed.

Chloramphenicol (it is the only member of its group) → Binds to 50S subunits and prevents coupling of amino acids carried by tRNA (prevents translocation). Ribosome translocation and codon-anticodon recognition are not affected. Limited use due to serious effects.

Macrolides → binds 50S subunit and interferes with translocation of ribosome.

### Exploitable differences: The respiratory electron transport chain (ETC):

5-nitro-imidazoles → It acts as an acceptor of electrons only at sufficiently low electro potential. These drugs were developed as anti-protozoal agents but also found effective in anaerobic microorganisms. If O2 is not the terminal electron acceptor, the electro potential of the ETC is lower. Ferredoxin (Eo = -460mV, sufficiently low potential) is the component of ETC of anaerobic microorganisms that transfers 2 e- to 5-nitro-imidazoles. This molecule (imidazole) is then converted into a chemical cross-linker which subsequently disrupts DNA integrity. The ETC in humans starts at -300mV which is too high to donate electrons to 5-nitro-imidazoles.

Pharmacokinetics & Anti-fungal drugs & Resistance & Adverse effects in Note.

## Chemotherapy: Anti-viral drugs:

### Inhibit viral entry:

In HIV, the use of small CCR5 (=CCKR5?) ligands (e.g., RANTS & MIP-1α, MIP-1β) may have a therapeutic use as the entry of HIV happens after it binds to 2 receptors → CD4 and CXCR4 (T-lymphocytes) or CCR5 (macrophages). Inhibition of CD4 does not have effect, and people carrying CCR5 mutation carry the HIV virus without having infected leukocytes.

In the therapy of influenza A, Amantadine/Rimantadine is used to bind the M2 protein (a viral-coded H+ channel) to prevent endosome acidification, which (Low pH) is a crucial condition for viral fusion with endosomal proteins and release of viral content into host cells.

Reverse transcriptase (RT) inhibitors (Target retrovirus):

1. Nucleoside analogue reverse transcriptase inhibitors (NRTIs) → (e.g., AZT, ddI, ddC, 3TC) phosphorylated by host kinases to become nucleotide analogues. These drugs have no OH- group at the 3' position so further addition of nucleotides is prevented after these agents are inserted into the growing DNA chain. Host DNA polymerase these RT inhibitors (after phosphorylation) in a less efficient way, accounting for their side effects including peripheral neuropathy & bone marrow damage.

2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs): (e.g., Nevirapine, C1-TIBO & L697,6671). These agents are noncompetitive inhibitors, and they bind to an allosteric site which influences the catalytic site of RT for DNA synthesis.

The major problem of these groups of drugs are rapid onset of resistance. However, the resistance to one of the RT inhibitors does not confer the resistance towards another (even if they are from the same class). Besides, one RT inhibitor can suppress the resistance that a virus has developed towards a second inhibitor.

These RT inhibitors (NRTIs and NNRTIs) can be used to treat HIV and hepatitis B.

Aciclovir is another antiviral prodrug converted into Alciclovir triphosphate by "viral" enzyme – thymidine kinase (not host) at first to become a monophosphate, and then by host thymidine kinase to become a triphosphate → greater specificity, excellent safety profile. Ganciclovir and Penciclovir are both aciclovir analogs. Resistance developed against alciclovir: see Note.

Protease inhibitors:

Unlike mammalian mRNA, most viral mRNA is polycistronic 多顺反子 (all the genetic information (coding for all viral proteins) is coded by one piece of mRNA). Thus, only one resultant polypeptide (propeptide) is produced by the translation. In this case, viral protease is necessarily required to break the propeptide and yield structural viral proteins. Viral protease is thus a selective target. In HIV, the viral protease cleaves gag/pol propeptide to produce structural proteins.

Saquinavir, Ritonavir, Indinavir are compounds showing good clinical effects, whereas resistant HIV mutants are beginning to appear.

Highly active antiretroviral therapy (HAART) → A therapy for HIV patients with decreased possibility of mutations conferring resistance. (At least 3 drug combined; Details in Note)

Inhibition of DNA polymerase (some of which have anti-cancer and/or anti-viral use):

5-Iodo-2'-deoxyuridine → treating herpes keratitin 疱疹性角膜炎

Adenosine arabinoside → treating encephalitis and neonatal herpes 疱疹: lack 3'OH group.

Foscarnet is a pyrophosphate analogue and it is also a DNA polymerase inhibitor in terms of its structure.

Inhibition of protein translation and assembly of the virus:

Interferon family of cytokines → interferon-α, β, γ have their actions on protein translation by inducing proteins that inhibit viral mRNA translation. Flu-like side effects can be severe. Used against papillomavirus infections and immune-suppressed patients.

Summary table of anti-viral drugs in Note.

Chemotherapy: anti-cancer drugs:

Alkylating agents→Form covalent links with DNA and inhibit replication:

They can cause the inhibition via crosslinking of 2 nucleotides, guanines in particular.
1. Nitrogen mustards (mechlorethamine, chlorambucil, melphalan, busulfan & cyclophosphamide) → Alkylation occurs due to the formation of positively charged carbonium ions (e.g., CH3+) which is unstable and reacts with an electron-rich site, particularly on DNA/RNA. Most of these clinically used alkylating agents possess 2 alkylating groups for crosslinking. Cyclophosphamide – an alkylating agent: Undergoing enzymatic and chemical modification to form the active phosphoramide mustard.

2. Nitrosoureas (lomustine & carmustine) → The active unit in these molecules is urea, they work similarly to nitrogen mustards. Additional effect: Cytotoxicity on account of the formation of carbamoylated protein. This group of compounds are lipophilic, so they can cross the BBB.

1+2 → administrated orally/intravenously, treating Burkitt's lymphoma, etc.

3. Cisplatin (cisplatin, carboplatin, oxaliplatin) → Cisplatin is a square planar complex with 2 chlorides and 2 ammonia molecules. Its action is analogous to that of alkylating agents: an ability of cross-linking adenosine and guanine nucleotides. Used for combination therapy as using only alkylating agents results in an increasing probability of mutations. This type of drug (alkylating agent) can sensitize cells to radiation therapy.

Anti-metabolites→Inhibit one or more steps involved in DNA synthesis:

Methotrexate (MTX; a folate analogue) → MTX inhibits dihydrofolate synthase and prevents the subsequent synthesis of dTMP from dUMP. If the concentration of MTX is high, purine synthesis will be inhibited as well. Dihydrofolate reductase is involved in the synthesis of tetrahydrofolate (FH4) from dihydrofolate (FH2) and FH2 from folate. The mild selectivity of MTX towards cancer

cells can be attributed to the presence of a higher concentration of glutamate-adding enzymes in cancer cells, which enhances the inhibitory effect of MTX towards FH2 reductase and prevents the cellular efflux of the drugs.

Pemetrexed Disodium → A folate mimetic. Similar mode of actions to other folate analogues with fewer side effects.

5'-fluorouracil (5FU) → dUMP analogue, has a similar action as the anti-viral compound idoxuridine. The enzyme thymidylate synthase deems it as dUMP and attempts to convert it into dTMP, after which this enzyme is inhibited.

Cytarabine (cytosine arabinoside) → a cytosine nucleotide analogue. It has a similar action as the viral inhibitor adenosine arabinoside (abovementioned). It is recognized as a true nucleotide by deoxycytidine kinase and is thus phosphorylated to become the triphosphate form (araCTP). It lacks the 3' OH moiety so DNA chain termination is given rise to. In other words, it interferes with the action of DNA polymerase in DNA elongation.

Cytotoxic antibiotics→Microbial derived agents which inhibit mammalian cell division:

Doxorubicin & actinomycin D → It is believed that this agent stabilizes the DNA polymerase-topoisomerase(II)-DNA complex while the DNA is kept in its nicked "open" form. Thus, DNA replication ceases. Topoisomerase II is a vital enzyme involved in unwinding and nicking the 2 DNA strands during replication. It is also important for the action of DNA polymerase in the synthesis of new DNA, after which the enzyme is responsible for the healing of the nicks.

Dactinomycin → It acts as an intercalating agent that intercalates in the minor groove of DNA, forming a drug-DNA complex that interferes with the binding of RNA polymerase for transcription.

Bleomycin → This agent breaks DNA backbone through binding to a DNA molecule and generating superoxide (O2-) as well as hydroxyl radicals via the Fe(II) pocket within bleomycin. Consequently, DNA fragmentation is induced, so that DNA replication and transcription cease.

Plant derivatives (alkaloids)→Inhibition of microtubule function and thus mitosis.

Vinca alkaloids (vincristine, vinblastine & vindesine) → These compounds act on microtubule assembly by preventing microtubular polymerization (and thus the process of spindle formation in mitosing cells). Although these drugs may interfere with other processes requiring microtubules (e.g., phagocytosis, migration), the toxicity of vinca alkaloids is relatively low.

Etoposide (The mandrake root-derived alkaloid) → shares a similar action to Doxorubicin & actinomycin D.

Taxanes (paclitaxel & docelatel) → These drugs have similar effects to Vinca alkaloids: Freezing microtubule polymerization.

Hormones→ These drugs suppress hormone secretion or antagonize hormone action.

No example is listed in Note.

Miscellaneous→Diverse mechanisms which cannot be classified into one of the above:

L-asparaginase → It breaks down the amino acid L-asparagine which becomes an essential amino acid in tumor cells. As the metabolic need of transformed (cancer) cells greatly increases, the synthesized amino acids in the cell become insufficient. In this case, it is believed that some non-essential amino acids would become essential. Take childhood leukemia as an example: the transformed cells lose the ability to synthesize the non-essential amino acid L-asparagine.

The next step in developing anti-cancer agents, the side effects of the abovementioned drugs, resistance, combination therapy → See Note