Pharmacology for students of bachelor's programmes at MF MU (special part)

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Obsah

2 Pharmacology of the autonomic nervous system

The autonomic nervous system (ANS) is responsible for signal transduction between the central nervous system (CNS) and effector tissues or organs independent of voluntary control (e.g., smooth muscles, myocardium, exocrine glands, etc.) and regulates adaptive reactions of the organism according to changes in the exogenous and endogenous environments. Among the principal processes controlled by the ANS belong the contraction and relaxation of smooth muscles, secretion from all exocrine and some endocrine glands, heart action, some metabolic processes, and immune system functions. The ANS can be traditionally divided into three main branches: the sympathetic, parasympathetic, and enteric nervous system. Many physiological functions are influenced by the sympathetic and parasympathetic systems in a contradictory manner, which is called physiological antagonism, such as their effect on heart activity. Nevertheless, for some body functions, the synergism of both systems (i.e., sympathetic and parasympathetic) is required, for example in the regulation of gonadal system functions.

2.1 Pharmacology of the sympathetic nervous system

The sympathetic nervous system (SNS) has a role in controlling main life functions through its basal activity as well as in accordance with the need of the body to adapt to an acute stressful event. Following exposure to a stressor (e.g., a tiger roaring toward us from a few metres away), there is an immediate release of catecholamines from the adrenal medulla, and in a few seconds, the body is activated for the "fight or flight" reaction. Activation of the sympathetic system is essential for the maintenance of homeostasis and preparation of the organism for physical activity or coping with an injury.

Under baseline conditions, noradrenaline is produced in nerve terminals, which is the predominant status physiologically; whereas in a "fight or flight" situation, the activation of the sympathetic receptors is further stimulated by adrenaline and noradrenaline released from the adrenal medulla. These mediators bind to the adrenergic receptors, which can be divided into five major subclasses: $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$, and $\beta 3$ (see Tab. 4).

The consequences of adrenergic receptor activation can be rationally derived from demands on the organism when exposed to a life-threatening situation in which a quick response is required; emphasis is put on a sufficient supply of oxygen and energy sources for the heart, lungs, brain, and muscles (provided by an increase in blood pressure, bronchodilation, vasoconstriction in peripheral organs and skin, and limitation of kidney blood perfusion). Further, stimulation of the process of platelet clotting and immune system response as well as increased alertness and accommodation of the eye to distance occurs. Many physiological functions (e.g., digestion) are less important in a situation of sudden physical activity. They are inhibited and postponed for later management. Energy is saved for the organism to maintain its basic life functions for survival.

To understand pharmacological drug effects, we need to distinguish the individual adrenergic receptor subtypes, their localization, and the consequences of their activation. For more comprehensive studies, a physiology textbook is recommended for reference. The summary provided here synopsizes the minimal knowledge essential for understanding of the basic pharmacological mechanisms.

Tab. 4 Review of adrenergic receptors

Receptor	Typical localization	Function
α1	vessels, eye, smooth muscles of the urinary and gastrointestinal tract (GIT), myometrium, CNS	vasoconstriction, smooth muscle contraction in GIT and urinary tract, dilation of pupils (mydriasis), anorexic effect
α2	presynaptic location (CNS), blood vessels, GIT, pancreas, platelets	negative feedback for regulation of noradrenaline release, platelet aggregation, local vasoconstriction
β1	cardiac muscle (myocardium), CNS, β-cells of the pancreatic islets, juxtaglomerular cells in kidneys	stimulation of heart functions (positive ino-, chrono-, dromo-, bathmotropic effects), renin release
β2	bronchial, vascular, and uterine smooth muscles, eye, skeletal muscles, mastocytes	bronchial and uterine relaxation, vasodilation in active skeletal muscles, myocardial stimulation, increased contractility of skeletal muscles, relaxation of the ciliary muscle and increased intraocular pressure, increase of blood glycaemia
β3	urinary bladder, adipocytes	relaxation of detrusor muscle, lipolysis

Drugs activating receptors (i.e., agonists) are called mimetics in terms of the pharmacology of the ANS, whereas drugs which are receptor antagonists are called lytics. According to their selectivity for a specific receptor subtype, we can divide sympathotropic drugs (i.e., agents affecting SNS) into several classes as follows:

Drugs affecting sympathetic system
Sympathotropics

- **Sympathomimetics**
  - Non - selective
    - Direct — Catecholamines
    - Non-direct — Amphetamine
  - Selective
    - β1 — Dobutamine
    - β2 — Salbutamole
    - β3 — Mirabegron
    - α1 — Naphazoline
    - α2 — Moxonidine
- **Sympatholytics**
  - β — Beta-blockers
  - α1 — Doxazosine
  - α — Ergot alkaloids
  - α2 — Yohimbine
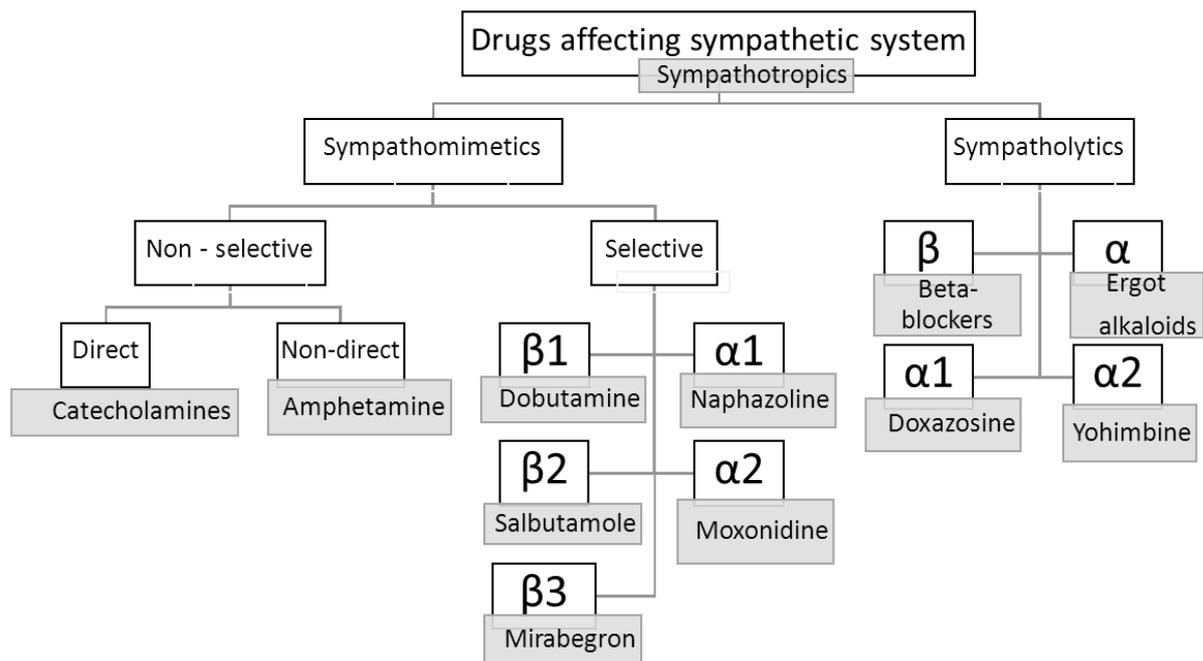
2.1.1 Sympathomimetics

2.1.1.1 Non-selective sympathomimetics

Catecholamines

Noradrenaline (syn. norepinephrine, NA) is the main neurotransmitter of the sympathetic nervous system. In therapeutic doses, it predominantly stimulates α receptors with a smaller effect on β1 receptors and almost no effect on β2 receptors. This causes a potent vasoconstrictive effect and leads to heart activation. After noradrenaline administration, both the systolic and diastolic blood pressure increase, which leads to reflexive bradycardia.

Noradrenaline is administered only parenterally, and this particular administration route is chosen according to the indication. For intensive care medicine, it is typically used in the central venous catheter as a vasopressor infusion or bolus; it is diluted in a 5% glucose solution. Administered locally, it can be used for its vasoconstrictor effect as part of the local anaesthesia. Common indications include shock and critical hypotension states, apart from the local use mentioned earlier.

Adverse effects include arrhythmias (both brady- and tachycardia), chest pain, changes in blood pressure (both hypotension and hypertension), and changes in local peripheral circulation, particularly after extravasal administration. An overdose most frequently manifests as hypertension, but thanks to the short biological half-life of noradrenaline, the situation can be handled by discontinuation of the infusion. In pregnancy, NA significantly decreases maternal placental blood flow. Interactions with other drugs may also be of clinical

relevance; especially risky interactions are those with other sympathomimetics, halothane, and tricyclic antidepressants. Contrarily, sympatholytics can inhibit effects of noradrenaline.

Adrenaline (syn. epinephrine), compared with NA, has a different affinity to adrenergic receptors. At low doses, it stimulates α1 receptors, and at higher doses, its vasoconstrictive effect is comparable with noradrenaline. Likewise, at higher doses, it also significantly stimulates β receptors (including β2 receptor subtypes, which are almost unaffected by NA). Thus, the effects of adrenaline differ from those of noradrenaline, and the difference is thought to be due to β2 receptor activation. Therefore, effects of noradrenaline and adrenaline are similar in many organs, however they are different in tissues with a high density of β2 receptors.

Heart activity is stimulated by adrenaline; specifically, the rise in systolic blood pressure and heart rate frequency is significant, whereas the diastolic blood pressure can drop after a low dose as increased peripheral vascular resistance due to vasoconstriction resulting from α1 receptor stimulation manifests only at higher doses. Contrarily, vasodilation occurs in other tissues (e.g., due to β2 receptor effects, this especially occurs in cardiac and pulmonary tissues as well as the blood vessels of active skeletal muscles). Importantly, effects on bronchodilation are mediated via a direct effect on β2 receptors in the respiratory tract. Adrenaline also has anti-allergic and anti-anaphylactic effects. These effects account for how the blood circulation, respiratory tract, and immune system are modulated (i.e., inhibition of histamine release from mast cells). Adrenaline also supports metabolic processes leading to increased glycaemia (i.e., increased glucose plasma levels, especially due to the hepatic glycogenolysis). Adrenaline also activates platelets. Its antispasmodic effect on the myometrium (i.e., uterine smooth muscle) is not negligible either.

Adrenaline, like noradrenaline, is administered exclusively parenterally. Among the most important indications belong asystole, peripheral circulatory collapse, anaphylaxis, septic shock (i.e., endotoxin shock), bronchospasm, and Quincke's oedema, and after topical administration, it can be used as a nasal decongestant, to reduce capillary bleeding, or combined with local anaesthetics for its vasoconstrictive effects. Side effects of adrenaline are similar to those of NA.

Dopamine differs from noradrenaline and adrenaline by its affinity to dopamine receptors, indicated as D_1-D_5. In the organism, it acts preferentially as a neurotransmitter and is synthesized in a large amount in the CNS. However, it is present in different concentrations in many other tissues in the entire body.

Dopamine effects are dependent on the dose administered:
- At low doses, it influences renal D receptors and induces vasodilation in renal and splanchnic blood vessels. At this low dose, sometimes referred to as a "**renal dose**", dopamine increases renal blood flow and can be used as a renoprotective agent in circulatory shock situations.
- **Intermediate doses** (i.e., from two to 10 μg/kg/min) stimulate β1 receptors; thus, they increase heart activity causing a rise in systolic blood pressure and positive ino- and chronotropic effects.

- At higher doses, dopamine also starts to influence α1 receptors ("**pressoric doses**"). Vasoconstriction also occurs in renal vessels causing a rise in blood pressure.

Dopamine is indicated in acute maldistribution of renal and splanchnic blood flow, shock situations, and heart failure. It is administered exclusively in a diluted form via an intravenous infusion. Dopamine is chemically incompatible with alkaline solutions, including sodium bicarbonate. Saline, 5% glucose, and Ringer solution are considered as suitable solvents. Monitoring is required during dopamine infusion. Side effects include cardiac conduction abnormalities (ventricular arrhythmias) and peripheral cyanosis due to impaired peripheral blood circulation with a risk of ischaemic necrosis of tissue (gangrene). Dopamine does not cross the blood-brain barrier; thus, it cannot be used for the therapy of Parkinson´s disease.

Ephedrine and pseudoephedrine

Ephedrine is a natural plant alkaloid with both direct and indirect effects on alpha and beta receptors. Its effects include positive inotropic, chronotropic, dromotropic, and bathmotropic effects on heart functions, vasoconstriction, bronchodilation, inhibition of motility of the gastrointestinal (peristalsis) tract and genitourinary systems, and central stimulatory effects. Ephedrine is indicated for the treatment of allergic disorders, such as bronchial asthma. It was formerly used as a pressor agent in peripheral circulatory collapse (vasomotoric collapse) and nycturia (nocturnal enuresis) and as a central nervous system stimulant in narcolepsy. It has a wide range of side effects, such as drug addiction. Ephedrine is classified as a precursor of narcotic and psychotropic drugs, and for its prescription, a special prescription form with blue stripes is required (i.e., it is bound to the blue stripe prescription form).

Pseudoephedrine is a diastereomer of ephedrine. Its effects especially manifest in the respiratory tract as bronchodilation and nasal decongestion. It is available as a constituent of combined pharmaceutical preparations, which are used for symptomatic therapy of colds and other respiratory inflammatory disorders (e.g., MODAFEN), but these preparations can be misused for extraction of the pseudoephedrine component for synthesis of methamphetamine (Pervitin). In the Czech Republic, these preparations are currently listed as OTC ("over the counter") drugs with a limited distribution; thus, there are a limited number of packages handed out (issued), and the client must show her/his ID document with each purchase.

Indirect sympathomimetics

Their mechanism of action cannot be explained by the direct binding of adrenergic receptors, instead they function by increasing endogenous neurotransmitter levels. Therefore, they induce non-selective effects influencing all adrenergic receptors.

Ephedrine (mentioned above), **amphetamine**, and its analogues are examples of drugs which stimulate neurotransmitter release from storage vesicles. Drugs, such as **MDMA** (commonly known as ecstasy) and **methamphetamine** (Pervitin), belong to this group. These agents are addictive, and their use is associated with a wide variety of adverse effects, both physical and psychical. In addition to their stimulatory activity, they induce anorexia. Sometimes they are available on the black market as food supplements, energy boosters, and weight loss products.

Phentermine, sometimes prescribed as an anti-obesity medication (anorexia drug), has a similar effect.

Cocaine and **tricyclic antidepressants** are blockers of neurotransmitter reuptake from the synaptic cleft. Thereby, they increase neurotransmitter levels.

Another mechanism leading to a higher level of neurotransmitters is achieved by inhibiting the degradative enzyme responsible for their metabolism, in other words, blocking neurotransmitter biodegradation. Thereby, **MAO A** (monoamine oxidase A) **inhibitors** are used in clinics as antidepressants as are **MAO B** (monoamine oxidase B) **inhibitors** and **COMT** (catechol-O-methyltransferase) **inhibitors** used in the clinical setting as antiparkinson agents. Use of these drugs is associated with a higher incidence of severe drug interactions when combined with other drugs, especially sympathomimetics, such as adrenaline and noradrenaline.

2.1.1.2 Selective sympathomimetics – β1

Dobutamine is a chemical compound similar to dopamine, but with a dominant effect on β1 receptors. At doses used in clinics, it has an especially positive inotropic effect without a significant influence on the heart rate. Among its indications are cardiac failure, shock situations, and diagnostic tests. Dobutamine is administered intravenously by infusion.

2.1.1.3 Selective sympathomimetics – β2

Therapeutic use of these agents targets β2 receptors in the myometrium (uterine smooth muscle) and respiratory tract. Their tocolytic effect is used for relaxation of the uterus to manage premature contractions or to postpone delivery (i.e., labour suppressants). Their anti-asthmatic effects include bronchodilation and immunoprophylaxis. Most side effects result from concurrent β receptor stimulation in other tissues and organs. Examples include tachycardia, ischemia (due to increased myocardial work), myocardial necrosis, and skeletal muscle tremor.

Anti-asthmatics are mostly delivered as aerosol formulations through inhalers, in tablets, or in acute situations given intravenously by injection. They can be divided according to the duration of their effect into three categories:

- Short-acting agents, which are used to manage acute bronchoconstriction (e.g., acute asthmatic attack), for example salbutamol, hexoprenaline, and fenoterol,

- Long-acting agents, such as those used for chronic anti-asthmatic therapy or night asthma, examples include salmeterol, formoterol, and clenbuterol, and

- Ultra-long-acting agents include indacaterol.

According to the onset of action, we can distinguish drugs used for attack relief through rapid onset of action (RABA), such as **formoterol**, from those which have a slow onset of action (> 30 min), such as **salmeterol**, which cannot be used in case of an acute bronchospasm.

Tocolytic agents, such as **hexoprenaline**, should only be used short term (i.e., maximum duration being 48 hours) for patients between the 22nd and 37th week of gestation. Ritodrine is not registered in the Czech Republic.

2.1.1.4 Selective sympathomimetics – β3

The most well-known representative of this modern class of beta-mimetics is **mirabegron**. By influencing β3 adrenergic receptors in the detrusor muscle in the bladder, it leads to muscle relaxation and an increase in urinary bladder capacity. Thus, it increases the period of bladder filling and delays episodes when the patient suffers from urge incontinence. Mirabegron is used for the therapy of an overactive bladder. Side effects include urinary tract infections and increased basal heart rate and blood pressure, which are signs of cardiovascular stimulation due to its influence on beta receptors in other localizations.

2.1.1.5 Selective sympathomimetics – α1

The stimulatory effect on α1 receptors can be used to stimulate vasoconstriction of blood vessels, shrink swollen blood vessels and tissues (i.e., the mucosal effect of nasal decongestants), strengthen sphincter muscles in the urinary tract (urine retention), and for mydriasis in the eye. Agents with a strong peripheral vasopressor (antihypotensive) effect are called peripheral analeptics, and they are indicated in critical shock situations.

Representative drugs of this group are **phenylephrine** and **midodrine**. Other frequently used medicines are imidazole derivatives with names sharing the ending, "-zoline", such as **naphazoline**, **tramazoline**, **xylometazoline**, **tetryzoline**, and oxymetazoline. These have a rapid vasoconstrictor action and relieve nasal congestion. Thus, they can be used as additives to local anaesthetics; in the form of eye and nasal drops or sprays, they treat flu (influenza virus) symptoms by reducing swelling when applied to mucous membrane, and they treat nose bleeds and eye redness (conjunctivitis). After long-term use (i.e., more than one week), they can cause rebound chronic congestion called rhinitis medicamentosa ("*sanorinismus*" in Czech), followed by degenerative changes (i.e., atrophy of nasal mucous membranes).

2.1.1.6 Selective sympathomimetics – α2

Stimulation of central α2 receptors in the CNS can induce a negative feedback response leading to an inhibition of the sympathetic activity of the autonomic nervous system. These agents are used as antihypertensive and antiglaucoma agents. They have sedative effects. Central activation of the α2 receptors is thought to be responsible for side effects such as sedation, dry mouth, confusion, and body weight gain. Sudden withdrawal can lead to a hypertensive reaction, also referred to as rebound hypertension or the rebound phenomenon.

Examples of α2 agonistic agents are **clonidine**, **moxonidine**, and **rilmenidine**. **Methyldopa** belongs to this class of centrally acting antihypertensives, as well. Apart from its antihypertensive effect, it improves placental blood flow and is considered as a drug of choice for the therapy of hypertension in pregnancy. It is necessary to mention that methyldopa is a drug of first-choice for severe hypertensive states. The centrally acting agent, **urapidil** (i.e.,

an agonist of central 5-HT$_{1A}$ receptors in cardiovascular centres), has additional peripheral antihypertensive effects mediated by a blockade of the α1 receptors. Thus, it can modulate blood pressure both by its central effect and through peripheral vasodilation without causing significant reflex tachycardia. More details can be found in the Chapter 5.1 Antihypertensive drugs, diuretics.

2.1.2 Sympatholytics

2.1.2.1 Sympatholytics – β blockers

Beta blockers inhibit the activity of the sympathetic nervous system both centrally and peripherally. Their effect on heart action is negatively chronotropic, inotropic, dromotropic, and bathmotropic. Beta blockers also decrease renin secretion, inhibit tremor of the skeletal muscles, and lower intraocular pressure. The most important pharmacological effect of beta-adrenergic blockers is their cardioprotective effects including:

- an anti-ischemic effect due to a decrease in cardiac output (i.e., to reduce oxygen demands of the heart),
- an antiarrhythmic effect owing to an increase of the fibrillation threshold,
- and bradycardia which is associated with a longer diastole, and thereby, with better coronary arterial blood flow.

Apart from the therapy of hypertension, beta blockers are used for the management of cardiac arrhythmias, ischemic coronary disease (angina), glaucoma, and tremor.

Beta blockers can be divided into two categories. According to their selectivity for a specific receptor subtype, we can distinguish between non-selective (i.e., influencing both β1 and β2 receptors) beta blockers and β1-selective beta blockers. According to their intrinsic sympathomimetic activity (ISA) or their ability to activate the receptor (at least partially), we can distinguish between agents with inner sympathomimetic activity (partial agonists) and without any inner sympathomimetic activity (antagonists). Names of beta blockers typically end with -**olol**. Examples of different agents are given in the table 5 below:

Tab. 5 Classification of beta blockers.

	nonselective	**β1 selective (cardioselective)**
without ISA	competitive antagonists **propranolol**, **sotalol**	with fewer extracardiac side effects (asthmatic symptomatology) **betaxolol**, **atenolol**, **metoprolol**, **bisoprolol**, **esmolol**

with ISA	with fewer cardiac side effects (bradycardia, negative inotropic effect), mild metabolic side effects **pindolol**, **bopindolol**, **oxprenolol**, **alprenolol**, **carteolol** (topical use in glaucoma)	**acebutolol**, **celiprolol**

Labetalol and **carvedilol** are beta blockers with combined α and β effects on different adrenergic receptor subtypes.

Common side effects of beta blockers include cardiac insufficiency and conduction disorders with a potential risk of arrhythmias. The risk of bronchoconstriction increases for patients with bronchial asthma as well as patients with chronic obstructive pulmonary disease (COPD). Beta blockers have a disadvantageous metabolic effect in diabetic patients, and additional caution is necessary because they can mask the symptoms of hypoglycaemia (e.g., palpitations, tremor). Beta blockers should not be abruptly withdrawn due to the risk of rebound phenomenon occurring.

2.1.2.2 Sympatholytics – α

Ergot alkaloids

These are produced by fungi of the genus *Claviceps* (e.g., *Claviceps purpurea*) that attack cereals as well as a variety of grass species. Ergot alkaloids are a large group comprised of alkaloid compounds with complex effects influencing the vascular and uterine muscles (i.e., due to targeting α-adrenoreceptors and dopaminergic receptors as well as influencing serotonin levels and indirect effects). Chemically, these compounds are related to lysergic acid (LSD) because they too possess hallucinogenic properties due to their affinity for serotonergic 5-HT receptors.

Modern clinical approaches include derivatives with a more targeted action: Vasodilator effects are potentiated with dihydrogenated derivatives, such as **dihydroergotamine (DHE)**, **dihydroergocristine**, **dihydroergotoxine**, **dihydroergocornine**, and **alpha- and beta-dihydroergocryptine**. These agents are less widely used owing to their adverse effects and they are no longer permitted in some EU countries. Previously, they were used for the treatment of central and peripheral blood circulation disorders (e.g., during recovery after a stroke, age-related cognitive impairment) and to treat migraines.

The uterotonic effect is expressed more using methylated derivatives, such as **methylergometrine**, which is generally used to control post-partum bleeding or to stop bleeding after an abortion or other surgical intervention in gynaecology.

2.1.2.3 Sympatholytics - α1

The α1 receptor is localized in different tissues, but in pharmacotherapy, the α1 receptors in vascular smooth muscle and the urinary tract are usually the targets. Alpha-blockers initiate vasodilation in blood vessels as well as relaxation of prostatic smooth muscle and the sphincters of the urinary tract. Apart from the therapy of hypertension, they can also be used to treat symptomatic benign prostatic hyperplasia.

Prazosin is no longer registered in the Czech Republic. The only currently registered α1 receptor blocker is **doxazosin**. Its indications are hypertension (for its vasodilator effect, used even in monotherapy) and urinary retention in patients with urinary flow restriction in the urethra, for example due to benign prostatic hypertrophy (BPH). Its side effects are mediated by its vasodilatory effect as well as its α1 binding at other localizations. Some side effects are vertigo, orthostatic hypotension, dyspnea and respiratory tract infections, dyspepsia, and xerostomia (dry mouth).

Tamsulosin is a selective blocker of the α-1A adrenergic receptor subtype present in smooth muscles of the prostatic gland and ureter, which is used for the therapy of BPH. Its most frequent side effects are retrograde ejaculation, vertigo, arrhythmias, and nasal congestion.

Another α1 antagonist used in clinical settings is the previously mentioned agent, **urapidil**.

2.1.2.4 Sympatholytics - α2

Yohimbine is contained in the bark (cortex) extract from the tree with the common name Yohimbe (*Pausinystalia johimbe)*, native to central and western Africa. Traditionally, it has been used as aphrodisiac medication owing to its vasodilator effects in the pelvic area. Its cardiovascular side effects are tachycardia and hypertension.

2.2 Pharmacology of the parasympathetic system

The parasympathetic part of the autonomic nervous system controls activities performed at rest and during digestion. Its fibres extensively innervate the gastrointestinal tract, glandular system, heart, lungs, eye, and genitourinary tract. The functions of the gastrointestinal system are generally stimulated by the parasympathetic division of the autonomic nervous system, while myocardial activity is inhibited (i.e., negative chronotropic effect). The parasympathetic system is also responsible for defecation and urination.

The main neurotransmitter of the parasympathetic system is acetylcholine, which binds to muscarinic receptors at the cellular level of effector organs. At the same time, acetylcholine plays a signalling role in all autonomic ganglia (i.e., both the sympathetic and parasympathetic ganglia) and at the neuromuscular junction in skeletal muscles. In both above-mentioned localizations, it binds to the nicotinic type of acetylcholine receptors. Also, acetylcholine acts as the neurotransmitter in the CNS. Therefore, according to localization and function, it must be distinguished as to whether the neurotransmitter, acetylcholine, or other drug groups have influence at a certain synapse.

Drugs which influence cholinergic receptors (both the nicotinic and muscarinic types) are called cholinotropics, and they can be divided into cholinomimetics and cholinolytics. The term, parasympathomimetics or -lytics, are related to drugs that influence signal transduction specifically at muscarinic receptors. **Ganglioplegics** are agents influencing nicotinic receptor types and inhibiting signal transduction in the autonomic ganglia. **Muscle relaxants** (**myorelaxants**) inhibit signal transduction in the neuromuscular junctions. (See the Chapter 12.1 Muscle relaxants.)
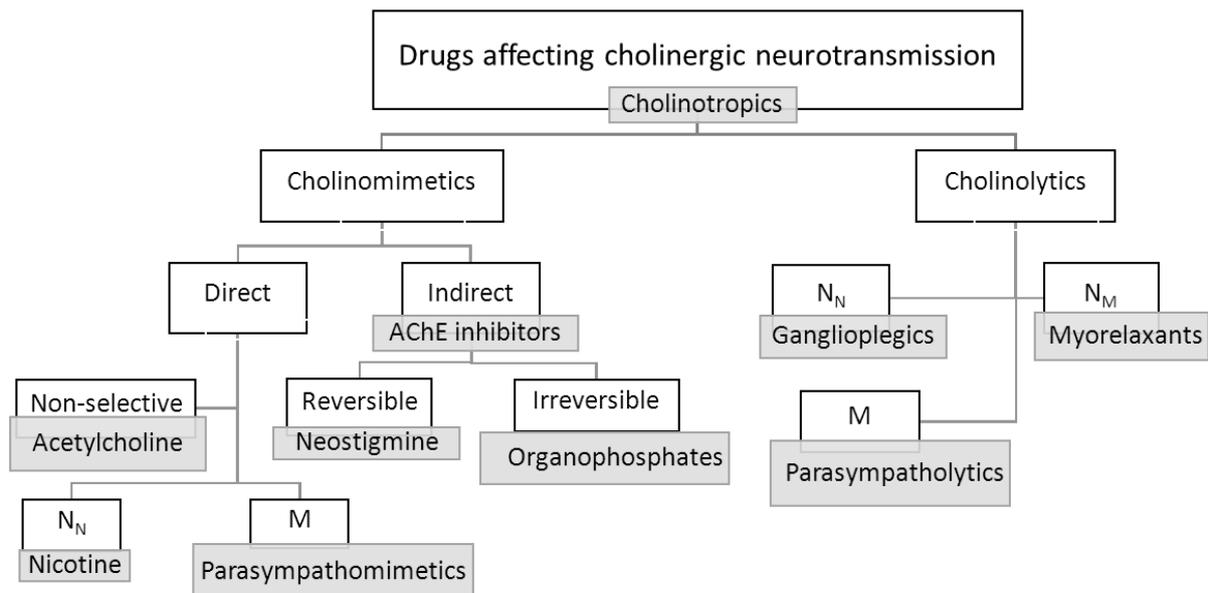
The chemical structure of drugs greatly influences their pharmacokinetics. Molecules containing a quaternary ammonium cation (quaternary amines) are charged; therefore, they do not penetrate biological membranes well. Whereas, tertiary amines, due to their uncharged molecules, are easily distributed in the body; thus, they can also penetrate the blood-brain barrier (BBB).

2.2.1 Cholinomimetics

2.2.1.1 Acetylcholine and its analogues

Acetylcholine has a quaternary chemical structure; therefore, it incurs difficulty with membrane penetration and has a limited absorption after oral administration. It also has a limited distribution after parenteral use. Furthermore, its biological half-life is very short, after an intravenous bolus dose, it is metabolised by the enzyme, acetylcholinesterase, within 20 seconds. Therefore, acetylcholine is not a suitable agent for practical use.
Clinically, acetylcholine derivatives like **carbachol** and **methacholine**, which have a longer biological half-life, are preferable for use.

2.2.1.2 Acetylcholinesterase inhibitors

Acetylcholine concentration in the synapse is thoroughly regulated in the organism, and its fast degradation is essential for homeostasis and life functions. Acetylcholinesterase is the key enzyme necessary for acetylcholine metabolism. Through the inhibition of its degradation, the acetylcholine effect in the synaptic cleft can be prolonged. This effect is nonspecific to a receptor subtype, and both muscarinic and nicotinic receptors are affected simultaneously. The effect of acetylcholinesterase inhibitors is systemic and manifests as bradycardia, a decrease in myocardial contractility, increased motility of the gastrointestinal (peristalsis) and genitourinary tract, stimulation of exocrine glands, and skeletal muscle fasciculations and twitching.

Acetylcholinesterase inhibitors can be divided into two groups according to the reversibility of their effect. The agents with a reversible mechanism of action are used in pharmacotherapy of myasthenia gravis (skeletal muscle weakness), glaucoma, urinary retention, and intestinal atony, examples include **neostigmine**, **physostigmine**, **pyridostigmine**, and **distigmine**. Agents with a long-term effect, such as **donepezil**, **galantamine**, and **rivastigmine**, are used for the therapy of Alzheimer´s dementia, which has been associated with acetylcholine deficiency in the CNS.

Irreversible acetylcholinesterase inhibitors, **organophosphates**, are toxicological in nature. They include insecticides, **parathion** and **malathion**, and nerve gases (chemical weapons), such as **sarin**, **tabun**, and **soman**. The symptoms of intoxication with irreversible acetylcholinesterase inhibitors include salivation, lacrimation, urination, incontinence, vomiting, miosis, tremor, skeletal muscle convulsions, and life-threatening bronchospasms and bronchorrhea (i.e., increased mucous secretion in the respiratory tract).

In case of organophosphate intoxication, urgent therapy is required. It comprises mechanical ventilation, therapy of muscle convulsions (intravenous diazepam), the parasympatholytic drug, atropine, administered as an antidote until signs of atropinization (mydriasis) occur, and **obidoxime** should be administered as an acetylcholinesterase reactivator (pralidoxime and trimedoxime are not currently registered in the Czech Republic).

2.2.2 Parasympathomimetics

Parasympathomimetics are muscarine receptor agonists. **Pilocarpine** administered locally is used as a miotic antiglaucoma agent in ophthalmology. **Muscarine**, a natural alkaloid from the fly amanita (*Amanita muscaria*), having given its name to the acetylcholine receptor subtype, has a toxicological basis. However, the muscarine content is too low to play a significant role in symptomatology of poisoning with this mushroom.

2.2.3 Parasympatholytics

Parasympatholytics are direct muscarine receptor antagonists. Their effects include tachycardia, bronchodilation, a decrease in glandular secretion, a decrease of gastrointestinal motility, urinary retention, xerostomia (decrease in salivation/dry mouth), xerophthalmia (dry eyes), mydriasis, and cycloplegia (i.e., blockade of ciliary muscle function and impaired nearsightedness). The wide clinical importance of parasympatholytics surrounds their use as antiasthmatics, antispasmodics, antiemetics, mydriatics, and antiparkinson agents.

2.2.3.1 Agents with a tertiary amine group

Atropine is an alkaloid from the deadly nightshade plant (*Atropa belladonna*), one of the most poisonous plants in the northern hemisphere. It is used for the therapy of bradyarrhythmia, as an antidote for an overdose with acetylcholinesterase inhibitors, in premedication prior to a surgical procedure under general anaesthesia (to block the vagus nerve reflexes), as a spasmolytic agent in urology and gastroenterology, and in ophthamology, for therapeutic mydriasis by administering it locally.

Symptoms of *Atropa belladonna* intoxication cannot be attributed only to its atropine content, but also to other natural alkaloids present, such as **scopolamine (hyoscine)**. Intoxication is presented by mydriasis, xerostomia, tachycardia, and dry hot skin (caused by an inhibition of sweat production). After higher doses, urinary retention and constipation can be observed, and there is a risk of hallucinations and coma. Therapy of intoxication with parasympatholytics is symptomatic. Physostigmine can be used as an antidote.

Tropicamide and **cyclopentolate**, with shorter effects than atropine, are used to diagnose mydriasis in ophthalmology.

2.2.3.2 Agents with a quaternary ammonium cation

Due to the poor absorption of quaternary amines, these are mostly administered parenterally. As inhalation antiasthmatics, a short-acting antimuscarinic agent, **ipratropium**, and long-acting antimuscarinic bromides, **tiotropium**, **aclidinium**, and **umeclidinium**, are used. **Butylscopolamine**, available in parenteral forms, and **phenpiverine**, are spasmolytics. Phenpiverine is often used in spasmoanalgesic combinations along with nonsteroidal anti-inflammatory drugs (e.g., metamizole) and musculotropic spasmolytics (e.g., pitofenone). **Otilonium** is used for the therapy of spasms of the distal part of the gastrointestinal tract, and **tolterodine** and **trospium** are used to treat an overactive bladder.

2.2.3.3 Uroselective parasympatholytics

Parasympatholytics which bind selectively to M_3 receptors in the urinary tract (i.e., M_3 muscarinic receptors in the detrusor muscle of the bladder), **darifenacin** and **solifenacin**, are used for the therapy of overactive bladder syndrome.

3 Psychotropic substances, drug dependence

3.1 Psychotropic substances

The main expected effects of psychotropic substances are changes in mental states and affecting of mental functions (e.g., effects on anxiety, mood, vigilance). Psychotropic substances are divided according to their main therapeutic effect.

3.1.1 Treatment of affective disorders (antidepressant drugs)

Depression is a severe and life threatening mental state that manifests as depressed mood in the persons affected. Approximately 10-15% of population suffers from depressive disorder and women are affected twice as frequently.

A widely-accepted hypothesis explaining the development of depression is based on monoamine theory. It was postulated after observing which hypertensive patients treated with reserpine (i.e., a plant alkaloid inducing depression) developed depression as result of this treatment. According to monoamine theory, depression is a consequence of a deficit in serotonergic and noradrenergic synaptic neurotransmission in the brain. Antidepressant drugs increase monoamine levels in the synapse, which results in a whole cascade of processes manifesting as the anti-depressive effect.

The effect of all antidepressant drugs appears earliest after two weeks of administration; substances of choice are SSRIs.

3.1.1.1 Monoamine reuptake inhibitors

Tricyclic antidepressants

Tricyclic antidepressants and structurally similar antidepressant drugs non-selectively block serotonin and norepinephrine reuptake from the synaptic cleft to presynaptic part of neuron. This mechanism prolongs the presence of neurotransmitters in the synaptic cleft, which subsequently leads to compensation of their shortage during depression. Typical tricyclic antidepressants involve for example, **amitriptyline**, **imipramine**, **dosulepin**, and **clomipramine**.

The most frequent adverse effects are as follows: sedation, weight gain, anticholinergic effect, cardiotoxic effects (e.g., arrhythmia, QT interval prolongation), and postural hypotension. They can interfere with corticosteroids and neuroleptic substances at the level of elimination, and their concomitant intake with alcohol leads to respiratory depression. They can also be used for the treatment of neuropathic pain in chronic pain syndromes.

Selective neurotransmitter (serotonin, norepinephrine and dopamine) reuptake inhibitors

SSRI (Selective Serotonin Reuptake Inhibitors) are the first substances considered for the treatment of depression. Furthermore, they are used in therapy of obsessive-compulsive

disorder (OCD), panic disorder, mental anorexia and bulimia, or pathological gambling. Typical SSRIs are **fluoxetine**, **citalopram**, **escitalopram**, and **paroxetine**. They are well-tolerated, have low toxicity, and adverse effects include nausea, diarrhoea, anorexia, sexual dysfunction, and increased bleeding. SSRIs have a whole range of pharmacokinetic interactions; they inhibit enzymes of cytochrome P450, thus slowing down metabolism of other substances (metabolised by P450), and in this way they can cause the other substances' levels to increase (i.e., creating a risk of toxicity, overdosing).

NRI or NERI (Norepinephrine Reuptake Inhibitors), for example, **reboxetine**, are used for the treatment of depression associated with decreased psychomotor activity or attention disorder.

SARI (Serotonin Antagonist and Reuptake Inhibitors): Aside from blocking serotonin selective reuptake inhibition, these also block 5-HT$_{2A}$ receptors (e.g., **trazodone**). Trazodone is suitable for therapy of depression associated with insomnia. It acts in lower doses particularly as a hypnotic drug by blockade of the 5-HT$_{2A}$ receptor; in higher doses, it blocks serotonin reuptake.

NDRI (Norepinephrine and Dopamine Reuptake Inhibitors): An example in this category is **bupropion**. Unlike other antidepressant drugs, it has low rate of adverse effects on sexual functions. Aside from treating depression, it can also be used for therapy during smoking cessation and as a treatment for gambling.

SNRI (Serotonin and Norepinephrine Reuptake Inhibitors) such as **venlafaxine**, **duloxetine**, **milnacipran** are good examples of this type of antidepressant. Their main advantage is their fast onset and small number of adverse effects.

3.1.1.2 Inhibitors of monoamine degradation

Non-selective irreversible MAO inhibitors

Monoamine oxidase is an enzyme decomposing monoamines such as dopamine, serotonin, or norepinephrine. Mood is improved particularly effectively as a consequence of serotonin concentration increasing in the CNS; psychomotor activity is improved due to norepinephrine and dopamine concentration increase.

Because of the MAO blockade, it is necessary to follow a dietetic regimen and avoid food rich in tyramine (e.g., cheese, wine, beer, etc.), which is a precursor of catecholamine synthesis and is normally decomposed by MAO. Its accumulation could cause a dramatic increase in blood pressure and hypertonic crisis. **Tranylcypromine** is an example of a typical drug in this group.

Selective MAO-A and MAO-B inhibitors

These can selectively affect MAO subtypes. Selective irreversible MAO-B inhibitor, **selegiline**, besides being used for the therapy of depression, is used to treat Parkinson's disease and Alzheimer's disease. Selective reversible MAO-A inhibitor, **moclobemide**, is a newer substance, which does not require adjustment of the dietetic regime. It is indicated for mild to moderate depression and is also well tolerated by older patients.

3.1.1.3 Noradrenergic specific serotoninergic antidepressants (NaSSA):

The NaSSA group includes, for example, **mirtazapine**. Its advantages are fast onset of effects, and it has anti-depressive, anxiolytic, and sedative effects.

3.1.2 Treatment of anxiety disorders (anxiolytic drugs)

Anxiolytic drugs are used mainly for the therapy of anxiety disorders, phobias, and to treat posttraumatic stress disorder.

These substances include the **benzodiazepines** (e.g., **diazepam**, **oxazepam**, **bromazepam**, and **alprazolam**). They act through $GABA_A$ receptor complexes, which are coupled to chloride channels. Benzodiazepines (similarly to barbiturates) bind to the $GABA_A$ receptor and facilitate the binding of GABA (gamma-aminobutyric acid; a natural ligand of this receptor), which leads to the chloride ion channel opening; this causes hyperpolarization and inhibition of neural impulse transmission. Consequently, benzodiazepines possess anxiolytic, anticonvulsive, myorelaxant, and in higher doses, amnestic effects.

Benzodiazepines have excellent bioavailability after oral administration; they bind to plasmatic proteins in circulation, are biotransformed by the microsomal cytochrome P450 system, and finally excreted by kidneys.

Adverse effects involve sleepiness, dizziness, problems with coordination, and prolongation of sleep. A common property of benzodiazepines is tolerance, which becomes apparent through gradual fading of the desired effect. There is a high risk of psychological and physical dependence following chronic use.

Contraindications include concurrent use with alcohol (risk of respiratory depression), use during pregnancy and lactation (risk of cleft palate and abstinence syndrome in new-borns), in patients with multiple sclerosis, or in patients with alcohol or drug dependence. In case of overdose, **flumazenil** can be used, which is a specific antagonist of benzodiazepine receptors.

Anxiety can also be treated with **serotonergic substances** (e.g., $5\text{-}HT_{1A}$ receptor agonist buspirone) using low doses of antidepressants from the **SSRI** group, low doses of **antipsychotic drugs** (see below), **H$_1$ antihistamines of the 1st generation** (e.g., hydroxyzine, bisulepine, promethazine), **guaifenesin**, or **beta-blockers** (e.g., metipranolol).

3.1.3 Treatment of sleep disorders (hypnosedatives)

Hypnosedatives are substances damping the CNS. Hypnotics cause conditions similar to physiologic sleep; sedatives are calming. The border between them is not sharp – an increased dose of sedatives will cause a hypnotic effect; thus, they are termed hypnosedatives. The indication for these substances is insomnia. They act on $GABA_A$ receptor complexes coupled with chloride ion channels. Hypnosedatives are divided into three generations:

First Generation - Barbiturates

Barbiturates were the substances of choice prior to the discovery of BZDs. Presently, they are not used for the treatment of insomnia because of their narrow therapeutic range and addictive

potential. Some of them are used as anaesthetic drugs (**thiopental**) and antiepileptic drugs (**phenobarbital**).

Second Generation - Benzodiazepines (BZD)

Dissimilar to the third generation of hypnosedatives, benzodiazepines are not selective. They also have hypnotic, anxiolytic, anticonvulsant, and myorelaxant effects. There is a risk of physical and psychological dependence. They should not be used in geriatric patients due to paradoxical reactions (e.g., excitation, aggressiveness).

Third Generation – "Z" substances

"Z" substances include **zolpidem**, **zaleplon**, and **zopiclone**. They have a selective hypnotic effect and compared to the second generation, there is a lower risk of dependence. They act as selective agonists of ω_1 BZD receptors. They do not disturb the physiologic structure of sleep (i.e., the shortening of REM phase - deep phase of sleep with rapid eye movements) to such extent as does the previous generation.

Newer hypnotic drugs involve substances that affect melatonin receptors (e.g., **melatonin**, **ramelteon**), which successfully improve quality of sleep in patients older than 55 years of age with primary insomnia. Also, phytopharmaca can be used for the treatment of insomnia (e.g., containing common balm, valerian, hop, hawthorn, passionflower or St. John's wort).

3.1.4 Treatment of mental integration disorders (antipsychotic drugs)

Neurotropic substances affecting mental integration involve antipsychotic drugs, alternatively called neuroleptics. They are used particularly for the treatment of psychosis (e.g., schizophrenia, the manic phase of bipolar affective disorder). This group of drugs affects dopaminergic transmission through inhibition of the D_2 receptor in the mesolimbic and mesocortical system.

Targeting the dopaminergic system to treat schizophrenia is due to the dopamine hypothesis. According to this theory, schizophrenia is accompanied by hyperreactivity of the dopaminergic system. Part of the patient's clinical picture involves **positive psychotic symptoms**: delusions, hallucinations, aggressiveness, agitation, disorganisation; and **negative psychotic symptoms**: emotional and affective flattening, apathy, and anhedonia.

3.1.4.1 Classical (typical) antipsychotics

Sedative

These substances are intended for the treatment of psychomotor unrest; they have sedative and hypnotic effects, and weaker neuroleptic effects. Adverse extrapyramidal symptoms (e.g., dyskinesia - rhythmic movements of tongue and mimic muscles, stereotypic swinging movements of body, involuntary rhythmic movement of hands and legs) are rare. For example, this group involves **chlorpromazine** and **levomepromazine**.

Incisive

Incisive antipsychotics are used for treatment of positive psychotic symptoms (e.g., delusions and hallucinations). They have strong neuroleptic effects, but also cause significant adverse extrapyramidal symptoms. **Haloperidol** serves as a good example.

3.1.4.2 Atypical antipsychotics

Atypical antipsychotics are used for the treatment of negative psychotic symptoms (e.g., apathy, anhedonia). They are also suitable for maintenance therapy of schizophrenia, newly diagnosed schizophrenia, and when classical antipsychotics are not tolerated. Adverse effects involve minimal stimulation of prolactin secretion. In addition, substances of this group cause weight gain and increase risk of cardiovascular disorders.

- D_2, D_3 selective antagonists: **sulpiride**, **amisulpride**, and **tiapride**
- SDA (serotonergic and dopaminergic antagonists): **risperidone**, **ziprasidone**, **sertindole**, and **paliperidone**
- MARTA (multi-receptor antagonists): **clozapine**, **olanzapine**, **quetiapine**, and **zotepine**
- partial agonists of D_2 receptors/antagonists on 5-HT receptors: **aripiprazole**

3.1.5 Drugs affecting memory and cognitive functions

3.1.5.1 Treatment of Alzheimer's disease

Substances used for this indication improve cognitive functions such as attention and memory. Alzheimer's disease is characterised by an imbalance between dopamine and acetylcholine in brain, or in other words a lack of acetylcholine. Centrally acting reversible inhibitors of acetylcholinesterase are used (**donepezil**, **galantamine**, and **rivastigmine**).

Adverse effects involve diarrhoea, nausea, and tremor. For the treatment of Alzheimer's disease, **memantine** can be also used; this drug acts by partially inhibiting glutamatergic NMDA (N-methyl-D-aspartate) receptors.

3.1.5.2 Nootropics (cognition-enhancing drugs)

Nootropics are a non-homogenous group of substances supporting the activity of the brain, for example by improving blood flow or neuronal and glial metabolism. In practice, **piracetam** is used due to its positive effect on memory function; furthermore **pyritinol**, an antioxidant supporting metabolism of neurons, and **vinpocetine**, which improves microcirculation and glucose and oxygen uptake in blood, are used, as well.

3.2 Drug dependence

Dependence is a mass of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value. A central descriptive characteristic of dependence syndrome is the desire (often strong, sometimes overpowering) to take psychoactive drugs (which may or may not have been medically prescribed), alcohol,

or tobacco. There may be evidence that return to the substance use after a period of abstinence leads to a more rapid reappearance of other features of the syndrome than occurs with nondependent individuals (definition according to ICD - 10).

Basic features of dependence are:

- craving or feeling of urge to use a substance,
- decreased self-control, difficulties with control of the substance use,
- neglecting of work and hobbies,
- tolerance development, physical dependence,
- continuation of use despite clear evidence of harmful consequences (physical, mental, social), and
- withdrawal syndrome.

Tolerance means a gradual decrease in the effects of the dependence producing substance; in other words, the dose must be increased to reach the same effect. Following dependence-producing substance withdrawal, various somatic symptoms occur which are subjectively unpleasant and in some cases life threatening, and along with the psychological symptoms, so-called withdrawal syndrome arises.

The most frequent types of dependence producing substances

Central nervous system stimulants

The most well-known substances are nicotine and caffeine, but **amphetamine, methamphetamine (pervitin), cocaine, MDMA** (3,4-methylenedioxymethamphetamine = ecstasy), **ephedrine**, and some others are included in this group. Dependence is characterised by increased psychomotor activity, decreased appetite, and aggressiveness and can result in psychosis, hallucinations, and delirium. Indirect sympathomimetic effects on the cardiovascular system may cause hypertension, arrhythmias and changes in blood pressure.

Central nervous system inhibitors

The most common substance in this group is **alcohol**, followed by **opioids**, **benzodiazepines**, and **barbiturates**. Dependence is characterised by damping of the CNS resulting in sedation. Inhibition of the respiratory centre (particularly in the case of opioids, benzodiazepines, and barbiturates) is very dangerous and can even lead to death from asphyxia.

Hallucinogens and deliriogenics

This group involves **cannabinoids** (marijuana, hashish), **psilocybin** (found in some mushrooms), **LSD** (lysergic acid diethylamide), **mescaline**, and **ketamine**. Dependency is characterised by euphoria, hallucinations, fuzziness, loss of short-term memory, panic, anxiety, further flashbacks, and even acute paranoid psychosis may occur.

Inhalants and organic solvents

Typical examples involve **toluene**, **ether**, **acetylene**, **chloroform**, and **nitrous oxide**. Dependence is characterised by a short euphoric phase; dizziness, vomiting, and loss of balance also appear. Overdosing is very easy, subsequent death is caused due to respiratory centre paralysis or following a heart arrhythmia. The users emit an odour that is typical of this type of substance abuse.

Pharmacological treatment of dependence

- detoxification - slow elimination of the substance from body after dose decrease
- substitution - replacement of the drug by a safer substance
- prevention of relapses - application of an anti-craving drug

Sensitizing substances

These substances worsen tolerance to dependence-producing drugs. The aim is to lead the dependent person to avoidance of the particular substance. In practice, **disulfiram (Antabus)** is used for alcoholism treatment. When paired with alcohol, it causes vomiting.

Opioid antagonists

Naloxone and **naltrexone** are clinically used for the treatment of opioid intoxication.

Anti-craving drugs

Acamprosate is used to decrease craving for dependence-producing substances; **naltrexone** and **nalmefene** specifically decrease cravings for alcohol.

Substitution therapy

This consists of using a legally administered dependence-producing substance as a replacement for the original drug, for instance **methadone** and **buprenorphine** in persons dependent on opioids and eventually **nicotine chewing gum** and other means for smoking cessation.

4. Substances affecting respiratory system

4.1 Antiasthmatics

Asthma is a chronic inflammatory disease of the respiratory tract. A variety of immune cells (e.g., mastocytes, eosinophils, T-lymphocytes) producing signal molecules called cytokines (e.g., chemotactic cytokines - chemokines, leukotrienes and others) are implicated in the pathophysiology of asthma. Chronic inflammation in asthma is associated with the overreactivity of the bronchial tree and typical recurring airflow obstruction, which occurs spontaneously and can be reversed with pharmacotherapy. Bronchial asthma represents a multifactorial disease, which can occur in any age group. Endogenous (e.g., genetic background, physical exercise) and exogenous (e.g., allergens, exposure to air pollution, viral infections, or medication) environmental factors play a role in disease development. Most cases of bronchial asthma have an allergic component, primarily manifesting as atopy, wherein there is an excessive production of IgE antibodies in response to common allergens found in the environment.

Asthma is characterized by recurrent episodes of wheezing, difficulty in breathing (i.e., dyspnea or shortness of breath), chest tightness, and coughing (typically in the early morning or evening hours) after exposure to specific or nonspecific triggers in each individual patient. The reason for these respiratory problems is the contraction of bronchial smooth muscles leading to the narrowing of airways, oedema, thickening of the walls of the respiratory tract, and increased secretion of mucus. Apart from exacerbations, the patient may be asymptomatic; nevertheless, the inflammatory changes in airways are persistent. A prolonged (and often pharmacoresistant) asthmatic attack is called **status asthmaticus** (i.e., an acute and severe exacerbation), and it is a life-threatening, acute condition with the risk of irreversible bronchial obstruction of the respiratory airways and risk of death (i.e., a lethal ending). Therefore, it requires urgent hospitalisation in the intensive care unit (ICU).

The diagnosis of asthma is based on the anamnesis of the patient (i.e., personal, family, and pharmacological recollection) and a battery of spirometric tests to examine pulmonary functioning. Using spirometry, it is possible to detect pulmonary obstruction and assess its reversibility and variability. The most commonly used spirometric parameters are FEV_1 (**F**orced **E**xpiratory **V**olume in **1** second), understood as the volume exhaled in one second during the maximum expiratory effort, and PEF (**P**eak **E**xpiratory **F**low Rate). Often there is additional examination of bronchial overreactivity with use of the so-called bronchoconstriction trigger test. According to the parameters measured, occurrence of daytime and night-time symptomatology, and eventually, according to the medication necessary for optimal control of the disease, asthmatic patients can be divided into several categories and the pharmacotherapeutic approach adjusted according to the severity of the disease in the individual patient.

At present, there is a three-tier classification system for asthma, which is accepted according to the corresponding level of clinical control: **asthma under control**, **partially controlled**

asthma, and **uncontrolled asthma** (i.e., with insufficient control of asthmatic symptomatology). Optionally, classifications of asthma according to the severity of the disease, such as **intermittent**, **mild persistent**, **intermediate persisting**, and **severe persistent** asthma can be used to determine treatment based on the lowest degree of intensity of pharmacologic intervention necessary to maintain optimal control of the disease. A useful complementary diagnostic tool for differential diagnosis of asthma is represented by the allergologic examination, which can help to identify if an allergic component to the asthma (so-called atopic asthma) exists and to identify the risk factors for an attack. For this purpose, there are skin prick tests available and/or laboratory examination of the specific serum IgE antibodies responsible for symptom development.

Asthma is a disease which cannot currently be completely cured, but its symptoms can be efficiently controlled. Thus, the aim of therapy is to control the asthma, which includes alleviation of acute and chronic symptoms, maintenance of normal pulmonary function without limitation of daily activities (including sports) with minimal use of "reliever antiasthmatics" (see the Chapter 4.1.2.1 SABA), and the elimination of exacerbation while minimising the side effects of antiasthmatic therapy.

Drugs used for the therapy of asthma can be divided into agents for quick relief ("relievers") and preventative agents, also called control agents ("preventers"). The **quick-relief medications** ("rescue antiasthmatics" or "reliever agents") are used preferentially to quickly alleviate bronchoconstriction during acute exacerbation of asthma, such as bronchodilator agents with a fast onset of action (e.g., β_2 sympathomimetics with a quick and short-term effect), parasympatholytics, methylxanthines with a short-term effect, or systemic glucocorticoids. They should be only used for the shortest time necessary and at the lowest possible dose and frequency of administration.

Contrarily, **preventative antiasthmatics** are used for the long term (i.e., on daily basis) to provide control of asthma and prevent asthmatic attacks. For this purpose, anti-inflammatory drugs are used most often to keep asthma under clinical control (e.g., glucocorticoids, mast cell stabilizers, antileukotrienes, methylxanthines with a prolonged action, omalizumab, and long-acting β_2 sympathomimetics). H_1-antihistamines are used to treat the allergic type of asthma, preferentially those of the second and third generation (see the Chapter 8.6.2.2 H_1-antihistamines - 2nd generation and the Chapter 8.6.2.3 H_1-antihistamines - 3rd generation).

Antiasthmatics can be administered orally or intravenously (in severe cases), but administration via inhalation is generally preferred. The advantage of inhalation is the local effect in airways (i.e., a high concentration of drug at the site of action). Thus, there is a rapid onset of action with fewer systemic side effects. There are a wide range of the inhalation systems on the market, and for the efficacy of an anti-asthmatic therapy, it is very important to explain to the patient how to appropriately manipulate their individual inhalation system, and he/she should repeatedly practice the proper technique of inhalation with that given system.

Simplified, we can divide the inhalation systems into:

- **Pressurized Aerosol inhalers**, also-called MDI (**M**etered **D**ose **I**nhalers), with a

propellant gas,

- **Inhalers for powders**, also-called DPI (**D**ry **P**owder **I**nhalers), and
- **Nebulizers**, in other words devices producing humid aerosol.

Some patients, when using the aerosol metered dose inhalers, can have a problem with coordination of their inspiration and proper activation of the inhaler. For this purpose, there are **inhalation spacers** available, which can be inserted between the inhaler device and the mouth of the patient, enabling the drug to be released into the chamber of the spacer and to be inhaled subsequently. **B**reath **A**ctuated **I**nhalers (BAI) are novel inhalation systems facilitating antiasthmatic administration.

4.1.1 Glucocorticoids

Glucocorticoids (GC), with their multiple effects, are frequently used for a wide variety of indications (see the Chapter 8.5 Glucocorticoids). For the therapy of bronchial asthma, they represent an essential group of drugs due to having the most potent anti-inflammatory effects. Glucocorticoids not only block phospholipase A_2, an important enzyme for production of arachidonic acids, thereby decreasing the production of proinflammatory factors (eicosanoids), but they also decrease cytokine secretion, lower the permeability of endothelial cells, prevent migration of inflammatory cells to the site of inflammation, etc. As a result, there is decreased bronchial overreactivity, antiedematous effect, improved lung functions, reduced frequency and severity of exacerbation, and other effects observed in clinics. According to the route of administration, glucocorticoids can be divided into inhaled and systemic GC.

4.1.1.1 Inhalation glucocorticoids

GC, administered in the inhaled form, represent the first drug of choice for persistent asthma of all degrees of severity. These drugs belong to preventative antiasthmatics for long-term use.

Risk of the typical side effects of GC administration (e.g., osteoporosis, fat redistribution, etc.) can be decreased by using the inhalation administration route, but they cannot be completely excluded. Even after inhalation, there is a partial systemic drug absorption, which can differ according to the pharmacokinetic profile of the individual agent. Among side effects occurring after local GC administration are oropharyngeal candidiasis, dysphonia, and occasional coughing, owing to irritation of airways of the upper respiratory tract. To prevent these local side effects, it is recommended to use an inhalation spacer and to wash out the oral cavity with drinking water immediately after GC application.

If the standard dose of inhaled GC does not sufficiently control asthma, it is not effective to further increase the dosage due to an increased risk of side effects. In this scenario, it is better to include an add-on preventative antiasthmatic agent, preferably a long-acting β_2-sympathomimetic agent. The reason being the mutual positive potentiation of their effects, as glucocorticoids decrease receptor desensitization for β_2 agonists (i.e., increase the number of β_2 receptors). Thanks to their synergistic effects, lower doses of each individual agent can be used in combination than would be necessary for single agent therapy. Currently, there are fixed combinations available, thus the patient gets both the GC and β_2-sympathomimetic agents in one inhalation preparation. Examples of GC agents used for inhalation are **beclomethasone**, **budesonide**, **fluticasone**, **mometasone**, and **ciclesonide**.

4.1.1.2 Systemic glucocorticoids

Long-term therapy with systemic GC is only used to achieve full control over the disease in those with severe, persistent asthma. Oral administration is preferred to the parenteral drug route, but in both cases, it is necessary to consider the potentially serious side effects of GC. Asthmatic patients treated with systemic GC belong to the corticosteroid-dependent group of asthmatics, which is a group that has an increased risk of sudden death from asthma otherwise.

Systemic GC can also be administered as reliever antiasthmatics. Despite an extended onset of action of 4-6 hours, they can prevent asthma progression and exacerbation.

Among systemic glucocorticoids belong **prednisone** and **betamethasone**. (For a more comprehensive study, see the Chapter 8.5 Glucocorticoids.)

4.1.2 β2-sympathomimetics

β_2-sympathomimetics are agents with a selective agonistic action on β_2 receptor subtypes (for more details, see the Chapter 2.1.1.3 Selective sympathomimetics – β2). They elicit relaxation of the smooth muscles of the respiratory tract, increase mucociliary clearance, and decrease vascular permeability. Furthermore, their effects on the immune system have also been confirmed. For example, they inhibit the release of proinflammatory mediators from mast cells (mastocytes). β_2-sympathomimetics are either used as "reliever" inhalers for the management of asthma symptoms or as a preventative medicine for asthma. They can be administered orally or parenterally (in acute situations), but either way, inhalation remains the most preferred administration route.

Possible side effects experienced by patients during antiasthmatic therapy are primarily hypokalaemia, tachycardia, palpitation, or tremor of the skeletal muscle. Naturally, risk of side effects is higher after their systemic use. β_2-sympathomimetics can be categorized according to the duration of their effect.

4.1.2.1 Short-acting β2-sympathomimetics (SABA)

The abbreviation, SABA, comes from English and means Short Acting Beta$_2$-Agonists. These compounds include inhaled β_2-sympathomimetics with a fast onset of action (i.e., from three

to five minutes after administration) and with a short duration of action – from about four to six hours. In this group belong agents, which are used as "reliever" inhalers in the management of asthma symptoms, and according to the frequency of their use, the need for further therapy can be estimated. It is good to keep in mind that frequent and regular SABA administration for asthma management does not lead to satisfactory control of asthmatic symptoms.

Drugs from this group which are used in clinics include **salbutamol**, **terbutaline**, and **fenoterol**. Sometimes this pharmacological group is called the **RABA** (**R**apid **A**cting **B**eta$_2$-**A**gonists) group, owing to their fast onset of the effect. Therefore, **formoterol** can be included; despite its long-term effect, it has a very fast onset of action.

4.1.2.2 Long-acting β2-sympathomimetics (LABA - Long acting beta2-agonists)

β$_2$-sympathomimetics with effects lasting for a prolonged duration (i.e., up to 12 hours) are available in inhalable and oral drug dosage forms. Due to the greater intensity and more frequent development of adverse effects upon oral administration, administration via inhalation is preferred. For long-term therapy of asthma, LABA should not be used in monotherapy (inflammatory changes remain uninfluenced by these compounds), but should always be combined with inhalable glucocorticoids (e.g., possibly in the above-mentioned fixed combination) as a complement to long-term anti-inflammatory therapy. They can also be combined with long-acting muscarinic antagonists (see the Chapter 4.1.3 Parasympatholytics).

Examples of agents of the LABA group are **formoterol**, **salmeterol**, **clenbuterol**, and **procaterol**. Short-acting β$_2$-sympathomimetics can be included, if available in a retarded (modified-release) dosage form. **Indacaterol** and **vilanterol** are sometimes excluded from this group, as they are considered **ultra-long-acting β$_2$-agonists** (**U-LABA**).

4.1.3 Parasympatholytics (muscarinic antagonists)

Antimuscarinic agents block muscarinic receptors in the smooth muscle of the respiratory tract and prevent bronchoconstriction to treat of asthma (also see the Chapter 2.2.3 Parasympatholytics). The only parasympatholytic currently used as a reliever, or for so-called rescue asthma therapy, is **ipratropium**, which is used by inhalation. It has a relatively short-term effect; it influences neither the early, nor the delayed allergic responses, and it has no anti-inflammatory effect. During acute exacerbation, ipratropium can be combined with β$_2$-sympathomimetics (there are fixed combinations with fenoterol already registered), and it is also an alternative therapy for patients whom, for any reason, have a SABA contraindication.

Side effects of parasympatholytics include headache, vertigo, coughing, and other side effects typical of parasympatholytics (e.g., dry mouth, disorders of GIT motility, etc.). For completeness, other substances such as **tiotropium**, **aclidinium**, and **umeclidinium** are worth mentioning. They have long-term effects (sometimes called LAMA - long-acting muscarinic

antagonists) and are indicated for maintenance bronchodilator therapy in COPD, often in combination with LABA (see the Chapter 4.1.2.2).

4.1.4 Methylxanthines

Methylxanthines are agents whose mechanism of action is not fully understood. At high concentrations, they block the phosphodiesterase enzyme, thereby increasing the intracellular cAMP concentration. Other putative mechanisms of action are via the inhibition of the adenosine receptors or through modulation of the levels of intracellular calcium.

Methylxanthines have bronchodilator and weak anti-inflammatory effects (compared with GC) and a variety of extrapulmonary effects (e.g., diuretic, CNS stimulant, and other effects). Examples of methylxanthines are **theophylline** and **aminophylline**. Both are available in parenteral drug dosage forms and can be taken orally in the form of sustained-release tablets. Monotherapy can be used in patients with a mild persistent asthma, but more often they are used in combination with GC, primarily as long-term preventive antiasthmatics. The use of methylxanthines for the therapy of acute asthmatic exacerbation is controversial.

A disadvantage of theophylline use is its narrow therapeutic window, as it can cause serious side effects (i.e., affecting many organs) in higher doses, and in severe cases, it can even lead to a lethal end. Theophylline intoxication manifests as nausea, vomiting, diarrhoea, palpitations, a rise in blood pressure, and tremors. Side effects can be avoided by dose adjustment and the monitoring of serum concentrations. Theophylline is metabolised via cytochrome P450, which may lead to clinically significant interactions with concomitantly administered substances affecting this same metabolic pathway. Nicotine is a cytochrome P450 inducer; therefore, higher theophylline doses are recommended for smokers.

4.1.5 Mast cells stabilizers (immunoprophylactics)

In this group of drugs, we include agents that prevent release of proinflammatory cytokines through the stabilization of mast cell membranes. These agents are used for prophylaxis, and they are not suitable for management of acute health problems. When used for prophylaxis, they inhibit both the early and delayed phase of allergen-induced bronchoconstriction.

Immunoprophylactic agents include "**chromones**" and **ketotifen**. The term "chromones" is used to represent **sodium cromoglicate** (**cromolyn**) and **nedocromil,** both of which are inhaled to treat mild, persistent bronchial asthma. Their mechanism of action is not fully elucidated, but apart from mast cell stabilization, they inhibit the chemotactic responses of eosinophils and neutrophils.

Along with the stabilization of the mast cell membrane, **ketotifen** also acts as an H_1 non-competitive receptor antagonist (see the Chapter 8.6.2 H_1 antihistamines). It is administered orally for long-term prevention of asthmatic attacks. Side effects include dry mouth, vertigo, nausea, and body weight gain.

4.1.6 Antileukotrienes

Several mediators are involved in the pathogenesis of bronchial asthma, including leukotrienes, which have a pronounced bronchoconstriction effect. They influence chemotaxis, increase vascular permeability, stimulate mucus secretion, etc. Leukotrienes are produced intracellularly from arachidonic acid via the lipoxygenase enzyme.

Antileukotrienes are agents which inhibit leukotriene functions, either by blocking their receptors or through inhibition of the lipoxygenase enzyme. Among agents which **block leukotriene receptors** are **montelukast** and **zafirlukast**. They are given orally and used long-term for mild and intermediate forms of persistent asthma. They can be used in monotherapy, but when the sufficient control of asthma is unable to be accomplished, these compounds can be combined with inhalable GC.

The 5-lipoxygenase inhibitor, **zileuton**, belongs among agents **inhibiting the synthesis of leukotrienes** (currently, there is no lipoxygenase inhibitor registered in the Czech Republic).

4.1.7 Targeted antiasthmatic therapy

To date, the only targeted (biological) therapy approved for asthma, which was developed for patients with an eosinophilic asthma phenotype (which is proven to be caused by increased levels of IgE antibodies), is the monoclonal antibody, **omalizumab.** Its mechanism of action is mediated via IgE binding, which leads to a reduced amount of circulating IgE, thereby reducing their binding and preventing activation of the allergic response cascade to inhaled allergens. Omalizumab has been shown to reduce both airway and circulating blood eosinophils and is thought to be efficacious in reducing asthma exacerbations. It is administered subcutaneously in severe persistent allergic asthma, in such a case as inhalational/systemic corticosteroids (GC), even at very high doses, and long-acting inhalable β_2-sympathomimetics are insufficient in controlling the disease. Omalizumab´s main disadvantage is its high price.

4.2 Cough medicines

Coughing is among one of the basic defence reflexes of the body. It protects the airways from damage and it can help keep the throat clear from irritants. The centre of this reflex is in the medulla oblongata and is also the site of action for some drugs. Often, coughing occurs as a symptom of a pulmonary disease, but it can also be present in bronchial diseases and conditions of the upper respiratory tract (e.g., inhalation of air pollutants, the presence of a foreign body, and an affection of vocal cords). Cough can also be a side effect of some drugs, such as ACE inhibitors, which are used in hypertension. The presence of a cough should not be underestimated because although it is most commonly treated as a symptom of common colds (i.e., respiratory infections), it may also be indicative of more serious diseases such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchial asthma, and cancer.

In choosing the correct cough treatment, it is necessary to determine the cause and type of cough. A chronic cough lasts longer than three weeks. Acute coughing lasts for any shorter

period than three weeks, and both can be further distinguished as either a dry cough or a productive cough. The pattern of coughing may change during the course of an illness, and the phase of dry, irritable (in some cases, emetogenic) cough is often followed by a productive coughing phase.

According to the type of cough, agents suppressing cough (antitussives) or substances (ranging in molecular mechanism) affecting the composition, production, and mobility of the mucus in the airways (i.e., drugs for a productive cough) are prescribed. Concomitant administration of substances from the two above-mentioned groups is often not advised because they may produce counter-effects. For example, when combining an antitussive and mucus-producing agent, there is a risk of mucus accumulation in bronchus. A general rule that should be followed when treating all types of cough is to ensure a sufficient supply of fluids.

The majority of drugs used to treat cough are over-the-counter medicines.

4.2.1 Antitussives

Cough-relieving drugs functioning through central or peripheral mechanisms are particularly useful for the treatment of dry, irritable cough, which is usually physically exhausting for the patient and often occurs in night hours, disturbing sleep. Some representatives may also be given to children. Antitussive therapy should only be taken for a limited time and should not be prolonged if unnecessary. According to chemical structure, the groups can be divided into codeine and non-codeine antitussives.

4.2.1.1 Codeine antitussives

These substances are derived from opioid analgesics, and their central mechanism of action is reducing cough centre sensitivity in the medulla oblongata (see the Chapter 8.3 Opioid analgesic drugs). In higher doses, or after long-term administration, other opioid-like effects (e.g., respiratory depression, constipation, sedation, addiction, etc.) may manifest. They are contraindicated during pregnancy and should not be used for breastfeeding women. Also, they are used with caution in patients with bronchial asthma or COPD. At present, only products with **codeine** and **dextromethorphan** are registered. Codeine is a natural alkaloid that can be isolated from opium. In addition to its pronounced antitussive effect, which it achieves at low doses, it is also used for its analgesic effect and ability to potentiate the effect of some non-opioid analgesics, such as paracetamol (acetaminophen). Codeine administration is associated with more serious side effects than those incurred with dextromethorphan; therefore, it is not used for children, and codeine products are dispensed with a doctor's prescription. Dextromethorphan does not show analgesic properties. It also has no sedative effects at therapeutic doses and does not affect the respiratory centre. Side effects are rare; preparations with this substance are available over-the-counter (OTC), mostly in the form of tablets or syrups and are suitable for children, as well. Co-administration of serotonergic drugs (e.g., antidepressants) requires caution as there is a risk of developing serotonin syndrome.

4.2.1.2 Non-codeine antitussives

These drugs represent a group of synthetic substances whose antitussive effect is either central (i.e., inhibition of the cough centre), peripheral, or a combination of both mechanisms. The peripheral effect of these substances is mediated by action along the efferent nerve pathways of the cough reflex or by influencing its afferent fibres or nerve endings in bronchial mucosa (i.e., reducing sensitivity to irritant stimuli). The advantage of non-codeine antitussives is they do not affect the respiratory centre or carry risk of addiction. They can also be used in children under two years of age after consultation with a doctor. Currently used substances include butamirate, dropropizine, and levodropropizine. Butamirate has both a central and peripheral bronchospasmolytic effect and can be used for cough suppression before and after surgery (e.g. after intubation). Levodropropizine is the L-isomer of dropropizine with good tolerability. In addition to its peripheral antitussive effect, it also exhibits antihistamine and bronchospasmolytic effects.

4.2.2 Expectorants

Agents used for the treatment of a productive cough represent a heterogeneous group of drugs, and their classification is not uniform. Terminology differs for the various agents within this group. Depending on the mechanism of action, these agents can be divided into several subgroups: **mucolytic**, **secretolytic**, and **secretomotor agents**. However, very often their individual effects are combined; therefore, these drugs mostly belong to more than one subgroup. Thus, in clinics it is more practical to rely on the knowledge of all the usable effects of available drugs. They may have the ability to reduce mucosal viscosity (i.e., by influencing physicochemical properties of the mucus - **mucolytics**), stimulate the activity of the bronchial glands (**secretolytics**), or activate ciliary epithelium (i.e., through the stimulation of the mucociliary apparatus - **secretomotor substances**). Some expectorants may have additional antioxidant effects and can also potentiate antibiotic efficacy.

Drugs used for the therapy of a productive cough are not only used to treat acute inflammation of the respiratory tract, but some are part of long-term medication for chronic inflammatory diseases, such as COPD, cystic fibrosis, and chronic bronchitis, as well. Administration of all expectorants should be supplemented with a sufficient intake of fluids, whether administered as drops, syrups, or tablets.

Bromhexine is a prodrug whose active metabolite is **ambroxol**. It reduces the viscosity of mucus by decomposing mucopolysaccharides. Furthermore, it activates the mucociliary apparatus of the respiratory epithelium, thereby promoting mucus secretion. Bromhexine should not be given to patients with gastroduodenal ulcers (as it may affect the mucosal barrier) nor breastfeeding and pregnant women (especially in the first trimester). Concomitant administration of ambroxol with some antibiotics leads to an improved penetration of the antibiotic into lung tissue, which is why this combination is often used in practice. The European Medicines Agency is currently critically reviewing the use of ambroxol and bromhexine due to risk of allergic reaction (including anaphylaxis) as there have been reports of this type of adverse event occurring more frequently in recent years.

Acetylcysteine and **carbocysteine** are derivatives of the amino acid, cysteine. Both substances disrupt disulphide mucus bonds, thereby reducing mucus viscosity and facilitating

expectoration. In addition, carbocysteine normalizes the amount of mucus. They are not recommended in bronchial asthma due to risk of bronchospasm.

The active metabolites of **erdosteine** also disrupt disulphide bonds in the mucus. In addition, they have mild anti-inflammatory and antioxidant effects (i.e., capture free oxygen radicals), and they reduce adhesion of bacteria to airway epithelium. Erdosteine is also used in patients with chronic obstructive pulmonary disease.

Dornase alfa (deoxyribonuclease) is indicated primarily for patients with cystic fibrosis and is given by inhalation.

Guaifenesin (INN, or guaiphenesin - former BAN), in addition to its effects on the respiratory system (i.e., reduces mucosal viscosity and increases mucus secretion), it is exerting sedative, anxiolytic and myorelaxant effects.

4.2.3 Other expectorant agents

In addition to the above-mentioned substances, healing plants or their extracts can also be used in cough therapy. They can serve as alternative therapies, especially for higher risk groups of patients (e.g., older people, pregnant women, and children).

Plants with a high content of **mucilaginous substances** (slime) are used for their hygroscopic ability; polysaccharides absorb water and swell covering the mucous membranes, thereby moisturizing and protecting them. Examples of plants with these properties are, for example, the **common marshmallow** (*Althaea officinalis*), **English plantain** (*Plantago lanceolata*), and **coltsfoot** (*Tussilago farfara*).

Saponin-containing plants are used to treat productive cough because **saponins**, with their surfactant properties, can reduce the viscosity of bronchial mucus and stimulate bronchial glands. They include such plants as **common ivy** (*Hedera helix*), **common cowslip** (**primrose**) (*Primula veris*), and **dense-flowered mullein** (*Verbascum densiflorum*).

Essential oils from plants can also help to clear mucus as they affect bronchial glands, and through their direct irritation, they stimulate secretion of sputum mucus. Essential oils also have spasmolytic effects. Among plants containing a large volume of essential oils belong thyme species, such as **common thyme** (*Thymus vulgaris*), **Breckland wild thyme** (*Thymus serpyllum*), and **dwarf mountainpine** (*Pinus mugo*), etc. The above-mentioned plants may be included in tea mixtures, herbal lozenges, syrups, nasal drops, or administered in the form of oral drops.

The activity of the bronchial glands can also be stimulated by inorganic compounds such as **ammonium chloride** and **ammonium bromide**, which help to treat productive cough. Their irritating action on bronchial mucosa causes the production of excess respiratory tract fluid (i.e., a secretolytic effect). These salts are contained in some medicinal mineral waters suitable for gargling, sipping, and inhalation. Potassium iodide is medically used orally for thyroid gland hyperfunction, radiation emergencies, and to prevent iodine deficiency, but it is no longer used as a cough medicine.

5. Substances used in cardiology and haemathology

5.1 Antihypertensive drugs, diuretics

Hypertension can be defined as elevated blood pressure measured after 10 minutes of rest in at least two out of three measurements performed over the course of several days. The generally accepted threshold is a systolic blood pressure (SBP) of 140 mm Hg and a diastolic blood pressure (DBP) of 90 mm Hg in patients with no other complication. These also constitute the target values for treatment, while the values are lower for patients with chronic kidney disease or diabetes (i.e., 130/85). Hypertension is often correlated with being overweight, insulin resistant (or type 2 diabetes), and/or having dyslipidaemia. When seen together in one patient, these conditions are termed "metabolic syndrome" (i.e., Reaven's syndrome, syndrome X). Hypertension is an established risk factor for ischaemic heart disease, myocardial infarction, arrhythmias, ischaemic and haemorrhagic stroke, vascular dementia, and chronic kidney disease. While secondary hypertension, constituting 5-10% of all cases, is a result of a different underlying pathological state, most patients suffer from primary (i.e., essential) hypertension that develops due to impairment of several regulatory systems, such as increased water retention in kidneys, high vascular resistance, and sympathetic nervous system (SNS) or renin-angiotensin-aldosterone system (RAAS) hyperactivity. Therefore, the treatment typically addresses several mechanisms at once.

Pharmacological and non-pharmacological treatment can be distinguished when addressing hypertension. Non-pharmacological approaches include **lifestyle intervention** focusing on increasing physical activity, reducing psychical distress and weight, smoking cessation, lowering the amount of salt in the diet, and avoiding high alcohol intake. Lowering body weight by 1 kg leads to a 1 mm Hg reduction in blood pressure. On the other hand, changes in caffeine intake do not influence long-term blood pressure.

Renal sympathetic denervation is a relatively new surgical or endovascular interventional method aimed to severe the sympathetic innervation to the kidney. After initial promising results, its effects seem dubious in newer clinical trials, which is possibly a result of technical difficulties often making the denervation ineffective. Currently, the method is unlikely to replace pharmacotherapy and lifestyle intervention for the treatment of essential hypertension.

Pharmacotherapy affects several aetiopathogenetic mechanisms leading to elevated blood pressure. Some medications affect several mechanisms at once, and combinations of pharmaceuticals are often used to affect several signalling pathways. The fixed combinations of two active substances in one pill are frequently used to increase the patient's adherence to the pill-taking regimen. Hypertension not responding to the combination of three pharmaceuticals is classified as pharmacoresistant.

5.1.1 Pharmaceuticals affecting the renin-angiotensin-aldosterone system

This group contains substances aimed at downregulating the renin-angiotensin-aldosterone system (RAAS). However, different groups can be distinguished according to their target point in this signalling pathway. Of them, **angiotensin converting enzyme inhibitors** (**ACE-I**) inhibit the angiotensin converting enzyme (ACE), which cleaves two amino acids from angiotensin I, thereby converting it into angiotensin II with vasoconstrictive, aldosterone-enhancing, and cell-proliferative properties. **Angiotensin receptor type 1** (**AT1**) **antagonists** block the receptor that is responsible for most of the effects of angiotensin II leading to increased vascular resistance, aldosterone secretion, and cardiac or vascular remodelling as stated above. **Renin inhibitors** inhibit the enzymatic activity of renin, thus, disabling the formation of angiotensin I from its precursor, angiotensinogen. Other drugs, such as beta-blockers or mineralocorticoid receptor antagonists, also inhibit the RAAS action, and this is partly responsible for their antihypertensive effect.

5.1.1.1 Angiotensin converting enzyme inhibitors (ACE-I)

Currently, ACE-I are probably the most prescribed group of antihypertensive drugs, both in monotherapy and in combination with other groups. They act by blocking ACE, an enzyme responsible for the conversion of angiotensin I into angiotensin II. Further, since this enzyme degrades bradykinin into inactive fragments, ACE blockage results in increased bradykinin levels resulting in a beneficial effect (i.e., lowering of blood pressure) through increased vasodilation. On the other hand, bradykinin is responsible for some negative side effects, angioedema being the most significant. Along with substance P, another polypeptide degraded by ACE, bradykinin contributes to the development of a dry cough, a common side effect of ACE-I.

Besides vasodilation, ACE-I reduce the remodelling of vessel walls and cardiac hypertrophy in response to hypertension. There are also significant beneficial effects preventing cardiac remodelling after myocardial infarction or during chronic heart failure. Moreover, ACE-I have positive metabolic effects, most notably increasing insulin sensitivity. Through reducing angiotensin II-mediated sodium resorption in proximal tubules and aldosterone action in the kidneys, ACE-I have also natriuretic and potassium-sparing effects. Out of the three groups of RAAS inhibitors, ACE-I have the best results according to the data concerning mortality.

The typical ending of ACE-I names is –pril (e.g. **captopril**, **enalapril**, **lisinopril**, **ramipril**, **perindopril**, **spirapril**, and **trandolapril**). Captopril and lisinopril are ingested in their active form, whereas most other ACE-I are taken as prodrugs and activated in the liver. In the case of captopril, both the parent drug and its metabolite are active. It has a faster effect than the other ACE-I and is usually administered several times a day. On the other hand, spirapril, perindopril, or trandolapril have long-term effects.

5.1.1.2. Angiotensin receptor type 1 blockers (ARB, sartans)

AT_1 receptor antagonists have effects similar to ACE-I. They do not change the kinin levels and have a low occurrence of side effects resulting from their accumulation as is the case

during treatment by ACE-I; other similar side effects are hypokalaemia, teratogenic effects, and hypotension. Like ACE-I, ARB have antidiabetogenic, antiproliferative, and kidney protective effects. The typical ending for this group is –sartan (e.g., **losartan**, **eprosartan**, **valsartan**, **irbesartan**, **olmesartan**, **telmisartan**). ARB differ according to their elimination rate; while losartan has the shortest biological half-life and antihypertensive effect duration, telmisartan is eliminated with a half-life of 24 hours and is administered once daily.

5.1.1.3 Renin inhibitors

Renin inhibitors are a relatively new group of drugs aimed at blocking the enzymatic activity of renin. Their typical ending is –kiren (e.g., **aliskiren**, **enalkiren**, and **remikiren**). Their side effects include hyperkalemia, teratogenicity, diarrhoea, vertigo, and angioedema. The side effects potentiate those of ACE-I or ARB; so, based on recent large clinical trials, these groups should not be co-administered. These three groups of RAAS inhibitors should not be administered during pregnancy and in primary hyperaldosteronism, during which they are ineffective. They also should not be used in the case of significant renal artery stenosis. Even though they are effective for the treatment of renovascular hypertension, they can cause renal ischaemia.

5.1.2 Calcium channel blockers (CCB)

Calcium channel blockers selectively inhibit the membrane calcium channels in vascular smooth muscle cells and in cardiomyocytes. With the exception of **cinnarizine**, a drug with a multi-receptor effect that is used to treat vertigo, all CCB act on the L-type membrane of calcium channels in vascular smooth muscle cells and in cardiomyocytes. Although all CCB used in clinical practice target the same receptor, they differ by binding site, specific response of the channel, and in pharmacokinetic issues, such as tissue distribution. This makes CCB a relatively heterogeneous group. In general, CCB are able to reduce myocardial hypertrophy and have neutral effects on metabolism. The most common side effects are oedema of lower extremities and headache as a result of vasodilation.

CCB can be distinguished according to their chemical structure into **dihydropyridines** and other drugs, collectively designated as **non-dihydropyridines**. Two commonly used non-dihydropyridines with antihypertensive effect, **verapamil** and **diltiazem**, also have significant antiarrhythmic properties and represent the 4th class of antiarrhythmic drugs. Dihydropyridines have minimal effect on myocardial conduction, but do affect peripheral vasodilatory ability (while arterial smooth muscle contraction is entirely dependent on membrane calcium channels, the cardiomyocyte can also use the calcium stored in its sarcoplasmic reticulum). The typical dihydropyridine ending is –dipine (e.g., **nifedipine**, **nitrendipine**, **amlodipine**, **felodipine**, and **lacidipine**). Dihydropyridines differ according to the duration of their antihypertensive effect; for instance, while nitrendipine has a fast onset and wears off quickly, amlodipine and felodipine can perpetuate similar effects to nitrendipine throughout a 24-hour period (the through/peak concentration index is 60-70%).

5.1.3 Diuretics

Diuretics are a heterogeneous class of medicaments used to reduce the circulating volume and thereby, cardiac output through increased urine production in the kidneys. To achieve this, they use different mechanisms of action. Often, extrarenal action, such as vasodilation, contributes to the antihypertensive effect. The main disadvantages of diuretic treatment are the adverse metabolic effects (e.g., the decrease in insulin sensitivity and hyperlipidaemia). Moreover, the loss of water may be poorly tolerated by older patients. Diuretics are frequently combined with other drugs and administered in fixed combinations with, for example, RAAS inhibitors or CCB. Depending on their mode of action, they can be separated into several groups.

5.1.3.1 Thiazide and thiazide-like diuretics

This group of diuretics inhibits Na^+ and Cl^- resorption in the distal tubule of the nephron. The term, "thiazide-like diuretics", refers to sulphonamide diuretics that have a similar mode of action. Na^+ and Cl^- ions draw water molecules with them, which reduces the circulating volume. Because the water loss is accompanied by salt loss, this group has a saluretic effect, which is stronger in thiazides than in thiazide-like diuretics, wherein the vasodilatory effect is more pronounced. **Hydrochlorothiazide** and **chlorthalidone** are typical representatives of thiazide diuretics, while **indapamide** and **metipamide** are examples of thiazide-like sulphonamide diuretics. The advantage of this group is the relatively long duration of the antihypertensive effect.

The main adverse effects of thiazides and thiazide-like diuretics are hypokalaemia, which is induced by secondary hyperaldosteronism, and dehydration. Regarding adverse metabolic effects, this group can worsen glucose tolerance and enhance hyperuricemia. Therefore, thiazides and thiazide-like diuretics are contraindicated for patients suffering from gout.

5.1.3.2 Loop diuretics

Loop diuretics inhibit Na^+-K^+-Cl^- co-transport in the thick ascending limb of Henle's loop. Their acute diuretic and saluretic effects are greater than in thiazides. The diuretic effect is more pronounced than the antihypertensive one. Therefore, loop diuretics are mainly used in patients with oedemas and patients suffering from oligoanuric renal failure. Loop diuretics can be also used to induce forced diuresis, which is frequently the case for intoxications. Further, they decrease the plasma levels of magnesium and calcium, which can be used for the treatment of hypercalcemia. Examples of loop diuretics include **furosemide** or **torasemide**.

Adverse effects of loop diuretics involve the loss of ions resulting in hypokalaemia and hypomagnesemia leading to arrhythmias; hypocalcaemia can result in muscular spasms, and hypochloraemia can eventually lead to metabolic alkalosis. Other adverse effects involve dehydration and hyperuricemia; rarely, ototoxic or nephrotoxic effects can occur.

5.1.3.3 Potassium-sparing diuretics

Through various mechanisms, potassium-sparing diuretics increase the excretion of sodium ions without losing potassium ions. This group has a relatively low diuretic and antihypertensive effect and is frequently used in conjunction with thiazides or loop diuretics to prevent hypokalaemia. According to their mechanism of action, they can be further distinguished between aldosterone antagonists or blockers of the Na^+ channel in the collecting duct.

Spironolactone and **eplerenone** are the examples of **diuretics which antagonise aldosterone action** at the Na^+/K^+-ATPase pump. By blocking the mineralocorticoid receptors, these drugs also prevent cardiac remodelling occurring during heart failure. Spironolactone has a structure similar to steroid hormones and has frequent side effects, such as fertility disorders in both sexes and gynecomastia in men. Eplerenone does not have this kind of side effect.

Amiloride and **triamterene** decrease sodium reabsorption from the collecting duct. In turn, this prevents potassium excretion into the tubular lumen by reducing the electrical gradient on the apical membrane and reducing the Na^+/K^+-ATPase activity at the basolateral membrane of the ductal cell.

The adverse effects of potassium-sparing diuretics are largely opposite to previous groups and involve hyperkalaemia and metabolic acidosis. Hyperkalaemia is potentiated by the concomitant use of RAAS inhibitors.

5.1.3.4 Carbonic anhydrase inhibitors

This group has only a small diuretic effect and is not effective for the treatment of hypertension. The inhibition of carbonic anhydrase increases the excretion of HCO_3^- anions that are then followed by Na^+, K^+, and water. These drugs act mainly in the proximal tubule, where the water losses can be compensated for by the distal parts of the nephron. Carbonic anhydrase inhibitors are used to treat altitude sickness as well as other cases of alkalosis and for glaucoma. The main representative of this group is **acetazolamide**.

5.1.3.5 Osmotic diuretics

Osmotic diuretics directly increase the filtrate osmolarity, concomitantly increasing water loss. They are used for treating symptomatic oedemas, especially the brain oedema, or to induce forced diuresis. They are contraindicated in the case of renal failure; in such a condition, they increase the osmolarity of the blood and thus, contribute to hypervolemia or even pulmonary oedema. A typical example is mannitol.

5.1.4 Pharmaceuticals inhibiting the sympathetic nervous system (sympatholytics)

This group of antihypertensives exerts its effects through reducing sympathetic nervous system (SNS) action. They act either in the centres controlling SNS activity or at peripheral adrenergic α or β receptors. Some substances have combined effects and also affect other receptors.

5.1.4.1 Beta-adrenergic receptor antagonists (beta-blockers)

Beta-blockers are a group of substances with wide use in cardiology. Through the inhibition of myocardial β-receptors, they exert negatively chronotropic, inotropic, and dromotropic effects on heart. The beta-blockers are also used for antiarrhythmic indications, and they exert a protective effect on the myocardium by lowering muscle work and by enabling a longer diastole that enables better coronary flow. Many beta-blockers have selectively higher effects on β_1 receptors as compared to β_2 receptors; however, some also have effects on other receptors. Many beta-blockers exert partially agonistic action on β receptors (i.e., **intrinsic sympathomimetic activity – ISA**), which results in lower incidence of bradycardia, but also lower cardiac protective effects. The typical ending for this group of compounds is –olol, except for drugs with multiple receptor effects, which end in –lol (i.e., **labetalol** and **carvedilol** that also block the α_1 receptors and **sotalol** that blocks the K^+ channels). Depending on their pharmacodynamics, the beta-blockers can be divided into the following groups:
1)	Non-selective beta-blockers without ISA – e.g., **propranolol**,
2)	Cardiac (β_1) selective beta-blockers without ISA – e.g., **metoprolol, bisoprolol,** and **atenolol**,
3)	Non-selective beta-blockers with ISA – e.g., **bopindolol**, and
4)	Cardiac (β_1) selective beta-blockers with ISA – e.g., **acebutolol**.
Because of their cardioprotective effects, beta-blockers are preferable for patients suffering from ischaemic heart disease, heart failure, or after myocardial infarction. Their antihypertensive effect is generally lower than with ACE-I, CCB, or thiazide diuretics. Labetalol is one of the few drugs that can be used to treat hypertension during pregnancy.

The main adverse effect of beta-blockers is bradycardia. Through their action on β_2 receptors, they worsen bronchial obstruction in obstructive pulmonary diseases, which is less pronounced with the cardioselective beta-blockers preferred for COPD, while bronchial asthma is a contraindication for beta-blocker treatment. As well as the diuretics, the beta-blockers also have adverse metabolic effects; furthermore, they can cover the symptoms of hypoglycaemia in diabetic patients.

5.1.4.2 Alpha-adrenergic receptor antagonists (alpha-blockers)

Alpha-blockers block various subtypes of the α_1 adrenergic receptor. This counteracts the vasoconstriction induced by catecholamine's action and decreases peripheral resistance. The alpha-blockers also mediate smooth muscle relaxation in the urinary tract and prostate; therefore, they are also used to treat the urinary tract obstruction present in prostatic hypertrophy. The older, non-selective alpha-blockers were not tolerated well because of the

numerous side effects based on concomitant activation of presynaptic α_2 receptors and consequent enhanced β receptor stimulation.

Currently used drugs are mostly α_1 selective blockers and their typical ending is –osin or – zosin (e.g., **prazosin**, **doxazosin**, or **tamsulosin**, which are more selective for the α_{1A} subtype that is abundant in the urinary tract). **Urapidil** is an alpha-blocker with multiple effects; besides the peripheral α_1-antagonism, it also blocks the serotonin $5HT_{1A}$ receptors and has a weak β_1-blocking ability. This drug is often administered intravenously, which allows for a rapid antihypertensive effect, but it can be also used for chronic treatment.

The main side effect of alpha blockers is an orthostatic hypotension, headaches, tachycardia, and eventual worsening of pre-existing heart failure. Therefore, heart failure is a contraindication for the alpha-blocker therapy.

5.1.5. Central sympatholytics

Central sympatholytics seek to decrease blood pressure by affecting regulatory brain centres, efferent pathways in the spinal cord, and/or the sympathetic ganglia. They use several mechanisms of action: some stimulate the presynaptic α_2 receptors that induce the negative feedback, some activate the imidazoline I_1 receptors, and some block transmission in the sympathetic ganglia or deplete catecholamine and serotonin storage.

Imidazoline receptor agonists act mainly through the I_1 receptors that are abundant in the brain stem (i.e., rostral ventrolateral medulla, RVLM) and in the proximal renal tubules wherein they stimulate sodium excretion. The typical ending of imidazoline receptor agonists is –idine (e.g., **rilmenidine**, **moxonidine**). Aside from stimulating the I_1 receptors, they also have a lower affinity for presynaptic α_2 receptors. **Clonidine**, another chemically related substance, has higher affinity for α_2 receptors as compared to I_1 receptors and is used to treat some psychiatric disorders (e.g., to alleviate the abstinence syndrome).

Methyldopa is a selective **α_2 receptor agonist**; it is also a precursor of α-methyl-norepinephrine, which competes with norepinephrine binding to the adrenergic receptors. Methyldopa is the preferred antihypertensive drug for pregnancy.

The adverse effects of central sympatholytics are mostly mediated by α_2 receptors and consist mainly of orthostatic hypotension, sedation, and dry mouth. These effects are experienced less frequently when using selective I_1 receptor agonists.

5.2 Haemostasis-affecting drugs

Haemostasis is a complex process comprising platelet activation and fibrin net formation; conversely, it also involves activation of anticoagulant and fibrinolytic pathways to limit the former processes at the site of the injury. These processes are very sensitively balanced, and a wide spectrum of pathologies arise if disturbed. In the case of blood clot formation, this process alone can be separated into primary and secondary haemostasis, which work in

cooperation *in vivo*, but can be distinguished *in vitro*, and their disturbances differ in clinical manifestation. **Primary haemostasis** is based on platelet adhesion, activation, aggregation, and degranulation as well as subsequent vasoconstriction induced by platelet factors. The main characteristics of insufficient primary haemostasis are prolonged bleeding time and the occurrence of petechiae. Platelets also provide a surface for **secondary haemostasis**, which is based on the reactions of different coagulation factors (i.e., serine proteases and their inhibitors) and results in fibrin net formation. Insufficient secondary haemostasis typically manifests as delayed bleeding and haematomas.

The pathological activation of haemostasis in blood circulation is called **thrombosis**. Its risk factors can be grouped into three main fields, also called the **Virchow's triad**: slow blood flow (i.e., enabling reaction coagulation factors without being attached to the platelet's surface), endothelial damage (i.e., leads to platelet attachment and tissue factor exposure; also, a dysfunctional endothelium does not produce enough anticoagulant and fibrinolytic factors), and thrombophilic states defined as hyperactivity of both primary and secondary haemostasis. The thrombus may either cause local ischaemia when present in the arterial system or may travel to distant places through the circulation, which is referred to as an embolism (e.g., pulmonary or cerebral).

5.2.1 Anticoagulant drugs

Anticoagulant drugs either directly inhibit secondary haemostasis or enhance naturally occurring anticoagulant mechanisms. Secondary haemostasis consists of a series of reactions ending with fibrin polymerisation. Most reactions include a serine protease, its cofactor, Ca^{2+} ions, a negatively charged surface (usually provided by a platelet), and a substrate, which is the next coagulation factor in the cascade. The factors (i.e., serine proteases, their cofactors, and calcium) are designated using Roman numerals and their activated forms are referred to with the letter, 'a'. *In vitro*, coagulation can be induced by the tissue factor pathway (**extrinsic pathway**) or a negatively charged phospholipid (**intrinsic pathway**). Both pathways lead to the activation of factor **X** turning it into **Xa**. The coagulation cascade then leads to the activation of **thrombin**, factor IIa. Thrombin then cleaves the terminal sequences from fibrinogen, which then forms the fibrin fibres. Through the activation of factor XIII, thrombin also contributes to form the fibrin net. Thrombin also activates platelets by binding their PAR receptors, suppressing fibrinolysis, and activating factors XI, VIII, and V. Thus, the most important role of the intrinsic pathway *in vivo* is the creation of a positive feedback loop. This coagulation cascade is regulated by several **anticoagulant pathways** including the protein C/protein S pathway, **antithrombin III** (ATIII), and the Tissue Factor Pathway Inhibitor (TFPI). While the coagulation factors themselves are mostly produced in the liver, the anticoagulant pathways are dependent on endothelial function.

5.2.1.1 Heparins and related drugs

Heparin is a polysaccharide (i.e., glycosaminoglycan) produced endogenously by the mast cells and in the liver (hence the name). It is chemically similar to endothelial **heparan sulfate** and **dermatan sulfate**. All the three glycosaminoglycans act as cofactors for antithrombin III (ATIII), a protein that inhibits the activity of serine proteases, such as factor XI, IX, X, II, and VII; thus, their efficiency is ATIII-dependent. Pharmacologically, heparin is used either in the

long (**unfractionated heparin**, **UFH**) or short form (**low molecular weight heparins**, **LMWHs**). UFH and LMWHs differ both in their pharmacokinetics and pharmacodynamics.

Unfractionated heparin (UFH)

Unfractionated heparin is a parenterally (i.v. or s.c.) administered drug used for the treatment of thromboses, such as acute myocardial infarction, pulmonary embolism, and deep venous thrombosis. It is also used for the prophylaxis of thrombosis during haemodialysis or other blood-cleaning techniques. Heparin can be also administered transdermally with anti-inflammatory and oedema-reducing effects. UFH has a relatively short elimination half-life of around 100 minutes; therefore, it is suitable for acute treatment rather than for the long-term therapy. Because UFH also facilitates ATIII binding to thrombin and activates ATIII-independent deactivation of thrombin through heparin cofactor II, its effect on thrombin is more pronounced in comparison with the LMWHs, which preferentially inhibit factor X. The anticoagulation activity of heparin is monitored using the **activated partial thromboplastin time (aPTT)**.

The main adverse effects of heparin are bleeding and **heparin-induced thrombocytopenia (HIT)**, of which two forms can be distinguished: mild, which is caused directly by heparin, and severe, which is an autoimmune reaction against the complex of heparin and the platelet factor, PF4. If needed, the effect of heparin can be blocked by **protamine sulfate**, a highly cationic peptide that binds to the negatively charged polysaccharide molecule.

Low molecular weight heparins (LMWHs)

LMWHs are smaller fragments of heparin that retain the ATIII binding and activating ability. Compared to UFH, they have more efficient anti-factor X activity and less efficient anti-thrombin activity. They have a better pharmacokinetic profile and a longer elimination half-life, which makes them more suitable for long-term treatment. Similar to heparin, they are administered subcutaneously or intravenously.

LMWHs prolong aPTT to a variable degree, but monitoring is usually not needed due to low risk of overdose. In high-risk patients, such as in the case of renal failure, factor Xa activity rather than aPTT may be evaluated. The side effects are similar to UFH (e.g., bleeding, HIT, etc.), but they occur less frequently among patients. Protamine sulfate is less efficient as an antidote compared to UFH. Examples of LMWHs include **enoxaparin**, **nadroparin**, and **dalteparin**.

Heparinoids

Heparinoids, such as dermatan sulfate and heparan sulfate, are used for local application. Similar to heparin, they are obtained from animal entrails. They are usually used in gels or creams. **Danaparoid** is a mixture of heparan sulfate, dermatan sulfate, and **chondroitin sulfate** with anticoagulant effects, primarily targeting factor Xa using ATIII. It is used for systemic (i.e., i.v. or s.c.) application in heparin-intolerant patients.

Pentasaccharides

Pentasaccharide structure is similar to an active, ATIII binding site of heparin. An example from this group is **fondaparinux**, which is administered subcutaneously. Fondaparinux does

not cause HIT, but it should not be administered to patients with renal failure because its clearance is dependent on the kidneys. It selectively targets factor X.

5.2.1.2 Coumarins (anti-vitamin K)

Coumarins are derivatives of coumarin, naturally occurring in the tonka bean plant. While natural coumarin does not itself have anticoagulant properties, its metabolite, dicoumarol, causes cattle to bleed excessively after consumption. This discovery inspired its first use as rat poison. Subsequently, it has been used as an anticoagulant drug in human disease. The currently used coumarin derivative, **warfarin**, was also developed as a rat poison, but it is in wide use today as an anticoagulant.

Warfarin inhibits vitamin K epoxide reductase, an enzyme that is necessary to convert vitamin K into its active form (i.e., vitamin K hydroquinone), which is necessary for the carboxylation of **K-dependent coagulation and anticoagulation factors** (i.e., II, VII, IX, X, protein C, and protein S). The result is the production of non-functional factors. Warfarin inhibits both pro- and anti-haemostatic pathways; nevertheless, the resulting effect is anticoagulatory. The anticoagulant activity of warfarin is monitored by **prothrombin time** (i.e., **PT or Quick's time**), which is often expressed as a **dimensionless International Normalised Ratio (INR)**, with 1 corresponding to an "ideal" time in healthy person and 2-3 to efficient treatment by warfarin.

The disadvantage of warfarin is a relatively narrow therapeutic range, which requires regular monitoring of PT as well as interactions with other drugs and nutrients (especially sources of vitamin K). Warfarin also requires several days to establish full anticoagulant activity, and other drugs, such as LMWHs, must be administered during this time. The same applies for reducing its anticoagulant action in an overdose or because of bleeding complications. In such cases, vitamin K or donor blood plasma can be administered. Warfarin should not be administered during pregnancy because of its teratogenic effects.

5.2.1.3 Direct Xa inhibitors ('xabans')

Direct Xa inhibitors are a new group of drugs that directly inhibit the activated factor X without any mediating factor. They are used as a safer alternative to coumarins. Compared to coumarins, they have a rapid onset and offset of therapeutic effect as well as a lower occurrence of overdose and underdose. Their typical ending is –xaban (e.g., **rivaroxaban**, **apixaban**, etc.).

5.2.1.4 Direct thrombin inhibitors

This group of drugs selectively inhibits thrombin (i.e., factor IIa) without using any other mediating molecule. **Hirudin** is an anticoagulant peptide found in the saliva of medical leeches (*Hirudo medicinalis*), and it is the most potent naturally occurring thrombin inhibitor. Hirudin and its analogues, lepirudin or **bivalirudin**, are administered parenterally, mainly in patients with heparin intolerance. Perorally administered direct thrombin inhibitors are smaller molecules that are, similarly to xabans, used as an alternative to coumarins. Their typical ending is –gatran, and the most important representative today is **dabigatran**.

5.2.2 Antiplatelet drugs

Antiplatelet drugs inhibit the **activation** or **aggregation** of thrombocytes. Platelets can be activated by several factors (e.g., the von Willebrand factor, thromboxane A2, adenosine diphosphate, or thrombin). Their activation is mediated by elevating the concentration of intracytoplasmic Ca^{2+} that is released from the storage in the endoplasmic reticulum and passes from extracellular space inside the cell through membrane channels. The resulting effects include the release of platelet-activating and vasoconstriction factors, shape change, an increase in the negative charge on the platelet's surface that enables the attachment of coagulation factors, and platelet aggregation that is mediated by fibrinogen molecules acting as bridges. Antiplatelet drugs inhibit platelet surface receptors, decrease the production of platelet-activating factors, or aim to reduce the intracytoplasmic calcium levels by other means.

5.2.2.1 Cyclooxygenase inhibitors

Cyclooxygenase inhibitors act against the platelet production **of thromboxane A2 (TXA2)**, which is both an effective platelet activator and vasoconstrictor. Out of this group of drugs, **acetylsalicylic acid (ASA)** is, by far, the most widely used for the prevention of arterial thrombosis, such as is the case for coronary or brain vessel atherosclerosis. In low doses, ASA preferentially blocks the formation of TXA2, while in high doses it also inhibits the production of vasodilatory and antiaggregant, prostacyclin PGI2, in the vascular endothelium. Therefore, lower doses of around 100 mg are used for chronic medication. In the treatment of the acute arterial thrombosis, doses of about 500 mg are administered (e.g., in the case of myocardial infarction).

ASA is a widely available drug with rich clinical evidence. The main disadvantages are: an unavailability of routine *in vitro* tests to evaluate its therapeutic efficacy (about 10-20% of patients are resistant to the usual doses of ASA), side effects that include bleeding, gastrointestinal problems (e.g., peptic ulcer), or allergic reaction, and the absence of a specific antidote (thrombocyte concentrates can be given when necessary).

Indobufen is a reversible inhibitor of cyclooxygenase that is specific to reducing TXA2 production. It may be administered in the case of ASA intolerance.

5.2.2.2 Phosphodiesterase inhibitors

Phosphodiesterase inhibitors inhibit the enzyme which degrades intracellular cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP). In turn, these messenger molecules decrease the levels of intracytoplasmic calcium, thereby inhibiting platelet activation. The same effect is present in the vessel wall, wherein it results in lowering the vasoconstriction response. This group is especially efficient at treating peripheral artery disease, in which vasoconstriction plays an important role. Examples include **dipyridamole**, **cilostazol**, and **pentoxifylline**.

5.2.2.3 P2Y inhibitors

P2Y are a group of purinergic receptors, of which **ADP-binding P2Y12** is a subtype that is a therapeutic target of specific inhibitors. Blocking P2Y12 on the platelet surface inhibits platelet activation. P2Y12 inhibitors are often used for the acute treatment and secondary prevention of myocardial infarction, after endovascular stenting, and in peripheral artery disease. Often, P2Y12 inhibitors are used in combination with ASA. The currently used drugs can be divided into **thienopyridines** and **non-thienopyridines**. The oldest thienopyridine, **ticlopidine**, has been generally withdrawn because of its haematological side effects and was widely replaced by the newer agent, **clopidogrel**. The third generation thienopyridine, **prasugrel**, has the advantage of a better pharmacokinetic profile. Non-thienopyridines are represented by **ticagrelor**, which is a reversible P2Y12 inhibitor used for chronic treatment as are clopidogrel and prasugrel, and **cangrelor**, which is administered intravenously during acute coronary syndrome. The efficacy of treatment by P2Y12 inhibitors is measured by platelet function tests using ADP as an activator.

5.2.2.4 Glycoprotein IIb/IIIa (Gp IIb/IIIa) inhibitors

Glycoprotein (Gp) IIb/IIIa is a platelet receptor that binds fibrinogen molecules, thereby mediating platelet aggregation. Likewise, platelets become attached to the fibrin net. The Gp IIb/IIIa inhibitors are usually administered intravenously, and they exert their action through several mechanisms. **Eptifibatide**, a peptide derived from snake venom, is a low-affinity competitive inhibitor. Because of its low affinity, normal haemostasis is restored within 3-4 hours after cessation of the treatment. Hence, this drug is mostly used for the acute treatment of myocardial infarction. **Tirofiban** is another Gp IIb/IIIa competitive inhibitor with short-term action. **Abciximab** is an antibody fragment that changes the conformation of IIb/IIIa. Contrary to the aforementioned drugs, its effect is reversible, but long-term in the same time.

5.2.2.5 PAR-1 inhibitors

PAR-1 inhibitors inhibit the platelet receptors for **thrombin** (factor IIa), the most potent platelet activator. They are a new class of drugs currently represented by vorapaxar. Like P2Y12 inhibitors, **vorapaxar** is often administered in combination with ASA, and its efficacy can be evaluated using platelet function tests. Compared to P2Y12 inhibitors, vorapaxar is efficient at preventing arterial thrombosis, but has a higher rate of bleeding complications.

5.2.3 Fibrinolytic drugs

Under physiological conditions, **fibrinolysis** is ensured by **plasmin**, a serine protease present in the circulation as an inactive plasminogen. Plasminogen may be converted into its active form by tissue plasminogen activator (tPA), which is secreted by the endothelium with fibrin acting as its cofactor. Alternatively, plasminogen can be converted by epithelium-derived urokinase (uPA) or bacterial enzymes.

All fibrinolytic drugs convert plasminogen to plasmin, thereby contributing to fibrin degradation. They are used for the acute treatment of thrombosis or a thromboembolism, such as during an ischaemic stroke, myocardial infarction, or pulmonary embolism. The main side

effect of fibrinolytic drugs is the risk of severe bleeding; therefore, fibrinolytics are contraindicated for patients with a history of intracerebral bleeding, insufficient haemostasis, or advanced liver disease.

Fibrinolytics can be distinguished into three generations. The first one represents the fibrinolytics that act both in the thrombus as well as in the free plasminogen. This is linked to a higher risk of the occurrence of a bleeding complication. Examples include **urokinase** and **streptokinase**; streptokinase being an antigen for the immune system, which should be not administered repeatedly. The second-generation drugs act in the thrombus only and are represented by **alteplase**, which is a recombinant tPA. The third generation fibrinolytics are obtained by tPA modifications, and their main advantage is a bolus administration (older fibrinolytics must be administered continuously). Examples include **reteplase** and **tenecteplase**.

5.2.4 Pro-haemostatic drugs

5.2.4.1 Antifibrinolytics

Antifibrinolytics inhibit fibrinolysis, thus can be used to treat different bleeding conditions, such as menorrhagia, gastrointestinal bleeding, epistaxis, and minor surgery (e.g., dental), especially in patients suffering from haemophilia. They block the binding site on the plasmin molecule that mediates its attachment to fibrin as well as plasminogen conversion to active plasmin. Examples include **para-amino-methyl-benzoic acid (PAMBA)**, **tranexamic acid**, and **aminocaproic acid**.

5.2.4.2 Haemostyptics

Haemostyptics are a group of drugs whose purpose is to terminate bleeding. In the broader sense, the term "haemostyptic" refers to any drug with an anti-bleeding effect, for instance antifibrinolytic drugs, vitamin K, donor blood plasm, coagulation factors, and thrombocyte concentrates are all included. Locally, this includes fibrin glue, a **gelatin sponge**, or a **collagen sponge**, as well.

In the narrower sense, the term, "haemostyptics", refer to drugs that use vasoconstriction as their primary mode of action. A well-known example is **etamsylate**, a drug which increases platelet adhesion, activation, and vasoconstriction by way of mechanisms not yet elucidated. This drug can be used both systemically (with similar indications to antifibrinolytics) and locally through administration with a tampon. Another classical example of a haemostyptic drug is **terlipressin**, a vasopressin (ADH, antidiuretic hormone) analogue with a higher affinity to vascular V_1 receptors as compared to renal V_2 receptors. The affinity is about equal in the case of vasopressin, while **desmopressin**, another vasopressin analogue, shows higher affinity to V_2 receptors and is used to treat the diabetes insipidus. Terlipressin can be administered both systemically and locally and is often administered alongside endoscopic treatment of gastrointestinal or urogenital bleeding. The side effects are rare and include headache or gastrointestinal symptoms.

5.3 Antiarrhythmics

Antiarrhythmics treat disorders of the cardiac rhythm (i.e. **arrhythmias**, dysrhythmias). Arrhythmias can be distinguished between slow (**bradyarrhythmia**) and fast (**tachyarrhythmia**), resulting in slow or fast heart rate (i.e., bradycardia/tachycardia, respectively). The antiarrhythmics seek to reconstitute the normal sinus rhythm and to prevent recurrence of the arrhythmia. If this is not possible, the antiarrhythmics aim to control the arrhythmia and achieve haemodynamic stability.

Electrical activity of cardiomyocytes
Like other types of cells, the cardiomyocyte is negatively charged as compared to the extracellular space in its resting state. The electrical potential of the extracellular space is used as a reference, and therefore, the voltage, also called the **membrane potential**, has a negative value. In muscle cells including cardiomyocytes and in some other cells, such as neurons, the resting voltage can dramatically change in a process known as an **action potential**. In muscle cells, the action potential is linked to an increase in intracytoplasmic calcium, which mediates muscular contraction. The precise character of the action potential differs in the various cell types, including cardiomyocyte subpopulations.

In the most abundant subpopulation of **fast cells** (i.e., atrial myocytes, ventricular myocytes, and Purkinje fiber cells) that constitutes a working myocardium, five phases of their electrical cycle can be enumerated:
1)   **Phase 0 – fast depolarisation**, which is mediated by the sodium current through the voltage-gated sodium channels. Their opening is triggered by reaching the threshold potential, which is typically a result of ion influx from the neighbouring cell. Phase 0 is very fast, and in the end, the membrane potential reaches positive values.
2)   **Phase 1 – transient repolarisation** is mediated by a potassium current. After this phase, the membrane potential is close to zero.
3)   **Phase 2 – plateau**: During this phase, an efflux of potassium ions is at equilibrium with an influx of calcium. The membrane potential does not change. The calcium ions also help to open the calcium channel in the sarcoplasmic reticulum, which leads to further increase of the intracytoplasmic calcium. This is necessary for the cardiac contraction.
4)   **Phase 3 – rapid repolarisation**: This phase is enabled by the potassium efflux through the "delayed rectifier" and "inward rectifier" channels. These channels open more efficiently when the cell reaches the negative membrane potential once again. At the end of phase 3, the membrane potential reaches its resting state.
5)   **Phase 4 – resting phase**: The ions return to their original gradients using the ionic pumps and transporters. The muscle relaxes.
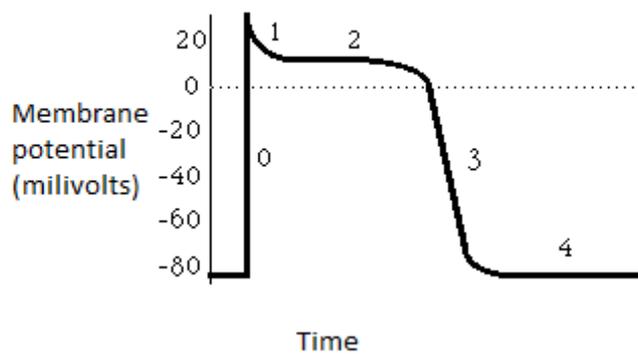
Figure XX. The membrane potential during the electrical cycle of a fast cell.

The **slow cells** differ in their depolarisation, which is not mediated by sodium, but by calcium and its channels. This makes depolarisation as well as signal conduction much slower, hence the name. Transient depolarisation and its plateau cannot be distinguished. Rapid repolarisation is similar to the process by which fast cells repolarise. Slow cells naturally occur in the **sinoatrial (SA)** and **atrioventricular (AV) nodes**. In the latter case, they are necessary for the delay between the atrial and ventricular contraction. They also filter electrical signals that reach the ventricles, in turn preventing haemodynamic compromise occurring with supraventricular tachycardia.

Pacemaker cells spontaneously generate an electrical signal without external stimulus. Pacemaker activity is a typical feature of slow cells, although some fast cells (e.g., in the Purkinje fibres) also have this ability. In pacemaker cells, positively charged ions (i.e., sodium, calcium) seep into the cell from the extracellular space until the threshold potential of the membrane is reached. Reaching the threshold potential can be facilitated by opening sodium or calcium channels, or alternatively, by closing potassium channels, while the opposite processes slow the spontaneous depolarisation and delay reaching the threshold. This is how the sympathetic and parasympathetic nervous system regulate heart rate. Under normal conditions, the threshold potential is first reached by the cells in the SA node; thus, the SA node serves as a **primary pacemaker** for the heart.

Arrhythmias result from disorders of both signal formation and propagation. The four main mechanisms involved in the disruption of this process include **altered pacemaker activity**, **conduction blocks**, **afterdepolarisations**, and **re-entry**. The term afterdepolarisation refers to premature depolarisation before (i.e., early afterdepolarisation) or after (i.e., delayed depolarisation) the cell repolarises below the threshold membrane potential during phase 3. Re-entrant tachycardia is defined by the occurrence of fast electrical circuits that depolarise the surrounding tissue and consequently the whole heart in place of its natural pacemaker centres. Arrhythmias can either be treated by **pharmacotherapy** or by the direct electrical stimulation of heart using an **artificial pacemaker** (**PM**), which is used in most bradyarrhythmias. In the case of re-entrant tachycardia, an electrical discharge can be applied, either externally or using an automatic **implantable cardioverter-defibrillator** (**ICD**).

Common side effects of antiarrhythmic drugs

Since antiarrhythmic drugs exert their action through modifying the cardiomyocyte action potential, their most common side effect is the development of arrhythmias. The onset of arrhythmias is generally dose-independent and hardly predictable. While many antiarrhythmics (e.g., beta-blockers and CCB) cause symptomatic bradyarrhythmias such as atrioventricular blocks, an occurrence of life-threatening ventricular re-entry, including ventricular fibrillation, cannot be excluded. A **long QT interval**, resulting from an extended duration of action potentials, indicates risk of early afterdepolarisations (i.e., the cells in phase 3 depolarise again before reaching the threshold membrane potential) and the "**torsade de pointes**" ventricular tachycardia that can also terminate in **ventricular fibrillation**. Antiarrhythmics should not be combined with other drugs that lengthen the QT interval (e.g., some antidepressants, antihistaminics, or antibiotics). Generally, antiarrhythmics are contraindicated if the patient's condition does not necessitate their use.

Another common side effect is the negatively inotropic action that can be potentiated during the simultaneous use of different antiarrhythmics (see below).

The antiarrhythmic drugs can be divided into four classes depending on their mode of action. Some antiarrhythmics have combined activity and belong to more than one class. Some have a distinct mode of action and do not belong to any group.

Class I. Sodium channel inhibitors
Sodium channel inhibitors block the opening of the voltage-gated sodium channel; therefore, they inhibit the depolarisation of the fast cells. They also inhibit spontaneous depolarisation in pacemaker cells and prolong the refractory period (i.e., the period when a cardiomyocyte does not depolarise in response to the external stimuli; this period is dependent on the state of the sodium channels). The class I antiarrhythmics are used for re-entrant tachycardia, which is defined by the occurrence of fast electrical circuits that replace the natural pacemaker activity and depolarise the surrounding tissue; consequently, the entire heart becomes depolarised with high frequency, resulting in the high heart rate.

Based on the shape of the action potential, class I antiarrhythmics can be further divided into three subclasses:
    Ia, also called the quinidine group, whose purpose is to prolong the action potential. Examples include **quinidine**, an alkaloid from the cinchona bark, and **prajmaline**.
    Ib, also called the lidocaine group, which shortens the action potential. These drugs are also used as local anaesthetics. The typical ending is "-caine" (e.g., **lidocaine**, **trimecaine**, etc.).
    Ic, also called the propafenone group, does not change the duration of an action potential. **Propafenone** is the most widely used class I antiarrhythmic with a relatively low proarrhythmogenic effect. Besides sodium channel inhibition, propafenone also acts as a weak beta-blocker. Because of its negatively inotropic effect, it should not be used in the patients with heart failure. Propafenone can be administered either intravenously to revert re-entrant tachycardia or perorally to maintain normal sinus rhythm in patients at risk of re-entry. Another drug from this group is **flecainide**.

Class II. Beta-blockers

The beta-blockers inhibit the spontaneous depolarisation of pacemaker cells in phase 4 as well as the conduction in the AV node; therefore, they slow down the heart rate and can be used as antiarrhythmics in tachycardia. The beta-blockers also prevent the occurrence of atrial or ventricular fibrillation, which is based on many small and unstable re-entry circuits. Examples of beta-blockers with the antiarrhythmic activity are **metoprolol** and **atenolol**. **Sotalol** has a combined beta-blocking and potassium channel-blocking effect.

Class III. Potassium channel inhibitors

The potassium channel inhibitors inhibit the potassium currents in phase 3, thereby prolonging the repolarisation as well as the refractory period of cardiomyocytes. This prevents the occurrence of re-entrant circuits and can stop those already under way.

Amiodarone is a commonly used antiarrhythmic drug. Besides its potassium channel-blocking action, it also inhibits sodium and calcium currents and has an alpha- and beta-blocking effect. It is used both intravenously and perorally for various tachyarrhythmias, both supraventricular and ventricular, including ventricular fibrillation. Its advantage is its efficacy in patients with heart failure and/or after myocardial infarction (MI). On the other hand, amiodarone has many side effects. Some of these result from its chemical structure, which is similar to thyroid hormones and includes iodine. Amiodarone can then cause both hyper- and hypothyroidism; it also forms deposits in the retina and fatty tissue. The most severe side effect is amiodarone-induced pneumonitis that is reversible, but can be life-threatening. The occurrence of side effects can be minimised by using the minimal effective dose.

Dronedarone is a drug with a multi-channel effect, which is chemically related to amiodarone. Because it does not contain iodine atoms, it does not have most of amiodarone's side effects. However, it is risky for patients suffering from heart failure, and it should not be used for these patients.

Sotalol is a combined class II and class III antiarrhythmic. It has lower effectivity than amiodarone, but does not have most of its side effects. It is often used in patients with amiodarone intolerance.

Vernakalant is a drug that blocks sodium and potassium channels. It is used to restore normal sinus rhythm in patients with atrial fibrillation. Vernakalant is not effective as a chronic medication.

Class IV. Calcium channel inhibitors

Calcium channel inhibitors (i.e., calcium channel blockers, CCB) have negatively inotropic, chronotropic, and dromotropic effects. Dihydropyridines selectively inhibit vascular resistance with little effect on the myocardium; for this reason, non-dihydropyridine CCB, **verapamil** and **diltiazem**, are primarily used as antiarrhythmics. Both of these drugs are hydrophilic and enter the calcium channel in its open state; this condition occurs more often in cardiomyocytes than in smooth muscle cells.

Verapamil and diltiazem are most effective at slowing down conduction in the AV node, for example in terminating AV nodal re-entry tachycardia. Because of their negatively inotropic effects, these drugs should not be used for patients with heart failure. Simultaneous use with

beta-blockers can be risky because of the complete inhibition of conduction through the AV node (i.e., AV block).

Other antiarrhythmics

Digoxin is a drug that inhibits cardiac sodium/potassium ATPase. This decreases the sodium and potassium gradients; secondarily, the lower sodium gradient inhibits the sodium/calcium exchanger, which leads to a higher concentration of intracytoplasmic calcium. Digoxin also centrally stimulates the parasympathetic nervous system and increases the refractory period in the AV node. Besides its pro-inotropic effects, digoxin can also be used to slow down heart rate during supraventricular arrhythmias when return to the normal sinus rhythm is not possible.

Adenosine opens potassium channels and closes calcium channels. It is administered intravenously and used to restore normal sinus rhythm in supraventricular tachycardia. Adenosine also temporally blocks the AV node and can be also used diagnostically to distinguish among different types of arrhythmias.

Atropine, an alkaloid isolated from *Atropa belladonna*, is an intravenously administered drug that treats symptomatic bradyarrhythmias. It inhibits the muscarinic M2 receptor of the parasympathetic nervous system. Side effects experienced result from the effects on the eye, gastrointestinal, and urinary tract system, and in higher doses, it can also cause skeletal muscle twitching or disorders of the central nervous system.

5.4 Cardiotonics (positive inotropes)

Positive inotropes increase myocardial contractility. Through various mechanisms, these drugs increase the level or effect of intracytoplasmic calcium, which enables increased muscular contraction. They are mostly used during acute decompensated heart failure (ADHF) and/or cardiogenic shock.

5.4.1 Cardiac (*digitalis*) glycosides

Digitalis glycosides are obtained from the *digitalis* (i.e., foxglove) plant, which is often kept as an ornamental flower and is highly toxic. The only currently used member of this drug group is **digoxin**. Digoxin is a sodium/potassium ATPase inhibitor. Therefore, digoxin causes sodium and potassium gradients to decrease; secondarily, the lower sodium gradient inhibits the sodium/calcium exchanger, which leads to a higher concentration of intracytoplasmic calcium. Digoxin also centrally stimulates the parasympathetic nervous system and increases the refractory period in the AV node. The resulting effect is positively inotropic and negatively chronotropic without increasing ATP consumption and needs.

The main disadvantage of digoxin is a narrow therapeutic range; therefore, there exists a high probability of overdose. Side effects include a wide range of arrhythmias (e.g., both brady- and tachyarrhythmias), some of which are specific to digoxin, and non-cardiac manifestation, such as nausea, headaches, confusion, and vision disorders (i.e., yellow vision). Thus, digoxin concentration must be monitored during treatment. While digoxin itself can cause

hyperkalaemia, hypokalaemia increases the risk of its side effects. Therefore, serum potassium should be monitored along with digoxin levels. Digoxin intoxication can be treated with diuretics and $MgSO_4$. Potassium is administered in case of hypokalaemia, while atropine can be given in case of bradyarrhythmias. Sheep antibodies against digoxin can be used as a specific antidote.

5.4.2 Phosphodiesterase III inhibitors

Phosphodiesterase III inhibitors increase intracytoplasmic cAMP, which induces increased calcium influx into cardiomyocytes. At the same time, cAMP decreases the contractility of vascular smooth muscle, decreasing peripheral resistance. The main disadvantage is a proarrhythmogenic effect. Therefore, the phosphodiesterase III inhibitors are only used for the short-term treatment. An example from this group is **milrinone**.

5.4.3 Calcium sensitisers

Calcium sensitisers are a group of drugs that aim to increase the effect of calcium on the contractile apparatus. **Levosimendan**, the only member of this group used today, is a drug that binds to the cardiac troponin C subunit and increases calcium-mediated pro-contractile action without increasing calcium levels. By opening the potassium channels, levosimendan also mediates peripheral smooth muscle relaxation. Levosimendan is intravenously administered and is used for short-term treatment. Its side effects are rare and include mild hypotension and nausea.

5.4.4 Sympathomimetics

Sympathomimetics increase cardiac contractility through their β_1 agonistic action. This activity is most strongly expressed with **epinephrine**, **dopamine**, and **isoprenaline**. **Dobutamine** is a selective β_1 agonist that is currently the drug most widely used to treat severe heart failure and cardiogenic shock. In severe shock states, dobutamine can be combined with **norepinephrine** to increase peripheral resistance at the same time.

5.5 Direct-acting vasodilators

Direct-acting vasodilators induce smooth muscle relaxation decreasing peripheral resistance. Unlike other groups with vasodilatory properties (e.g., ACE-I, renin inhibitors, and central sympathomimetics), they act directly on smooth muscle cells. Direct-acting vasodilators have an antihypertensive effect; they are also used for the treatment of angina pectoris, lower limb ischaemia, and cerebral ischaemia. Some other drugs not listed below (e.g., CCB, pentoxifylline – see respective sections: antihypertensive drugs, antiplatelet drugs))also have direct vasodilation as an aspect of their combined effect.

5.5.1 Nitrovasodilators

5.5.1.1 Nitrates

Nitrates work through the production of the **nitric oxide** (**NO**), a strong vasodilatory molecule also known as EDRF (endothelium-derived relaxing factor). NO activates guanylate cyclase, which increases the amount of intracytoplasmic cyclic guanosine monophosphate (cGMP). This molecule, like cAMP, decreases the levels of intracytoplasmic calcium in smooth muscle cells, thereby decreasing their contractility. It was hypothesised, that nitrates release NO through a reaction with thiol (-SH) groups, but some recent studies contradict this mechanism, and the NO-independent action of nitrates is also still discussed.

Unlike other vasodilators, nitrates relax venous smooth muscle more efficiently than arterial smooth muscle. This decreases the cardiac preload. Arterial dilation is responsible for the anti-ischaemic effects and decreased afterload. Nitrates are especially efficient at dilating coronary arteries. This eases the pain in **angina pectoris**, and the nitrates may be used for both the short-term and long-term treatment of this disease. On the other hand, the nitrates do not treat the atherosclerosis itself and ameliorate neither the prognosis of ischaemic heart disease nor the risk of mortality.

The use of nitrates is further limited by a rapid onset of **tolerance**, also called **tachyphylaxis**. In the past, this effect used to be explained by the depletion of –SH groups. Currently, four possible mechanisms are discussed: impaired formation of nitric oxide from nitrates caused by the downregulation of respective enzymes, oxidative stress, decreased endogenous NO production, and the counterbalancing action of other mediators, such as angiotensin II, catecholamines, or ADH. This limits the antihypertensive action of nitrates to being used as a short-term treatment for a hypertension crisis. Moreover, it creates problems for long-term nitrate treatment in angina pectoris. Nitrate doses for chronic use should be limited and pauses employed during treatment to lower nitrate plasma levels (i.e., pausing usually occurring at night).

Nitrates can be administered either intravenously, per os, nasally, sublingually, or transdermally, depending on their lipophilia. **Nitroglycerin** (**glyceryl trinitrate**, **NTG**) is a drug used for the treatment of angina pectoris and in pre-hospital first aid for a myocardial infarction. It has a rapid onset of action, a high first pass effect, and is mostly used for acute treatment in the form of spray or intravenously. **Isosorbide dinitrate** (**ISDN**) is another lipophilic nitrate with use similar to nitroglycerin; separately, it can be administered as a continuous infusion to treat a hypertension crisis, as well. It can be also administered perorally. **Isosorbide mononitrate** (**ISMN**) is a hydrophilic metabolite of isosorbide dinitrate, which is used perorally for chronic angina pectoris treatment. Its advantage is a low occurrence of nitrate tolerance. Both ISDN and ISMN are often administered in delayed-release capsules. **Pentaerythritol tetranitrate** (**PETN**) is another nitrate that is used perorally for the chronic treatment of angina pectoris.

The main side effect of nitrate use is systemic hypotension. Nitrates should be not used in the case of cardiogenic shock, and caution should be heeded when they are combined with other direct vasodilators, such as CCB or sildenafil. Hypotension is often accompanied by tachycardia, nausea, and headaches. On risky terrain (i.e., ischaemic tissue with collateral blood flow), nitrates may induce the steal phenomenon and cause worsening of the ischaemia.

5.5.1.2 Non-nitrate nitrovasodilators

Non-nitrate nitrovasodilators share the same mechanism of action with nitrates. They differ in their chemical structure and do not induce nitrate tolerance. **Sodium nitroprusside** has an enhanced vasodilatory effect in the arteries and is used intravenously to treat a hypertension crisis. **Molsidomine** is usually administered per os along with nitrates to treat chronic angina pectoris. Alternating molsidomine with nitrates reduces the development of nitrate tolerance and is employed for the treatment of severe chest pain when a 24-hour long effect is needed.

5.5.2 Other direct vasodilators

Nicorandil and **minoxidil** activate the ATP-gated potassium channels in smooth muscle cells, thereby increasing the membrane potential and reducing calcium influx into smooth muscle cells. They also release the NO. Nicorandil is used to treat stable angina pectoris in a manner similar to nitrovasodilators. Minoxidil was initially administered as an antihypertensive, but today, it is mostly used to prevent hair loss by facilitating local circulation.

Hydralazine is a direct vasodilator that is used to treat hypertension in pregnant women, along with methyldopa and labetalol. It is selective for arterial smooth muscle. Because of its short biological half-life, it is usually administered intravenously in the event of a hypertensive crisis.

Sildenafil is a **phosphodiesterase V inhibitor**, which blocks the removal of cGMP; therefore, calcium levels in the smooth muscle cells decrease. It was originally developed as a drug to treat angina pectoris, but currently it is widely used for patients with erectile dysfunction. It may also be administered to treat primary pulmonary hypertension. Sildenafil should not be used concomitantly with nitrates because this combination can cause severe hypotension and, in the case of an acute coronary event, circulatory shock. The combination may also induce the coronary steal phenomenon.

5.6 Treatment of the ischaemic heart disease

Ischaemic heart disease (IHD) is a result of limited blood supply to the myocardium, which causes its hypoxic damage. The most common cause of cardiac ischaemia is atherosclerosis of the coronary arteries. Depending on whether the onset of cardiac ischaemia is fast or slow, **acute** and **chronic** coronary syndromes can be distinguished.

Angina pectoris is a typical chest pain that occurs during transient myocardial ischaemia. **Stable angina pectoris** refers to the chronic condition that does not progress over time. Typically, it worsens during physical effort because of higher myocardial consumption of oxygen; although, sometimes the chest pain can be induced by the emotional stress, changing weather, etc. The main risk is the potential progression into acute coronary syndrome. **Unstable angina pectoris** is the most benign form of acute coronary syndrome and is typically displayed by a rapid progression of the chest pain, which can even be present at rest. It may develop from stable angina or occur *de novo*. Often, changes in the ECG are present.

Myocardial infarction is a form of acute coronary syndrome that is accompanied by cardiac necrosis. It is most often caused by the rupture of an unstable atherosclerotic plaque leading to local thrombosis. It is accompanied by changes in the ECG curve, which result from myocardial damage. The most severe form presents with an elevation of the ST segment (**ST-elevation myocardial infarction**, **STEMI**). This sort of infarction is the result of a complete occlusion of a coronary artery and requires its immediate recanalisation. In other cases of myocardial infarction (**non-STEMI**), the occluded coronary artery is usually partially recanalised. Hence, an intervention may be postponed if needed.

The IHD (both chronic and acute) is treated using **pharmacotherapy**, **endovascular intervention**, **surgery**, and **lifestyle intervention**. The lifestyle intervention focus is on controlling the modifiable risk factors, such as physical activity (e.g., light aerobic exercise is advised and preferable), dietary intake, smoking, and psychical stress. Patients with hypertension, dyslipidaemia, and diabetes mellitus should focus on adequate compensation for their disease.

Coronary intervention may be endovascular (**percutaneous coronary intervention**, **PCI**) or surgical (**coronary bypass**). In the first case, a wire is inserted into the site of stenosis/occlusion via the radial or femoral artery, and the coronary arterial lumen is then widened using a small balloon. In most cases, a **stent** (i.e., scaffold) is inserted into the site to keep the artery open. The stent can be bare metal, biodegradable (i.e., made from an absorbable alloy or polymer), or **drug-eluted**. In the last case, the metal is covered with a **cytostatic drug**, such as **sirolimus** or **paclitaxe**l, which locally inhibits the growth of vascular intima and restenosis. Coronary bypass surgery uses either a venous graft or one of the other chest arteries to bridge the site of stenosis/occlusion.

5.6.1 Pharmacological treatment of chronic IHD

The pharmacological treatment of the IHD must address several aspects at once. First, the progression of coronary atherosclerosis must be stopped or at least slowed down, and to do this, **statins** (i.e., HMG-CoA inhibitors such as **atorvastatin** or **rosuvastatin**) are administered as a lifelong treatment.

Second, **anti-haemostatic treatment** must be applied to prevent coronary artery thrombosis. **Acetylsalicylic acid** is the drug that is the most widely used for long-term treatment, which is accompanied by **P2Y inhibitors** after a coronary intervention.

Third, **vasodilation** that prevents angina pectoris must be ensured. In chronic treatment, a **CCB** can address both vasodilation and myocardial oxygen consumption; however, verapamil and diltiazem are contraindicated for patients with heart failure. Perorally administered **nitrates** and **molsidomine** further dilate the coronary arteries; the nitrates may be also used for acute chest pain.

Fourth, **cardiac metabolism** and oxygen consumption must be addressed, which is ensured by use of cardiac selective beta-blockers. **Beta-blockers** also have a strong supressive effect on angina pectoris.

In patients who cannot tolerate beta-blockers (e.g., in the case of severe bronchial asthma), **ivabradine** can be taken instead of beta-blockers. Ivabradine is an inhibitor of multi-ionic F-(funny) channels, which contribute to slow depolarisation in pacemaker cells. The closing of the multi-ionic F-channels lengthens the time necessary for creating the new action potential, thus slowing down heart rate. This has a beneficial effect regarding myocardium metabolic needs and oxygen consumption.

Trimetazidine is a cytoprotective drug that directly influences cardiac metabolism. It inhibits the oxidation of fatty acids and promotes glucose oxidation, which lowers the need for the oxygen supply.

5.6.2 Pharmacological treatment of the acute coronary syndromes

The term acute coronary syndrome refers to unstable angina pectoris and myocardial infarction. As a first aid for acute chest pain, **nitrates**, such as NTG, are administered. If the chest pain continues after five minutes, 500 mg of **acetylsalicylic acid** can be given (ideally the patient should chew the capsule due to better ASA absorption) and an emergency number called. As ASA is a commonly available drug, this simple pharmacological intervention is an accessible way to treat coronary thrombosis during first aid care as well as reduce myocardial thrombosis. Other treatment is only administered with medical assistance: analgesics (e.g., **opioids** such as morphine or fentanyl), anxiolytics (e.g., **benzodiazepines**), **heparin**, other **anti-platelet drugs** (e.g., clopidogrel), **atropine**, in the case of bradycardia, and **beta-blockers** during tachycardia. **Fibrinolytics** can be administered in case PCI is unavailable.

Following myocardial infarction, patients receive either combined anti-platelet therapy (e.g., **ASA + P2Y inhibitors**), **statins**, **beta-blockers**, and **ACE-I** or **sartans**. The inhibition of RAAS prevents myocardial remodelling after myocardial infarction.

5.7 Treatment of heart failure

Heart failure is a condition in which the heart is not able to maintain effective circulation. Heart failure can affect both pulmonary and systemic circulation. While **forward** effects lead to systemic hypotension, **backward** failure causes both peripheral oedema (in the case of **right heart failure**) and pulmonary oedema (in **left heart failure**). Heart failure is often associated with shortness of breath (i.e., cardiac asthma) and bad physical condition. Heart failure can be life-threatening when it results in cardiogenic shock or respiratory failure. In accordance with the speed at which the heart fails, **acute** and **chronic** failure can be distinguished.

Whereas acute heart failure is primarily caused by a severe myocardial infarction or by arrhythmias, chronic heart failure can be a result of IHD, dilated cardiomyopathy, valvular diseases, or developmental disorders. Chronic heart failure may also progress to acute heart

failure through a process called decompensation. Right-sided heart failure is often a result of pulmonary disease (**cor pulmonale**).

5.7.1 Acute heart failure

Acute heart failure must be treated without delay, and the treatment must focus on the underlying cause. In general, pharmacotherapy is administered intravenously. The loop diuretics, such as **furosemide**, are used to decrease preload (they are used either alone or in combination with **potassium-sparing diuretics**), and **nitrovasodilators** are used to decrease afterload if required (i.e., if hypotension is not present). **Opioids** are administered in the case of severe dyspnoea.

If acute heart failure progresses to cardiogenic shock, **catecholamines** are administered, preferably dobutamine or dopamine with positively inotropic effects, which can be combined with norepinephrine or epinephrine in case of continuing hypotension. **Levosimendan**, a calcium sensitiser, is often used for acute heart failure that has progressed from chronic heart failure. Therapy with **RAAS inhibitors** or **beta-blockers** is not started during acute heart failure, but if they have already been administered (i.e., usually during chronic heart failure decompensation), they are continued and kept at low doses.

Non-pharmacological approaches to treating acute heart failure involve temporary mechanical circulatory support, called **intra-aortic balloon counterpulsation**, or interventional treatment aimed at treating the underlying cause (e.g., PCI in the case of myocardial infarction).

5.7.2 Chronic heart failure

Chronic heart failure is a complex process consisting of factors damaging the heart and myocardial response to these factors. The response consists of myocardial hypertrophy, which is initially a compensatory process aiming to increase cardiac output, but later becomes harmful due to increased oxygen consumption and arrhythmogenic potential. Finally, the cardiomyocytes are replaced by fibrous tissue. When the heart is not able to maintain proper functions, clinical symptoms develop and heart failure becomes **manifest**. Therefore, the treatment of chronic heart failure must address cardiac **remodelling** as well as its underlying cause(s), if possible.

Beta-blockers are used because of their cardioprotective effect; the result of which is a lower heart rate. If the heart rate exceeds the 75 beats per minute, **ivabradine** can be used in combination with the beta-blockers. Ivabradine can also be administered in case beta-blockers are contraindicated. In terms of other treatments lowering heart rate, **digoxin** is used for advanced heart failure. Out of all available medications, treatment by **ACE-I**, **sartans**, and **spironolactone** prevent cardiac remodelling, since both angiotensin II and mineralocorticoid receptors are involved in the process. Spironolactone is usually administered with **furosemide**, which is used to prevent fluid congestion. Their dosing can be modified according to potassium levels in the blood (i.e., kalaemia).

The underlying cause is treated when possible. This includes the treatment of IHD (e.g., using ASA, statins, coronary interventions) or valvular disease (e.g., valve replacement). To prevent

fatal ventricular tachycardia, an ICD may be implanted in patients with severe heart failure, while symptomatic asynchrony of the ventricles can be corrected using a biventricular PM. Heart transplantation is the ultimate solution to severe heart failure, followed by immunosuppressive therapy.

5.8 The treatment of anaemias and haematopoiesis defects

Anaemia is a medical condition characterised by **reduced haemoglobin** (Hb) **content in blood**. More specifically, this occurs when the Hb level is below the physiological values defined based on age and gender. Depending on the cause, several different types of anaemia may result. Before initiating treatment, it is essential to determine which type is present. It is not unusual for anaemia to occur because of another serious condition, in which case, by treating the causative condition, the Hb levels might adjust, as well. During the diagnostic process, erythrocyte (red blood cell – RBC) count, as well as their size and shape, is evaluated (not all anaemias are accompanied by a lower RBC count). The presence and count of reticulocytes and erythroblasts (immature erythrocytes) should also be checked.

Despite differences, there are some symptoms common to all anaemias, such as fatigue, somnolence, palpitations, dyspnoea, headache, and paleness of both skin and sclera. Anaemia in children may also manifest as behavioural disorders and poor school performance. Alcoholics are often affected with anaemias caused by deficiency of nutrients (especially those who prefer hard liquor, as beer contains B vitamins) or due to blood loss linked to bleeding in the gastrointestinal tract in alcoholism.

Anaemias are classified according to several attributes. Depending on the mean corpuscular volume (MCV), macrocytic, normocytic, or microcytic anaemia can be determined. Due to variation in haemoglobin concentration, we recognize hypochromic, normochromic, and hyperchromic anaemia. The most common method of classification is to evaluate the etiopathogenesis of anaemia including **blood loss** (posthemorrhagic anaemia), **excessive destruction of red blood cells** (haemolytic anaemia), or a **defect in haematopoiesis** (e.g., pernicious, sideropenic anaemia, hematologic malignancies, anaemias due to chronic illnesses, or renal diseases). The most common type of anaemia is iron-deficiency anaemia, followed by anaemia associated with chronic diseases.

In the text bellow, frequent types of anaemias caused by a defect in haematopoiesis are described. These conditions can be resolved either through supplementation of the missing nutrient or stimulation of haematopoiesis in the bone marrow. In case of life-threatening haemoglobin deficiency, it is possible to use a transfusion (i.e., when haemoglobin decreases under ca. 70 – 80 g/L, depending on patients´ condition).

5.8.1 Anaemia due to deficiency of haematinic agents

5.8.1.1 Iron-deficiency anaemia

Often called sideropenic anaemia, this type of anaemia is one of the most frequent anaemias found in Central Europe. The main reasons for iron deficiency are insufficient diet (e.g., vegetarians, starvation, etc.), a defect in absorption (e.g., celiac disease, atrophic gastritis, etc.), and higher blood loss (e.g., repeated pregnancies, oesophagus varices, melena, etc.). Besides typical symptoms, problems with neuromuscular systems and epithelial tissue may occur (e.g., concave nails, burning of the tongue, etc.).

Due to the lack of an important constituent of haemoglobin, newly formed erythrocytes are small (so-called microcytes) and contain less haemoglobin (hypochromic anaemia). Because of the absence of this blood pigment, a decrease in oxygen transport results. To compensate for this, erythropoiesis is stimulated, which can lead to high number of erythrocytes. Typical signs of this type of anaemia are a high count of microcytes, low haemoglobin, and low iron levels in serum.

A crucial step in the treatment of sideropenic anaemia is to supplement iron either perorally or parenterally. The former is suitable for patients who do not have a problem with iron absorption and usually comes in the form of a **bivalent iron ion** (this form doesn't need the presence of hydrochloric acid for its absorption). Interactions with other drugs (e.g., antacids, tetracycline, and medicines containing calcium) are quite common; therefore, it is recommended to take the iron supplements alone, on an empty stomach with a four-hour gap prior to taking any other medication(s). While taking the medicine, washing it down with milk, alkaline drinks, or black or green tea should be avoided as they reduce its absorption. Oral administration of iron can often cause side effects such as obstipation, diarrhoea, absence of appetite, and stomach discomfort. If iron administered perorally is ineffective or cannot be administered, a **trivalent form of iron** is given parenterally.

5.8.1.2 Anaemias due to lack of folic acid and vitamin B_{12}

Vitamin B_{12} (cobalamin) is a cofactor essential for DNA synthesis. It is also important to maintain the proper activity of nerve cells and for the metabolism of folic acid (vitamin B9). Therefore, a lack of these vitamins is often interconnected. Deficiency of B_9 and B_{12} may be caused by malnutrition, malabsorption, or can develop as a side effect of drugs taken. In adults, the deficiency unfolds rather slowly because they have enough of vitamin B_{12} in liver to last for 5-10 years. However, with infants the progress of the deficiency is much faster and the shortage of vitamins may influence their development (i.e., mainly development of nervous system and brain; lifelong damage is possible).

A special type of anaemia, called **pernicious** (previously untreatable) anaemia, is the result of an absorption defect. This defect is caused by a missing intrinsic (Castle) factor, which is normally produced by parietal cells in the stomach and is essential for the formation of a complex with B_{12}, which is then absorbed. This disease is either autoimmune or can be present in severe alcoholics due to the chronic inflammation of their stomach mucosa.

Both folic acid and vitamin B_{12} are crucial for the synthesis of purine and pyrimidine bases, thus for the synthesis of DNA. Flaws in the synthesis of DNA lead to a low count of erythrocytes; however, the synthesis of haemoglobin remains unaffected. As a result, newly created erythrocytes have a large volume (macrocytes) and high content of haemoglobin (hyperchromic anaemia). Megaloblasts, enlarged precursors of erythrocytes, can be found in blood, as well, since they are released into the circulation from bone marrow. In conclusion,

typically in this type of anaemia, macrocytes and megaloblasts are present in peripheral blood while concurrently having low haemoglobin levels in blood serum. Common symptoms are fatigue, weakness, paresthesia of both upper and lower limbs, inflamed mouth, neuropathy, etc.

Pharmacotherapy for these types of anaemia is based on the supplementation of the missing nutrients. When only folic acid is given, the blood count may normalize, but the neurological symptoms due to the deficiency of B_{12} are not eliminated. Neither folic acid nor vitamin B_{12} should be given to patients suffering from an oncological disease.

Cyanocobalamin used for supplementation of the missing cobalamin is given parenterally (usually i.m.) until the blood count normalizes. Cyanocobalamin is a prodrug and accumulates excessively in the liver. If too much for the body to utilize is taken, the remainder is excreted by the kidneys as well as in bile. This results in enterohepatic circulation of cyanocobalamin. If pernicious anaemia is diagnosed, the patient must be treated with cyanocobalamin permanently.

Folic acid is given orally, and for a serious condition, can be administered parenterally. It accumulates and is metabolised by the liver and undergoes enterohepatic circulation. No serious side effects occur during the treatment. Folic acid is often given before and during pregnancy to avoid its deficiency, which are related to defects of foetus (i.e., during pregnancy, there is greater need for folic acid due to fast cell proliferation).

5.8.1.3 Anaemia due to lack of vitamin B6

Pyridoxine (vitamin B_6) is a precursor to the pivotal coenzyme, pyridoxal phosphate, which is responsible for the incorporation of iron into porphyrin, thus for production of haemoglobin. When B_6 is missing, iron accumulates in the mitochondria of developing erythrocytes, which leads to the formation of sideroblasts. Other causes of sideropenic anaemia involve congenital defects or haematologic malignancies (e.g., usually acute myeloid leukaemia).

While suffering from pyridoxine deficiency, not only are general signs of anaemia present, but symptoms of overload of the organism due to the accumulation of iron are also found. The most serious complications are heart diseases, such as arrhythmias. The lack of pyridoxine can be congenital or acquired as a result of alcoholism or as a side effect of drugs taken (e.g., some of the antituberculotics). To treat this type of anaemia, pyridoxine can be administered either orally or parenterally.

5.8.2 Erythropoiesis defects which are not linked to deficiency of nutrients

Haematopoiesis (i.e., formation of blood cellular elements) is managed by several growth factors, which have a role in the differentiation of cells into their respective blood lines and thus, blood components (e.g., erythrocytes, neutrophils, basophils, etc.). Growth factors bind to specific receptors expressed on the surface of haematopoietic precursors, which ensures their specific effect. This group of haematopoietic factors includes interleukins, erythropoietin, thrombopoietin, GM-CSF (granulocyte-macrophage colony-stimulating factor), G-CSF (granulocyte colony-stimulating factor), and more.

A defect in haematopoiesis can lead to several pathological conditions. That includes, for example, frequent **anaemia associated with chronic illnesses**, which is a secondary symptom and can be found in patients with persisting inflammatory or autoimmune diseases and tumours. Generally, this type of anaemia cannot be cured by the usual antianaemic treatment. While the iron level is within the normal value range, the iron is not utilised properly. Another potential cause for anaemia may be severe bone marrow suppression, wherein the production of all blood cells or just red blood cells is disrupted. Anaemias can also be associated with **haematological malignancies** (e.g., leukaemia, myelodysplastic syndrome, etc.).

Therapy for those conditions is rather complicated. It involves treatment of the causative disease, stimulation of haematopoiesis using haematopoietic factors, and (in serious cases) transfusion of erythrocytic mass.

Erythropoietin is a growth factor required for the proliferation and maturation of erythrocytes. In the human body, erythropoietin is synthetised by the juxtaglomerular cells of kidneys. Therefore, kidney diseases can be accompanied by insufficient erythropoiesis. In clinical practise, recombinant erythropoietin (**epoetin**) can be used to treat anaemia associated with chronic diseases (e.g., chronic kidney disease, patients undergoing chemotherapy, chronic infections) or to speed up the recovery of bone marrow after transplantation. It is given parenterally, the side effects being an increase in blood pressure, flu-like symptoms, deep vein thrombosis, etc.

G-CSF is a glycoprotein, which regulates the production and release of neutrophils from bone marrow. In the Czech Republic, some recombinant G-CSFs are now registered, namely **filgrastim**, **pegfilgrastim**, and **lipegfilgrastim**. Their main indication is to lessen neutropenia, which is common in patients treated with cytotoxic chemotherapeutics or patients with severe HIV infection. Analogues of thrombopoietin, such as **eltrombopag** and **romiplostim**, are registered as thrombocyte production stimulants. It is important to mention that the pharmaceuticals listed above are not used to treat anaemia.

6. Medications for Gastrointestinal Disorders

6.1 Drugs used for treatment of gastric ulcers (antiulcer drugs)

Gastric and duodenal ulcer disease is very common, usually chronic, and often recurring. Depending on its location, we distinguish between gastric and duodenal ulcers. According to its aetiology, the problem is either primary (e.g., *helicobacter pylori* infection acting as main factor) or secondary (e.g., stress-related, drug-induced, endocrine issues). The ulcer is characterised as a defect of the mucosa of the stomach or duodenum. Physiologically, the stomach and duodenal mucosa should be intact and protected against harmful agents by mucus and bicarbonates, which are secreted by epithelial cells, with local production of prostaglandins and NO giving further protection. A defect in the mucosa is caused by an imbalance in the presence of protective and harmful agents (e.g., hydrochloric acid (HCl), *Helicobacter pylori*, NSAIDs, alcohol, caffeine, nicotine). It is important to find out if the condition relates to the patients´ current habits (i.e., excessive consumption of stomach irritating substances). If this is the case, the first step is to recommend a lifestyle change. Then, if the lifestyle change fails, pharmacotherapy supporting protective factors is indicated.

According to their mechanism of action, several different types of anti-ulcer drug can be enumerated; ones which inhibit the secretion of HCl (e.g., proton pump inhibitors, H2 antihistamines, selective parasympatholytics), agents which neutralize stomach acid already present (antacids), and substances protecting gastroduodenal mucosa. A common cause of ulcer development is the presence of *Helicobacter pylori*. These gram-negative bacteria reside in gastric mucosa and cause dyspepsia and potentially eventually gastritis. *Helicobacter* is not affected by gastric acid because of its ability to produce basic substances (e.g., ammonia). To actually cure the patient (i.e., heal the ulcer), it is necessary to eradicate the bacteria using drug combinations (e.g., usually a proton pump inhibitor and antibiotics).

6.1.1 Proton pump inhibitors (PPI)

Proton pump inhibitors belong to a group of drugs inhibiting the production of HCl, as they irreversibly block the H+/K+ ATPase (i.e., gastric proton pump). This enzyme resides on the luminal side of parietal cells (covering the epithelium) of stomach mucosa. When inactivated, the transport of H+ ions into the gastric juice is inhibited as well as the formation of HCl. As a result, these drugs block both the basal and stimulated secretion of gastric acid, no matter the stimulus. Their effect is dose-dependent. Their half-life is about one hour, but due to the fact that they bind irreversibly to their receptor site, the effect is prolonged until new proton pump molecules are created. PPIs are usually taken once daily. The drugs themselves are prodrugs (i.e., becoming active metabolites in the acidic environment of parietal cells) and are classified as poor bases. To generate the desired effect, the molecule must enter parietal cells in its prodrug state. When given orally, the drug is encapsulated in an acid resistant structure ensuring that it does reach the parietal cell in its inactive, prodrug form. Then, the PPI is mostly absorbed in the small intestine. Intravenous administration is also possible and is used

for acute bleeding of the upper gastrointestinal tract or when a drug cannot be given to the patient orally.

The first introduced PPI for clinical use was **omeprazole**, followed by **lansoprazole**, **pantoprazole**, **esomeprazole,** and **rabeprazole**. All substances listed above bind extensively to plasma proteins and there is a very little difference in their clinical use. Most PPIs are metabolized (at least partially) via the enzymatic system by cytochrome P450 (CYP). Omeprazole and esomeprazole are proven inhibitors of cytochrome, mainly the isoenzyme, CYP2C19, which is the reason there is a high risk of clinically significant interactions (with other drugs administered simultaneously). Rabeprazole, which has only recently become registered in the Czech Republic, is mostly metabolized non-enzymatically and only in a small part through cytochrome, which is seen as an advantage. Rabeprazole is able to block the proton pump more quickly than other PPIs.

PPIs are indicated mainly for oesophagitis, gastropathy due to NSAIDs, secondary peptic ulcers, as a part of *Helicobacter pylori* eradication treatment, and in Zollinger-Ellison syndrome. Proton pump inhibitors are well-tolerated by both adults and children; side effects are usually moderate, such as dyspepsia, headache, nausea, and vomiting. Defects in haematopoiesis or defective vision (e.g., blurred vision) rarely occur. Currently, PPIs are the first choice for ulcer treatment and outshine some of the substances mentioned below.

6.1.2 H$_2$ antihistamines

Histamine H$_2$ antagonists are another group of drugs which inhibit stomach acid production as they block the action of histamine at H$_2$ receptors on parietal cells in the stomach.

Cimetidine was the first to be used, but was soon withdrawn due to its serious side effects (i.e., it is mainly anti-androgen in nature causing e.g., gynecomastia in men). Other, structurally similar compounds followed, such as **ranitidine** (three times more effective than cimetidine) and **famotidine** (lasting longer than ranitidine). However, both these compounds have fewer side effects than cimetidine and are still used. **Nizatidine** and **roxatidine** are H$_2$ blockers, as well, but are not registered in the Czech Republic.

H$_2$ antihistamines are usually taken orally, but it is also possible to administer them parenterally. Not only are the newer substances more effective and safer to use, they also do not influence cytochrome enzymes as much as does cimetidine. Their side effects are quite rare and rather mild – headache, nausea, constipation, diarrhoea – to name a few. The indication is the same as for PPIs, which are preferred because H$_2$ antagonists are not as effective. Although, they have the advantage of a lower price.

6.1.3 Selective parasympatholytics

Selective parasympatholytics are no longer used to lower the production of stomach acid. **Pirenzepine** acts as a competitive antagonist of M$_1$ receptors in paracrine cells (which release histamine). It is not as effective as previously mentioned drugs; furthermore, it can cause typical anticholinergic side effects. As a result, pirenzepine is neither used nor registered in the Czech Republic.

6.1.4 Antacids

Antacids are weak bases, which neutralize hydrochloric acid in stomach. As the pH in the stomach rises, it influences the production of pepsin and may interfere with the absorption of other medications or even create complexes with some drugs. At least a two-hour time gap is necessary before taking other medications if an antacid has been consumed. Antacids act quite fast, but their effect doesn't last very long. Therefore, is necessary to take them repeatedly; up to 6-8 times a day. Antacids are mainly used to treat mild discomfort, such as pyrosis (heartburn), dyspepsia with hyperacidity, or mild gastroesophageal reflux disease (GERD).

Antacids only treat symptoms and are no longer used for gastric ulcer treatment. It is recommended to only take them for a short period of time because their ions may be absorbed (Na^+, Mg^{2+}, Ca^{2+}), which results in their increased levels in blood. Through their effect, systemic and local antacids can be distinguished.

Systemic antacids

$NaHCO_3$ (baking soda, sodium bicarbonate) is absorbed in the stomach, but at the same time, it works to very quickly neutralize hydrochloric acid. The problem with this process is the generation of CO_2, which is formed as a by-product of the reaction. Carbon dioxide often causes discomfort in patients and can also lead to hypersecretion of gastric juice.

Local antacids

$CaCO_3$, **$MgCO_3$**, **$Mg(OH)_2$**, **$Al(OH)_3$**, **$Mg_2(SiO_3)_3$**, and **hydrotalcite** are absorbed rather insignificantly. Although, $CaCO_3$ is absorbed at around 10% of the administered dose and is sometimes counted among systemic antacids. $Al(OH)_3$ not only neutralizes gastric acid, but also creates a protective layer to shield stomach mucosa. When $Mg_2(SiO_3)_3$ is taken, SiO_2 is released. SiO_2 binds to HCl and pepsin and creates a protective layer, as well. Hydrotalcite (aluminium magnesium hydroxide carbonate hydrate) has a prolonged effect due to its formation of a grid-like structure. These different compounds are often found together in medicines combining antacid substances. To prevent gastrointestinal discomfort, magnesium and aluminium ions counteract each other's respective side effects; therefore, these two elements make an optimal combination (i.e., Mg^{2+} is laxative, Al^{3+} is constipating).

6.1.5 Mucosal protectants

This class of drugs includes chemicals of various structures, all of which have a local protective effect on gastroduodenal mucosa. They are used to treat gastroesophageal reflux disease, gastric ulcers, and to prevent gastric ulcer relapse.

Sucralfate is a complex of aluminium hydroxide and sulphated sucrose, which creates a protective layer around the ulcer. It binds to proteins in the necrotic tissue and prevents further progression of the ulcer caused by stomach juice. Furthermore, it stimulates the production of cytoprotective prostaglandins and improves blood flow in the capillaries of the mucosa, which leads to a faster recovery. For sucralfate to be effective, there must be an acidic environment in the stomach. Therefore, it is given on empty stomach. Also, it is not to be combined with any of the antiulcer or antacid drugs mentioned above. The most common

side effect are constipation, dyspepsia, and the accumulation of Al^{3+} ions in patients with renal insufficiency. It can also interfere with the absorption of some drugs (e.g., tetracycline, digoxin).

Bismuth salts (citrate, salicylate) interact with the proteins of ulcers and newly formed complexes create a protective layer. Bismuth salts stimulate prostaglandin secretion as does sucralfate. They also have a positive effect on *Helicobacter pylori* due to their antibacterial activity (mechanism of action not known), though they must be combined with other antibacterial drugs (e.g., registered combination of bismuth compound with metronidazole and tetracycline is available in a capsule form). When taking bismuth salts, discoloration of tongue and stool (i.e., black) may appear.

Alginate is a substance of natural origin, which can be transformed into a viscous gel in a low pH environment, which floats on top of the stomach content. Alginate is used to treat gastroesophageal reflux disease, since it prevents acidic stomach content escaping into the oesophagus. If reflux persists, the alginate layer with a nearly neutral pH is the first substance forced into the oesophagus. Alginate is often combined with antacids.

Synthetic prostaglandins (e.g., **misoprostol**, **enprostil**) still need to be registered for use as protective agents in the Czech Republic. They stimulate the production of protective mucus and lead to improved perfusion of the stomach mucosa. They cannot be used during pregnancy (i.e., they have an abortive effect). Side effects such as stomach ache and diarrhoea are quite common. Abroad, synthetic prostaglandins are used to prevent gastric ulcers in patients who are undergoing long-term treatment with NSAIDs.

6.1.6 Eradication of *Helicobacter pylori*

The occurrence of a gastric ulcer is a relapsing problem, often connected with the presence of *Helicobacter pylori* bacteria. For a successful recovery, it is necessary to test the patient for *Helicobacter* (invasive or non-invasive test) and secure its eradication when present. A successful eradication decreases the number of relapses to only occurring in 0-10 % of cases.

For treatment of *Helicobacter pylori* infection, "triple therapy" is used, which is given for seven days. It is a combination of a **PPI** and **two antibiotics** (e.g., amoxicillin, clarithromycin) or one antibiotic and one antimicrobial **chemotherapeutic** (e.g., metronidazole). If needed, bismuth salt can be also added in with these combinations.

6.2 Prokinetic agents

Prokinetic agents are substances that use different mechanisms to increase gastrointestinal motility by stimulating the smooth muscle of gastrointestinal tract. This leads to increased gastric emptying and
the intensification of peristalsis of the oesophagus and small intestine (i.e., improvement in gastroduodenal coordination). In clinical practice, we use substances affecting either the dopamine (D2 receptor antagonists) or serotoninergic system (5-HT4 receptors agonists) or which have a more complex effect (i.e., an effect on multiple systems).

Their indication is primarily a set of dyspeptic problems associated with delayed stomach

emptying (e.g., a feeling of fullness in the stomach, belching, flatulence, heartburn, nausea, and vomiting) and gastroesophageal reflux. Most of these substances also have antiemetic activity, most likely mediated by the blockade of D2 receptors in the chemoreceptor trigger zone located in the area postrema (near the centre for vomiting), which is outside the blood-brain barrier.

Metoclopramide acts as a D2 receptor antagonist and as an agonist of 5-HT4 receptors leading to acetylcholine release, which stimulates the motility of the gastrointestinal tract. This agent increases the tone of the lower oesophageal sphincter, thereby preventing gastroesophageal reflux. Metoclopramide crosses the blood-brain barrier affecting both peripheral and systemic effects, which may lead to the development of extrapyramidal disturbances (reversible). Other side effects that may occur during long-term therapy include elevated levels of prolactin.

Domperidone also acts as a D_2 receptor antagonist, but unlike metoclopramide, it barely passes through the blood-brain barrier and does not cause central side effects. However, it also causes prolactin release from the pituitary.

Itopride is prokinetic agent, which aside from being a D_2 receptor antagonist, has indirect cholinomimetic effects due to a blockade of acetylcholinesterase. An increase in prolactin levels is rare.

All prokinetic agents are administered preferably 15-30 minutes before a meal.

A previously widely used prokinetic agent is cisapride (agonist of 5-HT$_4$ receptors); however, due to its serious side effects, it is no longer used in clinical practice (i.e., due to a prolonged QT interval).

6.3 Spasmolytics of the gastrointestinal tract

Spasmolytics are diverse substances whose common feature is the ability to release spasms of the digestive tract´s smooth muscle. These are indicated as pharmaceuticals used to treat acute conditions (e.g., spasms of intestinal, biliary, and renal smooth muscles) and for the therapy of chronic diseases associated with hyperkinesia as well as hypertonia of the gastrointestinal tract (e.g., irritable bowel syndrome). Some can be used to relieve the spasms before diagnostic or therapeutic intervention (i.e., in endoscopy).

According to their mechanism of action, spasmolytics can be divided into **neurotropic** spasmolytics (i.e., effect is reached via the parasympathetic nervous system) and **musculotropic spasmolytics** (i.e., direct effect on the smooth muscle cells). Substances from both groups are combined to establish a reliable spasmolytic effect (contraindications can arise during the treatment of paralytic ileus). Spasmolytics are frequently administered along with analgesics (e.g., especially metamizole, codeine, and paracetamol). This combination is then called a spasmoanalgesic.

6.3.1 Neurotropic spasmolytics

Substances from the group of M receptor antagonists are used therapeutically as antispasmodics (see Chapter 2.2.3 Parasympatholytics). One such parasympatholytic agent with spasmolytic effects in the gastrointestinal tract is **atropine**; other agents (e.g., **tolterodine**, **trospium**, **oxybutynin**, **solifenacin**, and **darifenacin**) are rather uroselective, and they are used for the treatment of urinary incontinence or increased urinary frequency.

Atropine, which due to its structure passes through the BBB, has several central side effects. It is reported to act as a spasmolytic agent on the smooth muscle of gastrointestinal tract, but paradoxically, in the sphincter of Oddi and the urethral sphincter, it causes smooth muscle spasms. Atropine can be administered subcutaneously or intramuscularly and usually in combination with papaverine (see below).

Other substances used as spasmolytics include **butylscopolamine**, **otilonium**, and **fenpiverinium.**

Butylscopolamine contains a quaternary nitrogen in its structure; therefore, there is no penetration through the BBB. It has a spasmolytic effect on the smooth muscles of the gastrointestinal, urogenital, and biliary tracts. The adverse effects of butylscopolamine are typical of parasympatholytics (e.g., caution is necessary for patients with glaucoma, tachycardia, etc.), but in the case of butylscopolamine, the symptoms are milder than after atropine administration, for example.

Otilonium and **fenpiverinium** also have a spasmolytic effect on sphincters. Otilonium has a complex effect (making it sometimes classified among musculotropic spasmolytics) because, in addition to action on muscarinic receptors, it acts on tachykinin receptors and blocks Ca^{2+} channels. Fenpiverinium is often combined with musculotropic spasmolytics and analgesics; a combination used frequently consists of fenpiverinium, metamizole, and pitofenone.

6.3.2 Musculotropic spasmolytics

Musculotropic spasmolytics are drugs which directly relax smooth muscle cells via different mechanisms of action without affecting nervous system control. These include **papaverine** (opium alkaloid) and other more efficient substances derived from papaverine including **drotaverine, alverine, mebeverine**, and **pitofenone**.

Nowadays, **papaverine** is not used in clinical practice, nor is it used independently or in combined preparations, but **drotaverine**, with higher efficiency and fewer side effects, is available. The mechanism of action of these two compounds involves the inhibition of phosphodiesterase (PDE), an enzyme essential for the conversion of cAMP to AMP. Higher concentrations of cAMP decrease Ca^{2+} uptake in the cells and changes the distribution of calcium among the cells. Drotaverine may also have minor allosteric calcium channel blocking properties.

Alverine is a substance, which also inhibits PDE as well as blocks Ca^{2+} channels in smooth muscle cells. Today, it is used in combination with simethicone (i.e., a surfactant reducing the formation of gas and forming a silicon film on the mucosa of the digestive tract).

Mebeverine also has a direct effect on smooth muscle via several mechanisms, which are not fully understood. Most likely, these mechanisms involve blocking Na^+ and Ca^{2+} channels without anticholinergic effects (e.g., particularly suitable for irritable bowel syndrome).

Currently, **pitofenone** is only used in combination with other spasmolytics and analgesics, which can be used for the treatment of spastic dysmenorrhea.

6.4 Antiemetics

Antiemetics are drugs used for the treatment of nausea and vomiting, whether to reduce or completely relieve the symptoms. Substances with an antiemetic effect have different mechanisms of action, which are likely related to the different causes of nausea and emesis (e.g., pain, chemotherapy, psychological state, pregnancy, visual stimulus, and others). Drugs are available in different dosage forms (e.g., tablets, suppositories, injections, and infusions), which enable the selection of an appropriate form according to the urgency of the case.

Vomiting (emesis) is a defensive reflex of the body (involving expulsion of stomach contents). This is a difficult and complex process that involves not only the smooth muscles of the upper gastrointestinal tract, but also skeletal muscles (i.e., mainly muscles of the abdomen, diaphragm, etc.). The entire process is regulated in the **vomiting** (or **emetic**) **centre** located in the reticular formation of the medulla oblongata, which coordinates the muscles involved in emesis (via efferent pathways) in accordance with afferent stimuli from different places (e.g., the gastrointestinal system, coronary vessels, ganglion of the vagus nerve, vestibular system, area postrema, etc.).

Moreover, vomiting is regulated by the **chemoreceptor trigger zone**, which also lies in the medulla, but specifically, in the area postrema, wherein the blood-brain barrier is relatively permeable; thus, it is exposed to emetogenic agents found not only in the cerebrospinal fluid, but also in the blood. Depending which receptor system a substance works upon, we divide antiemetics into the following enumerated groups.

6.4.1 Muscarinic receptor antagonists

Scopolamine (hyoscine) is the only antiemetic drug in the group of muscarinic receptor antagonists. It is a compound which is structurally similar to atropine (also having a tertiary nitrogen); it acts as a non-selective antagonist at the muscarinic receptor, both in the peripheral and central nervous systems (the penetration of scopolamine into CNS is poor). It is mainly used to prevent motion sickness, and abroad, it is available mainly in the form of transdermal therapeutic systems applied on a hairless area behind an ear.

6.4.2 H_1 receptor antagonists

Some of the first generation H_1-antihistamines can be used as antiemetic agents (see Chapter 8.6.2.1). They penetrate the blood-brain barrier, and therefore, in addition to anti-allergic effects (also antimuscarinic), they also have central effects (e.g., sedation, antiemetic effect). These compounds are indicated mainly for the prophylaxis and treatment of motion sickness, vertigo, and vestibular disorders (e.g., Ménière's disease). Emesis in cancer patients is treated with H_1 antagonists after the application of cytotoxic drugs.

Moxastine (moxastine teoclate) can be combined with caffeine, which decreases the sedative or hypnotic effects of moxastine. Nevertheless, the medicine may influence driving capability or the operation of machinery as well as activities requiring quick judgment or working at heights due to its sedative effects. It can be administered to children from two years old on up; however, in some children and the elderly, it may paradoxically cause excitation instead of the expected sedation. In addition to the aforementioned side effects, hypotension and typical anticholinergic effects (e.g., dry mouth and urinary retention) may occur (especially in the elderly).

Embramine is used like moxastine against motion sickness and vertigo.

Dimenhydrinate has similar effects to the substances mentioned above; however, it is mainly used to treat motion sickness.

Promethazine has antagonistic effects on multiple types of receptors (e.g., cholinergic, histamine, alpha-adrenergic, and serotonin) resulting in its wider use, but it also has more side effects. Promethazine can be used for morning sickness during pregnancy (on the rare occasions when emesis is so severe that drug treatment is justified). Promethazine is also used for the treatment of allergic reactions.

6.4.3 D_2 receptor antagonists

The blockade of dopamine D_2 receptors in the chemoreceptor trigger zone includes compounds of several pharmacological classes (e.g., some neuroleptics and prokinetics). Antiemetic drugs with prokinetic effects include centrally acting **metoclopramide** and **domperidone**, which permeates the blood-brain barrier minimally, and its antiemetic effect is probably mediated by a combination of partial peripheral and central activity.

Both substances can be used for prophylaxis and the therapy of nausea and vomiting induced by chemotherapy, radiotherapy, or acute migraine; domperidone can also be used to treat the nausea and vomiting caused by other drugs (e.g., dopamine agonists, which are used to treat Parkinson's disease). The dose of these antiemetic drugs must be increased often to achieve sufficient antiemetic effects, which, in the case of metoclopramide, causes serious side effects.

Itopride also has an antiemetic effect through blockade of D_2 receptors in the chemoreceptor trigger zone.

Thiethylperazine and **droperidol** are the most commonly used antiemetic neuroleptics. They are used primarily for severe forms of emesis. Droperidol is indicated for the prevention and treatment of postoperative emesis. Thiethylperazine, in addition to D_2 receptor antagonism, acts directly in the vomiting centre (likely blocking autonomous impulses of the vagus nerve) and can be used for the treatment of vertigo (both of central and vestibular origin), the prevention and treatment of nausea, and vomiting after surgery, radiotherapy, in gastrointestinal diseases, etc. Unwanted effects of these substances commonly arise from their central action (e.g., sedation, extrapyramidal symptoms including dystonia and tardive dyskinesia, agitation, etc.; see Chapter 3.1.4 for more information).

Other substances from the group of neuroleptic drugs which have antiemetic activity are **haloperidol**, **perphenazine**, and **prochlorperazine**.

6.4.4 5-HT3 receptor antagonists (setrons)

5-HT_3 receptors antagonists (known as "*setrons*") act in both the chemoreceptor trigger zone and the periphery (especially the GIT). They are most effective in the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV), radiation-induced nausea and vomiting, and postoperative nausea and vomiting. **Ondansetron** was the first drug on the market; later, **granisetron** (with longer biological half-life) and **palonosetron** (highly selective antagonist) were authorized. Unwanted effects are relatively uncommon, but if present, they mainly manifest as headache and constipation or diarrhoea, hypotension, and QT prolongation. The concomitant administration of glucocorticoids significantly increases the efficacy of 5-HT_3 antagonists in preventing both acute and delayed CINV.

6.4.5 NK1 receptor antagonists

Aprepitant is a newer antiemetic chemical compound, which belongs to a class of drugs called substance P antagonists. Aprepitant is a highly selective antagonist of NK_1 receptors, which are highly expressed in the brain (medulla oblongata) as well as in the periphery (vagal afferent nerves). Substance P (i.e., a neuropeptide that induces vomiting) is an agonist at NK_1 receptors, which are likely to play a role in the late phase of emesis caused by cytotoxic drugs.

Due to its distinct mechanism of action, aprepitant may also be administered in combination with setrons and glucocorticoids. This triple combination is often used for preventative purposes in highly emetogenic chemotherapy. Unwanted effects include increased ALT, headache, dizziness, and weakness (not usually a reason to discontinue treatment). Aprepitant affects CYP3A4 (inhibitor and inducer); therefore, attention must be given to possible interactions with concomitantly administered drugs.

6.4.6 Other drugs

Glucocorticoids, on top of their synergistic effect with setrons, have their own antiemetic effect (i.e., mainly effective for delayed emesis), the mechanism of which is still not clarified. Mainly dexamethasone and methylprednisolone are used for this indication.

Benzodiazepines have no direct anti-emetogenic effect, but have proven to be complementary with anxiolytic therapy and in patients with reflexive vomiting.

Pyridoxine (vitamin B6) has an antiemetic effect in higher doses than commonly administered for the treatment of hypovitaminosis. Likewise, active ingredients (e.g., zingiberene and zingiberol) found in ginger rhizomes (*Zingiber officinale*) are used to relieve nausea and emesis and are primarily chosen for use in mild forms of hyperemesis gravidarum.

6.5 Laxatives

Laxatives (purgatives) are medicines, which accelerate the passage of food through the intestine and facilitate emptying of the intestinal contents. They are used for the treatment of constipation (particularly acute) and painful affections of the rectum, but also for cleaning of the bowel prior to surgery or examination. Constipation is defined as a decreased frequency of elimination or a strenuous bowel movement and should be assessed individually as compared to the patient's normal rhythm (i.e., assessing the change in consistency). Causes of constipation may differ; causes include dietary lapse, a lack of movement, lack of fluids, ongoing disease, or drug side effects (e.g., opioid analgesics, antihistamines, iron preparations, etc.). First, reduction or elimination of constipation by non-pharmacological means of dietary and lifestyle changes is attempted. Then, upon failure to relieve symptoms, pharmacological therapy is pursued. According to their mechanism of action, laxatives can be divided into the following groups.

6.5.1 Volume (bulk) laxatives

Indigestible polysaccharides can bind water and swell, thereby increasing intestinal contents and reflexively stimulating peristalsis. Sufficient fluid intake is necessary to support the effect of these substances, otherwise they may cause constipation to worsen. Natural polysaccharides are contained the **seeds of Indian plantain** (*Plantago psyllium*), **flaxseed**, **agar**, and **tragacanth**. These can also be used with a high fibre diet. Among the semisynthetic sources of polysaccharides, **methylcellulose**, **ethulose**, and **carboxymethyl cellulose** are included.

6.5.2 Salinic laxatives

The salts of strong acids and bases are poorly absorbed by the intestinal mucosa, but they become ionized and remain in the lumen of the bowel, wherein they trap increased volumes of fluid and accelerate the transfer of gut contents through the small intestine. This results in an abnormally large volume entering the colon, causing distension and purgation within about an hour. Abdominal cramps may occur. Sufficient fluid intake is required. **Magnesium sulfate**, **sodium sulfate** (Glauber's Salt), and natural **mineral waters** (Šaratice, Zaječická hořká / Saidschitzer Bitter-wasser etc.) are laxatives that fall into this category. These salts should not be used for small children and patients with poor renal function or heart failure (i.e., this can lead to partial absorption of Na^+ and Mg^{2+} ions as well as to a great loss of electrolytes).

6.5.3 Osmotic laxatives

These agents include compounds which have the same mechanism of action as saline purgatives (often classified altogether in one group). They are the sugar alcohols, which are not absorbed in the intestinal lumen and act therein as an osmotically active substance. This is a safe group of laxatives and can be used for children and the elderly and during pregnancy and lactation.

Lactulose is a disaccharide (fructose and galactose) *which* is degraded in the *colon* by bacterial microflora to simple organic acids (mainly lactic acid). Reduced pH in the gut causes an increase in osmotic pressure. This leads to increased water content in the faeces, thus a larger and more softened volume. Lactulose is administered orally as a syrup, and the laxative effect usually starts within 24 to 48 hours. Indications are habitual constipation, stool softeners, and hepatic encephalopathy (using the probiotic effect of lactulose).

Glycerol is only administered per rectum as suppositories. It is used to train the defecation reflex, in acute intermittent constipation, and it can be used to facilitate defecation during pregnancy and lactation.

Sorbitol and **macrogol 4000** are used (e.g., usually in the form of a rectal or oral solution) to prepare a patient before, for instance, endoscopic or radiological examination or prior to surgery in the colon.

6.5.4 Stimulant laxatives

The stimulant (i.e., contact) laxatives are substances directly irritating colonic mucosa and increasing peristalsis. They cause retention of water and electrolytes in the gut lumen, soften the stool, and stimulate defecation. These drugs are particularly indicated for acute constipation.

They should not be used long-term or at high doses because this can lead to abdominal cramping, dehydration, electrolyte imbalance, and the risk of damage to intestinal smooth muscle and its atony. Mucous membrane irritation enables easy absorption of toxic substances, which is why these laxatives are not indicated in poisoning. Their effect occurs after 6-8 hours. They are contraindicated for children, inflammatory bowel disease, and are not recommended during pregnancy and lactation.

This group contains plants whose active substance, **anthraquinones**, are derived from the leaves and fruits of senna, aloe juice, and rhubarb root as well as the synthetic drugs, **bisacodyl** and **sodium picosulphate** to give a few examples. Drugs are available on the market in multiple drug dosage forms, such as oral drops, tablets, and rectal suppositories.

6.5.6 Peripheral opioid receptor antagonists

These are among the latest class of drugs which have been designed to treat constipation caused by opioid analgesics (if other laxatives are ineffective). **Methylnaltrexone** is the only registered drug in this class which acts as a selective antagonist on the peripheral μ-receptors

(i.e., due to its structure, it does not pass through BBB). It is administered subcutaneously in adults over 18 years old.

6.6 Anti-diarrhoeal agents

Anti-diarrhoeal drugs are used for the treatment of diarrhoea. Diarrhoea can be defined as frequent emptying of a runny and unformed stool, but this requires an individual assessment in each patient. Diarrhoea can occur for various reasons, with a mild to life-threatening course. The primary complication of massive and prolonged diarrhoea is dehydration caused by the loss of large amounts of water, salt, and nutrients causing a disintegration of the internal environment of the organism (i.e., loss of ions, especially K^+). Thus, the most vulnerable groups are small children and older people (especially if they are being treated with diuretics, digoxin, etc.).

Diarrhoea requires different treatment in accordance with its cause, which can vary from dietary lapse or intestinal infection to anxiety or the side effect of certain drug. Appropriate pharmacotherapy is necessary to supplement adequate rehydration (rehydration solutions) and proper nutrition (e.g., rice, bananas, carrots, or biscuits). Prebiotics and probiotics are used as a preventive and supportive treatment. Anti-diarrhoeal drugs include compounds with different mechanisms of action by which they are divided into the following groups.

6.6.1 Intestinal adsorbents

Intestinal adsorbents are surface-active substances (i.e., surfactants) with a nonselective effect, which have the ability to bind the gases, toxic substances, and other materials (i.e., forming inactive complexes). These agents are not absorbed in the organism after oral administration and are excreted in faeces. They are a suitable treatment option for most diarrhoea (e.g., dietary lapse, toxins, etc.), but they must be administered in a sufficient dose and with caution given to possible interactions of concomitantly administered drugs.

The adsorbents include activated carbon (i.e., adsorbent/medicinal carbon or activated charcoal) and diosmectite. **Activated carbon** is available in tablet form. It can be administered to patients three years of age and up, and it is helpful to remember that the stool will be black in colour upon treatment with this substance. There are also products in which activated charcoal is combined with bismuth (i.e., causing astringent effects) and sodium thiosulfate (i.e., causing a laxative effect).

Due to its structure, **diosmectite** has high plastic viscosity and a mucoprotective effect, and its use is not limited by age.

6.6.2 Intestinal antiseptics

Intestinal antiseptics are used primarily to treat diarrhoea with an infectious aetiology (e.g., traveller's diarrhoea). If their expected effect fails, it means the cause of the infectious diarrhoea is severely pathogenic and requires more aggressive therapy with antibiotics or

antibacterial chemotherapeutics.

Chloroxine is the only OTC drug in the group of intestinal antiseptics. It has significant bacteriostatic, fungistatic, and antiprotozoal properties. It should not affect normal intestinal flora and can be administered to children over 40 kg.

Nifuroxazide is indicated for the treatment of acute bacterial diarrhoea with no signs of invasion. It is not absorbed from the GIT and acts only locally on the intestinal wall.

Rifaximin may be used to treat both acute and chronic diarrhoea caused by both G+ and G-bacteria as well as diarrhoea caused by the disruption of intestinal microflora. Its advantage is minimal absorption from the gastrointestinal tract, and its mechanism of action is RNA synthesis suppression.

6.6.3 Antipropulsives (opioids)

Antipropulsives are grouped with anti-diarrhoeals, both of which decrease intestinal motility by stimulating opioid receptors (μ mainly) in the GIT. Drugs in this group should be administered for diarrhoea of non-infectious origin (e.g., psychogenic) or when diarrhoea persists even after the cause has been eliminated. Anti-diarrhoeal agents which lower peristalsis are contraindicated for infectious diarrhoea (e.g., bloody stool, fever being symptoms), ulcerative colitis, and wherever the loss of peristalsis means serious consequences (e.g., toxic megacolon).

Loperamide is an OTC drug, which, in addition to the above effects, increases the tone of the anal sphincter and mainly operates selectively on the intestinal wall.

Diphenoxylate has a higher risk of penetrating the CNS (especially at higher doses), so side effects typical of opioids may be observed (see Chapter 8.3 Opioid analgesic drugs). This is the reason a medical prescription it is required in order for it to be dispensed in the pharmacy. Diphenoxylate may be combined with atropine allowing its use at lower doses.

6.6.4 Other anti-diarrhoeal agents

Racecadotril is among the latest drug intended for the treatment of acute diarrhoea. It acts as an anti-secretory (mainly in intestine) by blocking enkephalinase, an enzyme involved in the hydrolysis of exogenous and endogenous peptides (e.g., enkephalins). Racecadotril can be administered to adults, infants (i.e., from three months upward), and children (e.g., as a supplement to rehydration).

Cholestyramine is a non-absorptive ion exchanger, and in addition to bile acid diarrhoeal treatment, it is used as a hypolipidemic agent.

Octreotide is a synthetic derivative of somatostatin. It has similar, but longer-lasting, pharmacotherapeutic effects. It can be used to alleviate diarrhoea, for instance in carcinoid tumours, glucagonomas, and after a jejunostomy.

The intestinal astringents are substances of natural origin which contain **tannins** (e.g., black tea, blueberry fruit, rhizome of *Potentilla erecta*, etc.), which are responsible for their anti-diarrhoeal effect. They are able to denature the proteins of the intestinal wall, thus facilitating coagulation through the creation of membrane capturing microbes and preventing excessive secretion.

Eubiotics (**synbiotics**) are substances modulating the gut microflora. They are a mixture of prebiotics and probiotics. The correct composition of the intestinal environment is important for digestive processes, immunity, and to maintain intestinal barrier function.

Prebiotics are indigestible substances for eukaryotic cells (e.g., in humans), but act as substrates for the enzymes of prokaryotic microorganisms. They are often referred to as a food for probiotics, which allows them to grow and proliferate. Among prebiotics belong oligosaccharides (lactulose), polysaccharides, fibres, fibre cleavage products (e.g., pectin, cellulose), and B vitamins.

Probiotics are cultures of live microorganisms that have beneficial effects on colon flora. They are mainly of the following genera: *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces*. Probiotics destroy other unsuitable microorganisms (i.e., by outcompeting them for food sources), constitute the substrates involved in the regulation of intestinal functions, and participate in the enzymatic digestion of food. The source of probiotics may be quality-controlled fermented milk products or OTC products, mostly in the form of tablets and oral solutions. Their indications are diarrhoea, flatulence, constipation, dyspepsia, irritable bowel syndrome, colitis, and the prevention of diarrhoea caused by antibiotics as well as other causes.

7. Treatment of metabolic disorders and pharmacology of endocrine system

7.1 Treatment of diabetes mellitus

In the Czech Republic, approximately 8% of people have been diagnosed with diabetes mellitus. Around 5% of diabetic patients suffer from the insulin-dependent (type 1) form, while non-insulin-dependent diabetes (type 2) accounts for 94% of cases. The remaining 1% represents other types of the disease such as secondary diabetes.

Type 1 diabetes is an autoimmune disorder leading to the destruction of pancreatic β cells. It usually manifests in childhood. Currently, there are approximately 1,000 children younger than 15 years of age suffering from this type of diabetes in the Czech Republic. The incidence over the last 10 years has not changed; however, the number of patients with **type 2** diabetes has continued to increase. This type of diabetes is characterised by peripheral tissue resistance to the effects of insulin.

Diabetes, called **LADA** (latent autoimmune diabetes of adults), is a form of type 1 diabetes which develops during adulthood. It may be related to an immune reaction to a viral infection. **MODY** (maturity onset diabetes of the young) refers to a group of monogenic disorders which manifests as type 2 diabetes. It is autosomal dominant and is based on a disruption in pancreatic β cell regulation.

Gestational diabetes may develop in the 26th to 28th week of pregnancy due to hormonal changes. Should insulin resistance develop during this period, complications in the pregnancy, delivery, and overall health of the newborn (e.g., high body weight, urinary tract infections, hypoglycaemia, neonatal jaundice, etc.) may occur. It also seems to predispose offspring to glucose tolerance distortions in adulthood.

Secondary diabetes may follow other diseases (e.g., chronic pancreatitis, Cushing's syndrome) or may be induced by pharmacotherapy (e.g., steroid-induced diabetes after glucocorticoid treatment).

Inadequate compensation of diabetes leads to micro- and macroangiopathies, which typically manifest as nephropathy, worsening eyesight, and wound-healing complications. Another hallmark symptom of type 2 diabetes is neuropathy, which is responsible for neuropathic pain and the so-called diabetic foot. In 2011, there were approximately 10,000 diabetic patients who had undergone surgery to amputate a limb.

7.1.1 Insulin therapy

The first insulin used for experimental treatment of diabetes was administered to humans in 1922. Till then, type 1 diabetes was a lethal condition. This experimental "drug" was a substance isolated from bovine pancreatic juice. Later, purified **animal insulins** were introduced and became a routine treatment for diabetes. These preparations were isolated from bovine or swine pancreata. These animal insulins differ from human insulin by their amino acid structure. Swine insulin is closer to human insulin, but it is still not structurally identical. Due to the difference in structure along with inadequate purification procedures, adverse allergic and anaphylactic reactions were common occurrences. Nowadays, only highly purified human insulin and their analogues are used, both being products of recombinant biotechnology methods. These preparations have minimal risk of immune system activation.

7.1.1.1 Insulin effects

Physiologically, insulin binds to the insulin receptor, which is a membrane receptor linked to tyrosine hydroxylase activity. After its activation, a cascade of reactions is initiated leading to anabolic metabolism. This increases the transport of glucose and amino acids to the cell, intensifies their utilization, protein synthesis, and glycogen synthesis, increases triacylglycerol (TAG) formation, and supresses catabolic processes, such as β-oxidation and glycogenolysis. Likewise, gluconeogenesis is decreased. As a result, blood glycaemia is decreased. Insulin is usually administered subcutaneously, but inpatients may receive it intravenously. Subcutaneous administration can be performed by the patient him-/herself using insulin pens or automatically via an insulin pump. Patients are also educated as how to regularly self-monitor the level of blood sugar in their peripheral blood by a glucometer and assessment of glycosuria and ketonuria using urine strip test kits.

The most dangerous side effect of insulin treatment is **hypoglycaemia**. It may occur when the patient administers insulin, but does not consume enough food or exercises more than planned. Another reason for the occurrence of hypoglycaemia may be infectious disease with high fever. In this case, the dose of insulin should be properly adjusted. Severe hypoglycaemia resulting in coma is preceded by symptoms of sympathetic (e.g., tachycardia, skin pallor, sweating, tremor) and parasympathetic (e.g., hunger, nausea) activation. Other symptoms are neurological (e.g., irritability, aggressiveness, sleepiness, seizures, and coma). Noteworthy, sympatholytic drugs (especially β-blockers) may mask the symptoms of hypoglycaemia and the patient may fall unconscious very quickly (coma treatment is discussed later).

Other side effects of insulin therapy are **lipodystrophy** of the subcutaneous tissue (i.e., loss of adipose tissue) on an immunological basis. This may develop after repeated administration of insulin to the same area. The preventive measure is regularly switching the administration site (e.g., upper arm, thigh, gluteus, and abdomen). Generalized **allergic reaction** to modern insulins is rare, but a local reaction may occur (e.g., redness, swelling, and itching). It usually normalizes within few days.

7.1.1.2 Types of insulin preparations

Insulins are used mainly for the treatment of type 1 diabetes; however, even patients with the type 2 disorder may benefit from insulin therapy. There are a variety of human insulin preparations and insulin analogues.

Human insulins

These preparations are recombinant products which have the same amino acid sequence as endogenous insulin.

Short-acting human insulins are clear molecular solutions which can be administered 20-30 minutes before meal. This time is required to initiate their effect, whereas peak plasma concentration occurs 1-2 hours after administration. The total time of the effect is expected to be between six and eight hours. It is possible to prolong the effect by mixing the insulin with protamine and Zn^+ cations.

Intermediate-acting human insulins are marked as NPH or the isophane type of insulin. They are suspension formulations which require shaking before administration and can never be administered intravenously. Insulin is slowly released from the subcutaneously administered deposit and its pharmacokinetic profile is modified: The onset of the effect appears after 1-2.5 hours; peak plasma concentration occurs 4-12 hours after administration, and the effect is present altogether for 12-16 hours.

Two different types of insulin may be combined in some preparations. These are stabilized insulin mixtures usually containing a short-acting human insulin and NPH insulin in a suitable ratio (e.g., available preparations contain different ratios, such as 30:70). These mixtures are used in dosage regimens in which short and intermediate insulins are used at the same time. Single dose administration is comfortable for the patient, and there is a low risk of confusion in home care.

Insulin analogues

Insulin analogues are peptides prepared using recombinant technology and differ from human insulin by amino acid sequence. These changes are designed to alter the solubility in subcutaneous tissue and by extension the pharmacokinetic profile of the product.

Ultrashort-acting analogues are administered immediately before a meal. The onset of their effect occurs within minutes after injection, peak plasma concentration occurs after approximately 30 minutes, and the effect ends after 3-4 hours. These analogues closely mimic physiological postprandial insulin secretion. There are currently three ultrashort analogues: **lispro**, **aspart**, and **glulisine**.

Long-acting insulin analogues are administered only once a day. Their effect starts after 1-2 hours and persists for 24 hours. They mimic basal insulin secretion with no apparent concentration peaks. There are currently three long-acting analogues: **glargine**, **detemir**, and **degludec**.

Likewise, as human insulin preparations can be combined, there are also combinations of the analogues. These products are called biphasic analogues and contain an ultrashort analogue with a prolonged release insulin in protamine complex. The long-acting insulin resembles human NPH insulins with its pharmacokinetics. Biphasic analogues are administered twice a day and substitute both basal and postprandial insulin secretion.

7.1.1.3 Insulin regimens

Administration of insulin in home care is organized as regular dosing schemes, or administration regimens. These also require regular self-monitoring of glycaemia and ketonuria. In patients with partial endogenous insulin production, a **conventional regimen** can be employed. It consists of subcutaneous insulin administration once or twice a day. There are different types of conventional protocols:

- Intermediate-acting human insulin once a day,
- Long-acting insulin analogue once a day,
- Stabilized mixture of human insulins once or twice a day, and
- Biphasic analogues once or twice a day.

Intensified regimens require three or more insulin injections a day or continuous delivery via an insulin pump. Generally, these regimens are more demanding for the patient (e.g., exact timing, more injections, stringent hygiene, etc.), but they better mimic physiological insulin secretion. There are several schemes:

- Short-acting insulin before meals, three times per day,
- Ultrashort-acting insulin analogue before meals, three times per day,
- NPH insulin once a day + ultrashort-acting analogue before meals, three times per day,
- Long-acting analogue once a day + ultrashort-acting analogue before meals, three times per day,
- Biphasic analogues three times per day, and
- Insulin pump regimen consisting of basal-bolus administration.

Insulin pumps always deliver (ultra-) short-acting insulin in the form of basal-bolus administration; in other words, they automatically maintain the basal insulin level at a pre-set time or depending on the results of glycaemic monitoring (still in development). On top of acting as a basal delivery system, it also administers prandial boluses. Patient needs to change the cannula every three to five days as well as the insulin cartridge and batteries. Cannulas are most commonly inserted into the abdominal or gluteal subcutaneous tissue. In 2012, there were 80 thousand insulin pump users in the Czech Republic.

Treatment of type 1 diabetes may sometimes be intensified by **metformin**, an oral antidiabetic drug. This combination allows the required insulin dose to be gradually decreased.

7.1.2 Oral and new antidiabetic drugs

Treatment of type 2 diabetes requires lifestyle adjustments, such as diet, exercise, and administration of antidiabetic drugs. The classical antidiabetics are administered orally, hence the name oral antidiabetic (OAD). Recently, new antidiabetic preparations were developed and introduced into clinical practise; they are usually listed under the OADs, but these are administered subcutaneously. For this reason, we divide the antidiabetic drug classes as follows:

- classical oral antidiabetics – biguanides, sulphonylurea derivatives, meglitinides (glinides), thiazolidinediones (glitazones), and α-glucosidase inhibitors and
- new antidiabetics administered orally or subcutaneously – incretin mimetics, gliflozins, and amylin analogues.

7.1.2.1 Biguanides

Biguanides are oral antidiabetics, originally based on naturally occurring glucokinins found in the tops of bilberry (*Vaccinium myrtillus*, family Ericaceae) and galega (*Galega officinalis*, family Fabaceae) plants. These herbs were traditionally used in herbal infusions for the treatment of diabetes. Later, the active compounds responsible for the hypoglycaemic effect were identified and served as model compounds for the synthesis of the antidiabetic drugs, biguanides.

Metformin is the only drug in this group still in use. It is also the first-choice medication for use in obese patients with type 2 diabetes. Considering obesity and insulin resistance are closely correlated, this drug happens to be the most widely used antidiabetic drug as well as one of the most prescribed drugs (belonging to the top 20 list in the Czech Republic and top 10 in the USA).

Metformin is an insulin sensitizer, but its exact mechanism of action is not fully explained. It decreases insulin resistance, enhances glucose utilization in skeletal muscles, stimulates anaerobic glycolysis, and decreases hepatic gluconeogenesis. Another beneficial feature is use carries no risk of inducing serious hypoglycaemia.

Adverse effects of metformin are GIT problems, taste distortions (i.e., a metallic taste in the mouth), and rarely, lactic acidosis. Lactic acidosis is provoked by several factors combined (e.g., renal dysfunctions, stress, hypoxia, etc.) and is correlated with metformin accumulation in the body. Decreased gluconeogenesis, which uses lactate in normal situations, leads to severe disruption of acid-base homeostasis. Chronic treatment with metformin may increase the patient's requirement for vitamin B_{12} and folic acid supplementation. There exists the possibility of developing B_{12} deficiency with prolonged use, but clinical evidence remains insufficient.

7.1.2.2 Sulphonylurea derivatives

The hypoglycaemic effect of sulphonylurea (SU) derivatives was discovered accidentally in research on sulphonamide chemotherapeutics. SU derivatives belong to the insulin-releasing drug group, secretagogues. Their mechanism of action is an interaction with the K^+ channel on the pancreatic β-cell membrane. SU binding leads to depolarization and exocytosis of stored insulin vesicles.

SUs are taken before meals so they can support the postprandial insulin secretion. Their effect requires partially conserved pancreatic secretion. Beside their direct effect on insulinemia, they also enhance peripheral sensitivity to insulin, influence expression of glucose transporters (GLUT 1-13), and inhibit hepatic gluconeogenesis. SUs are usually taken two to three times per day. Their dose needs to be adjusted in accordance with their glycaemia and ketonaemia status.

Their pharmacokinetics are problematic due to high plasma protein binding (i.e., up to 98%). Some drugs may compete with SUs at the binding sites leading to severe hypoglycaemia. The majority of SUs are excreted in urine; therefore, they are contraindicated in patients with renal impairment who would be at higher risk of having hypoglycaemic episodes.

Hypoglycaemia is the most common adverse effect of SUs occurring in all patients, even those with no renal impairment, co-morbidities, or drug interactions. Similarly, as in insulin treatment, in SU administration, it is necessary to follow regular daily routines, especially regarding eating habits. Other adverse reactions are GIT problems (e.g., nausea, flatulence, etc.), rarely blood count disorders, hepatopathies, eyesight distortions, and skin reactions. SUs are not suitable for obese patients as they may cause an increase in appetite and body weight.

First generation drugs, tolbutamide and chlorpropamide, are not used anymore. Second generation drugs have a better safety profile. Second generation drugs are **glibenclamide**, **glimepiride**, **glipizide**, **gliclazide**, and **gliquidone**. Gliclazide is available in a slow-release drug dosage form, which can be used once daily. Gliquidone is the only SU drug not excreted in urine and can be safely used in renally impaired patients. SUs can be combined with metformin.

7.1.2.3 Meglitinides (glinides)

Another class of insulin releasing drugs are glinides. Their mechanism of action resembles SUs (i.e., due to the interaction with the K^+ channels on β-cells), but they bind to a different site. They are used orally before meals (three to four times daily), and their dose needs to be adjusted in accordance with glycaemia and ketonaemia values. They are excreted in the bile. Common adverse reactions are GIT problems (e.g., bellyaching, dyspepsia, nausea) and episodes of hypoglycaemia. Rare adverse effects are hepatopathies, skin reactions, and eyesight disorders. Both **repaglinide** and **nateglinide** can be combined with metformin. Glinides have a lower effect on appetite leading to lower risk of body weight gain.

7.1.2.4 Thiazolidinediones (glitazones)

Thiazolidinediones belong to the insulin-sensitizer family. Their mechanism is based on interaction with PPARγ receptors. PPAR (peroxisome proliferator-activated receptors) are nuclear receptors found in cytoplasm. After binding to a ligand, a complex is formed and transported into the nucleus. There, it binds to the responsive elements of DNA, which regulate the transcription of the genes responsible for catabolism and anabolism of lipids. PPARγ are primarily present in adipose tissue, wherein they regulate adipocyte differentiation and lipid anabolism.

Thiazolidinediones are agonists of PPARγ receptors which combat insulin resistance in peripheral tissue, inhibit gluconeogenesis, and enhance glucose uptake in peripheral cells. Their effect increases gradually, and it is followed by a beneficial adjustment of the blood lipid spectrum, which is a side effect of PPARα receptors being partially targeted. Thiazolidinediones are used once daily orally.

The most common adverse effect of all drugs in this group is water retention, which may cause leg oedema and heart failure. Rarely, these substances may also cause eyesight problems connected to macular oedema. Individual drugs have specific adverse effects unique

to each individually, which in some cases, led to market authorisation withdrawal. **Troglitazone** is hepatotoxic and not used anymore. **Rosiglitazone** is not hepatotoxic, but seems to increase risk of cardiovascular morbidity (e.g., stroke, myocardial infarction). Due to this effect, it was discontinued in the European market, and it is closely monitored in the USA. Its cardiovascular safety is still under investigation, and thus far, definitive evidence of negative cardiovascular side effects remains to be seen.

Pioglitazone has neither of these risks. It is currently the only thiazolidinedione registered and used in the Czech Republic. Results of multiple clinical trials support the possibility of enhanced risk of developing bladder cancer. The adverse effects specific to each drug provide a basis for the multiple contraindications seen within this group. They cannot be used in patients with heart failure, liver diseases, bladder cancer, and unexplained hematuria. Pioglitazone may be used in monotherapy or combined with metformin, SUs, and insulin. Hypoglycaemic episodes may occur, but only with combined treatment.

Thiazolidinediones may enhance appetite and increase body weight. Due these and the other characteristics of these drugs, they are NOT a first-choice medication for type 2 diabetes.

7.1.2.5 α-glucosidase inhibitors

Di-, oligo-, and polysaccharides from food are broken down in the small intestine by the α-glucosidase enzyme into monosaccharides, which can be transported to the blood stream. Pharmacological inhibition of these enzymes leads to a lowering of the postprandial glycaemic peak and consequently lower insulin demand. α-glucosidase inhibitors are administered orally three times daily paired with conditions of low sugar diet.

Adverse effects are mainly GIT related – flatulence, nausea, diarrhoea, bellyache – and may be worsened by inadequate diet. Rarely, these adverse effects may cause a paralytic ileus. Less frequent side effects are liver function impairment with exceptionally severe hepatopathies. When used in monotherapy, α-glucosidase inhibitors do not induce hypoglycaemia. These drugs can be combined with other antidiabetics.

Acarbose is a tetrasaccharide derived from cultured broths. It is hardly absorbed from the GIT (i.e., bioavailability is 1-2%); therefore, its effect is considered local. It can be used in diabetes type 2 treatment; in some countries, it is also administered to prediabetic patients and patients with impaired glucose tolerance to prevent worsening of the symptoms. **Miglitol,** currently unregistered in the Czech Republic, is an iminosugar which is, unlike acarbose, well absorbed in the GIT. It is not metabolized and gets excreted unchanged in the urine. Another drug from this class is **voglibose**, which is also unregistered in the Czech Republic.

7.1.2.6 Incretin mimetics

Incretins are hormones released locally into the GIT after a meal. The most important one is GLP-1 (glucagon-like peptide 1), which stimulates biosynthesis and the release of insulin into pancreatic β-cells. Its effect is followed by a feeling of satiety and slowed gastric emptying, which results in decreased appetite. Due to its peptide structure, it has a very short half-life, and it is broken down by peptidase enzymes.

GLP-1 analogues

GLP-1 analogues have a modified structure allowing a convenient pharmacokinetic profile, especially a longer half-life. The peptide substance acting as a GLP-1 analogue was discovered in saliva of the Gila monster (*Heloderma suspectum*, family Helodermatidae), a venomous lizard from Central America. The synthetic peptide derived from this substance is called **exenatide**, and its derivative is **liraglutide**. Both are administered subcutaneously twice daily before meals. Exenatide is also available in a dosage form allowing subcutaneous administration once a week.

Albiglutide is a dimer of GLP-1 bound to albumin, which is also administered subcutaneously once a week. The main advantage of incretin mimetics is their ability to stimulate biosynthesis and release insulin only when glycaemic levels are elevated. Therefore, the risk of hypoglycaemia is minimal. These products also lead to rapid lowering of body weight when administered chronically. The most common adverse effects (seen up to 50% of patients) are nausea and diarrhoea, which tend to gradually diminish and disappear.

DPP-4 inhibitors

The dipeptidyl peptidase 4 (DPP-4) is the enzyme which breaks down GLP-1. Therefore, its inhibition enhances concentrations and the effect of endogenous GLP-1 in the GIT.

These drugs are called gliptins, and they are administered orally once a day. Currently, there are: sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin; other drugs are in development. Gliptins can be successfully combined with metformin as well as other antidiabetic drugs.

Regarding the safety profile of incretin mimetics, there are concerns about the development of severe pancreatitis and an increased risk of thyroid gland cancer. However, it is still unclear whether these risks are really caused by chronic administration of incretin mimetics.

7.1.2.7 Gliflozins

Gliflozins are new antidiabetic drugs administered orally once a day. They inhibit co-transporters for Na^+ and glucose. These transport proteins are called SGLT (sodium-glucose linked transporters), and they are divided into two subtypes. Gliflozins predominantly inhibit SGLT2, which is found in the proximal tubule and regulates glucose reabsorption from primary urine. Pharmacological blockade of SGLT2 enhances excretion of glucose causing a decrease of glycaemia. Body weight loss was also proven to occur.

Importantly, gliflozins are suitable only for patients with no renal pathology. The main adverse effect is polyuria and mild dehydration with no clinical relevance. More important is the increased incidence of urinary tract infections due to the elevated amount of glucose in the urine. Gliflozins do not induce hypoglycaemia in monotherapy. There is one drug registered in the Czech Republic – **dapagliflozin**. **Canagliflozin** is registered in the USA, and other drugs are in development.

7.1.2.8 Amylin analogues

Amylin (IAPP – islet amyloid polypeptide) is a peptide secreted by pancreatic β-cells along with postprandial insulin. Despite a very low amount secreted, it contributes to glycaemic regulation. It induces feelings of satiety, slows gastric emptying, and enhances the release of

gastric juices and insulin while it decreases glucagon release. It also inhibits gluconeogenesis. An amylin analogue is **pramlintide**, a drug currently registered only in the USA. It is administered before meals by a subcutaneous injection. Pramlintide can be used for the treatment of both type 1 and type 2 diabetes and can be combined with metformin and other antidiabetic drugs.

7.1.3 Treatment of acute coma related to diabetes

The most common cause of coma in diabetic patients is hypoglycaemia. Several symptoms precede the patients' collapse; therefore, the patient should take simple sugars as soon as possible (e.g., sweet beverage, 4 cubes of sugar slowly dissolved in mouth, etc.) and have a meal. Importantly, some drugs may mask symptoms of hypoglycaemia (e.g., β-blockers).

When coma occurs, the first aid involves immediate intravenous administration of **glucose** or intramuscular injection of **glucagon**. A glucagon kit for subcutaneous or intramuscular administration can be prescribed to the patient to carry on the person at all times.

In case of hyperosmolar hyperglycaemic coma with ketoacidosis, **saline** is administered intravenously followed by a slow infusion of insulin (e.g., 6 units per hour) and K^+ supplementation (i.e., in the form of potassium chloride).

Furthermore, intravenous **heparin** or subcutaneous **low-molecular heparins** may be administered to prevent thromboembolism.

7.2 Treatment of dyslipidaemias

Dyslipidaemia is a distorted concentration of blood lipids (e.g., cholesterol and/or triglycerides and/or HDL cholesterol). It is one of the most common metabolic disturbances in the Czech Republic. Dyslipidaemia is a major risk factor of atherosclerosis, related cardiovascular morbidity, and acute pancreatitis.

The main treatment approach is a change in lifestyle and diet, in other words, one which excludes animal fats. Should these measures fail, it is necessary to treat the condition pharmacologically. Drugs which treat dyslipidaemia are called **lipid-lowering agents** or **hypolipidemic drugs**.

Lipoproteins

There are a spectrum of lipids naturally occurring in blood plasma: cholesterol, triglycerides, phospholipids, and fatty acids. Because these substances are not dissolved in water, their transport is mediated by the binding of non-polar lipids (e.g., triacylglycerides and cholesterol esters) to proteins and more water-soluble polar lipids (e.g., phospholipids and cholesterol) forming **lipoproteins**, which are miscible with water.

The protein parts (**apolipoproteins**) are located on the surface of the particles and enable lipid exchange among different lipoproteins and cells in the body. Mechanisms responsible for this exchange are enzyme and transporter induction or inhibition or the binding of ligands to specific receptors. In some cases, apolipoproteins may also be exchanged between lipoprotein particles. Apolipoproteins (Apo for short) are classified by the letters, A-L.

There are different congenital apolipoprotein defects or defects of related enzymes and transporters. These defects lead to rare, but serious, monogenic dyslipidaemias eligible for gene therapy. An initial product has been released, **alipogene tiparvovec** (Glybera®), which contains a gene for the lipoprotein lipase enzyme as well as a viral vector. It is used for the treatment of serious hypertriglyceridemia caused by lipoprotein lipase deficiency. It is the first gene therapy approved in EU countries; it received marketing authorisation from the European Medicines Agency in 2012.

There are five groups of lipoproteins which can be distinguished by their protein to lipid ratio:

- **Chylomicrons** are lipoproteins with the lowest density. They are formed by lipids from gut absorption and they contain the highest amount of lipids (i.e., mainly triglycerides from food).
- **Very-low density lipoproteins** (**VLDL**) are formed in liver, and they transport triglycerides from the liver to peripheral tissues. They are metabolized in the bloodstream into IDL particles, which the liver reuptakes and converts to LDL.
- **Intermediate-density lipoproteins** (**IDL**) are the transitional form between VLDL and LDL.
- **Low-density lipoproteins** (**LDL**) supply peripheral tissues with esters of cholesterol. There, particles contain the highest proportion of cholesterol. Their endocytosis is mediated by a specific LDL receptor.
- **High-density lipoproteins** (**HDL**) play a part in the metabolism of chylomicrons and cholesterol transport back to the liver for further use in the periphery (i.e., reverse cholesterol transport).

Classification of dyslipidaemias

Dyslipidaemias classified based on which lipids are out of proportion:

- Hypercholesterolemia – isolated elevation of cholesterol level,
- Combined hyperlipidaemia, and
- Hypertriglyceridemia – isolated elevation of triglyceride levels.

Distinguishing based on the pathophysiology involves:

- Primary dyslipidaemia caused by genetic disorders of lipid metabolism (e.g., familiar hypercholesterolemia, an autosomal dominant disorder caused by a mutation in the LDL-receptor gene and/or gene for ApoA) and
- Secondary dyslipidaemia caused by another disease which impairs or distorts lipid and lipoprotein metabolism (e.g., diabetes mellitus, thyroid, kidney, adrenal gland, pituitary, or liver dysfunctions).

Table 6: Reference values of cholesterol and triglycerides

Lipids	Target values [mmol/L]
Total cholesterol	< 5
LDL cholesterol	< 3
Triglycerides	< 1.7

7.2.1 Drugs for treatment of dyslipidaemias

7.2.1.1 Statins

Currently, statins are considered the most powerful drugs used to treat hypocholesterolaemia. They act as inhibitors of a key enzyme in cholesterol biosynthesis, HMG-CoA reductase (hydroxymethylglutaryl-coenzyme A reductase). Statins also have other effects not related to lipids (pleiotropic), especially anti-inflammatory effects. Lower cholesterol synthesis induces a relative deficit of cholesterol in hepatocytes, which then enhances LDL receptor synthesis. This mechanism contributes to the quick lowering of blood cholesterol levels. The anti-inflammatory effect is appreciable mainly in endothelium. Inflammation of endothelial cells represents an important pathophysiological mechanism of atherosclerosis development. Aside from these effects, statins also possess antiaggregant and antiproliferative activities, support endothelial functions, stabilize atherosclerotic plates, etc. Due to all these beneficial effects, they became the first choice for treatment of atherosclerosis. For this diagnosis, they are always prescribed independent of blood lipid levels.

Statins are well-absorbed from the GIT, and they largely undergo the first pass effect. Cytochrome P450 is responsible for their metabolism, and they are excreted in the bile. The most important adverse effects of statins are myalgia (muscle pain), myositis, and rarely, severe rhabdomyolysis followed by renal insufficiency. The risk of rhabdomyolysis is increased when statins are combined with cytochrome P450 inhibitors, specifically the 3A4 subtype (e.g., fibrates, macrolide antibiotics, azole antimycotic drugs, etc.). These drug-drug interactions result in a several-fold increase in the plasma levels of statins, which are predominantly metabolized by the 3A4 isoenzyme (especially simvastatin, lovastatin, and atorvastatin). Less dangerous adverse reactions are increased liver transaminase levels, dyspepsia, constipation, and headache.

The drug list includes: **lovastatin**, **simvastatin**, **fluvastatin**, **atorvastatin**, and **rosuvastatin**.

7.2.1.2 Fibrates

Fibrates suppress mainly triglyceride levels, but to some extent, they also decrease LDL and the total cholesterol level while slightly enhancing HDL cholesterol. Their mechanism of action is through the activation of nuclear PPARα (peroxisome proliferator-activated) receptors. This leads to enhanced lipolysis, the activation of lipoprotein lipase, and fast degradation of VLDL particles. Two of the currently used drugs are **fenofibrate** and **ciprofibrate**.

The most common adverse effects of fibrates are GIT-related (e.g., increased risk of gallstones, vomiting), myalgia, and fatigue. They also increase the risk of myositis and rhabdomyolysis when combined with statins.

7.2.1.3 Ezetimibe

Ezetimibe is the only drug that belongs to the family of selective inhibitors of cholesterol absorption in the small intestine. It does not affect absorption of fatty acids, triglycerides, and bile acids. Low cholesterol supply to the liver upregulates production of LDL-receptors and

results in a higher uptake of the LDL particles from the blood. However, low intake of cholesterol from food enhances endogenous cholesterol synthesis. Therefore, ezetimibe, combined with statins which block endogenous synthesis, is an advantageous approach (i.e., dual inhibition).

Adverse reactions are headache and GIT problems (e.g., bellyache, diarrhoea).

7.2.1.4 Ion-exchangers (resins)

Resins do not get absorbed and act locally in the intestine wherein they bind to bile acids. This bond prevents bile acid absorption and interrupts their enterohepatic recirculation. In order to balance the enteral loss of bile acids, liver cells use cholesterol to synthetize them *de novo*. This requires an increased density of LDL-receptors on the hepatocytic membrane to enhance LDL-cholesterol uptake from plasma. Ion-exchangers are the only hypolipidemics which may be administered to **children** and **pregnant women** (or women planning to become pregnant).

Given that resins are not absorbed, they also do not induce systemic adverse reactions. The typical adverse effects are GIT related, for instance dyspepsia, constipation, steatorrhea, or malabsorption of lipid soluble vitamins. Other drugs shall be taken either one hour before or four hours after resin administration.

The currently used drugs are **cholestyramine**, **colesevelam**, and **colestipol**.

7.2.1.5 Nicotinic acid (niacin)

Niacin belongs to the group of B vitamins, but for the treatment of dyslipidaemias, its dosing is substantially higher than with general vitamin supplementation (i.e., in terms of grams administered). It is currently not registered in the Czech Republic because clinical trials conclude its adverse effects outweigh its benefits. Currently, it is considered obsolete.[1]

7.2.2 Indications of lipid-lowering drugs

As was previously mentioned, in atherosclerosis diagnosis, statins are always prescribed with no regard to current blood lipid levels. When the patient suffers from atherosclerosis combined with hypertriglyceridemia, a combination of statin and fibrate is prescribed, and the patient is carefully monitored for adverse reactions.

Isolated hypercholesterolemia

The drugs of choice for isolated hypercholesterolemia in children and pregnant women are statins or resins. When the lipid-lowering effect of statin is insufficient, the statin is combined with ezetimibe. The second choice treatments are ezetimibe or resins.

Combined hyperlipidaemia

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[1] Niacin at high doses has a particularly adverse reaction – skin flush, probably caused by prostaglandin release. For this reason, it is always combined with prostaglandin antagonist laropiprant.

Statins are prescribed when the LDL cholesterol level is predominant, whereas fibrates are used when the principal distortion of the lipid profile is due to triglycerides. When the patient requires enhancement of HDL levels along with lowering triglycerides, the most suitable combination is fibrates (e.g., fenofibrate seems to be the best in this case) with a statin or a statin with omega-3 fatty acids.

Isolated hypertriglyceridemia

For this type of dyslipidaemia, a non-pharmacological approach is preferred: restricted consumption of alcohol and simple carbohydrates, losing body weight, etc. When pharmacotherapy becomes necessary, a fibrate or statin is prescribed, particularly statins in the case of concurrent atherosclerosis. Omega-3-fatty acid supplementation is also beneficial, while nicotinic acid is considered obsolete for this indication and is not marketed in the Czech Republic.

7.3 Pharmacotherapy of obesity

Global rates of overweightedness and obesity continue to increase. Body weight control is not only a concern of the adult population, it also threatens children. There is a well-established correlation between obesity and cardiovascular morbidity or mortality. Furthermore, obesity is associated with an increased risk of cancer, diabetes type 2, infertility, psychiatric problems, joint disorders, etc. Metabolic syndrome is linked to hypertension, dyslipidaemia, systemic inflammatory and procoagulation states, etc. A typical obese patient is polymorbid, takes several drugs (e.g., antihypertensive, lipid-lowering, antithrombotic, and other drugs), and is therefore, at a higher risk of drug-drug interactions.

A 5-10% body weight reduction creates substantial benefits for patients' health. Blood pressure may be lowered, hyperglycaemia, and insulin resistance may not be apparent anymore and joint and back pain can be alleviated. The major challenge in the complex treatment approach for obesity remains to be the patients' motivation. This approach consists of five key pillars:

- Suitable diet, usually a substantial change of eating habits,
- Adequate physical activity,
- Psychotherapy, psychological support of the lifestyle changes,
- Pharmacotherapy, and
- Surgery.

Pharmacotherapy of obesity may be initiated for different reasons, but it should remain the second choice after lifestyle change, inclusive of diet and regular physical activity. Obesity medications are drugs which help to reduce body weight in overweight or obese patients. The drugs which act in the central nervous system and lead to appetite suppression and a feeling of satiety are called anorectic drugs, and there are drugs which act peripherally. These peripheral

drugs prevent digestion of certain nutrients. All available obesity medications are administered orally, and they are contraindicated during pregnancy and breastfeeding. There is not enough evidence for safe use in children.

7.3.1 Centrally-acting obesity medications

Anorectic drugs decrease appetite through a central mechanism of action on brain neurotransmitters which regulate feeding behaviour. These neurotransmitters are namely noradrenaline, serotonin, and dopamine. There are anorectic drugs which act as sympathomimetics or have a combined effect.

Some of these drugs induce a peripheral thermogenic effect which helps to reduce adipose tissue deposits. Considering their adverse effects (see text below), central obesity medications are contraindicated in patients with cardiovascular morbidity (e.g., hypertension, ischemic heart disease, etc.), patients suffering depression, insomnia, and a tendency to develop drug addictions.

7.3.1.1 Ephedrine

Ephedrine is an alkaloid isolated from jointfir (*Ephedra distachya*, family Ephedraceae). Its effects on the CNS have been known since ancient Greece. In traditional Chinese medicine, it was used to treat asthma and respiratory diseases. This use of ephedrine is now obsolete, but its derivative, **pseudoephedrine**, is still in use as a treatment for the common cold.

Ephedrine acts as an indirect sympathomimetic drug. It releases noradrenaline from the presynaptic cell and simultaneously stimulates both α- and β-adrenergic receptors. Clinical signs of its effect are psychostimulation, cardiac stimulation, vasoconstriction, and bronchodilation. The anorectic effect is related to psychostimulation. Ephedrine has an addictive potential.

Historically, ephedrine was combined with **caffeine** for the treatment of obesity. This preparation was called **Elsinore pills**. Caffeine is a methylxanthine derivative with a psychostimulant profile and weaker cardiostimulant and diuretic effects. It acts as an adenosine receptor antagonist and phosphodiesterase inhibitor. The combination of ephedrine and caffeine enhances peripheral thermogenesis. Adverse effects of this preparation are substantially more common when it is administered chronically. Cardiovascular side effects include hypertension, cardiac palpitations, and cardiotoxicity related to prolonged vasoconstriction. Central adverse effects are irritability, nervousness, mood disorders, and most importantly, insomnia. Use of the combination of ephedrine and caffeine is banned in the USA. In the Czech Republic and Slovakia, it is legal, but obsolete.

7.3.1.2 Phentermine

Phentermine is structurally similar to noradrenaline and amphetamines (see Chapter 2.1.1.1 Non-selective sympathomimetics). It acts as an indirect sympathomimetic drug. It can be used for obesity treatment for a short period of time because its effect is usually transient (i.e., one to two months). Due to risk of addiction, it should not be prescribed for longer than three months. Adverse effects are similar to those of ephedrine – cardiovascular and central.

7.3.1.3 Sibutramine

Sibutramine acts via multiple mechanisms. The anorectic effect is most likely due to the inhibition of catecholamine reuptake in the hypothalamus, mainly of noradrenaline, but to some extent serotonin and dopamine, as well. It acts selectively on centres for food intake control and has a lower psychostimulatory effect compared to ephedrine and phentermine. However, serious adverse effects are the induction or decompensation of hypertension, psychic symptoms (e.g., insomnia), and GIT disturbances (e.g., dry mouth, constipation). Sibutramine was found to be associated with increased cardiovascular events and strokes and was withdrawn from the market in many countries in 2010.

7.3.1.4 Antidepressants

Due to their mechanism being based on neurotransmitter reuptake inhibition, antidepressants may be used as "off-label" medication for obesity. "Off-label" use means the prescription of a drug for use other than that which has been indicated by the registration authority (e.g., EMA, SUKL, FDA…). **Bupropion** is an example of one such drug from the NDRI (noradrenaline and dopamine reuptake inhibitors) class of antidepressants. One of its adverse reactions is appetite suppression followed by body-weight loss.

There is empirical evidence of the bupropion anorectic effect in patients without depression. However, it is not usually prescribed. It may be beneficial in patients who suffer from comorbid obesity and depression as co-occurrence of these two diagnoses is common. Clinical trials assessing the effectivity of antidepressants in obesity treatment are ongoing. The most prescribed antidepressants – SSRI drugs – lead to weight loss during the first six months of treatment, whereas later, they tend to increase body weight.

7.3.1.5 Cannabinoid receptors antagonists

The endocannabinoid system contributes to food intake regulation, as well. Endocannabinoids like anandamide regulate the perception of hunger and satiety, energy homeostasis, and lipid metabolism. A typical example of this regulation is seen with the effects of Δ^9-THC. Many *Cannabis* users report, among other effects of intoxication, a strong feeling of hunger, as well. Δ^9-THC is an agonist of CB_1 receptors; therefore, CB_1 antagonism was hoped to translate to an effective obesity medication.

The first drug with CB_1 antagonistic mechanism was **rimonabant**, which successfully passed all clinical trials and was registered as an obesity medication. However, in the 2008 it was withdrawn from the market due to incidence of psychiatric events (e.g., depression, suicidal attempts) related to its use. Rimonabant is not used anymore, but research on the endocannabinoid system's regulation of appetite is ongoing.

7.3.2 Peripheral obesity medications

This class consists of food, drugs, or food supplements with a high content of indigestible carbohydrates. Roughage swells in the GIT and stimulates the stomach wall and intestines leading to feelings of satiety and enhanced peristaltic movements. The only drug in this class of peripheral obesity medications is **orlistat**.

7.3.2.1 Orlistat

Orlistat is a semi-synthetic compound. The original substance was isolated from soil microorganisms (*Streptomyces* bacteria). Its mechanism of action is irreversible **inhibition of lipase enzymes** present in the GIT. The effect is: Fat from food does not break down to monoacylglycerols and fatty acids to be absorbed, but remains in the intestine and is evacuated with faeces. Orlistat is administered orally and acts locally in the intestine; in other words, it does not get absorbed.

This drug is sometimes considered "educational" because it is necessary to follow a low fat diet. When orlistat is administered with fatty food, it will lead to the production of stool with a very high proportion of indigested fat. This causes typical GIT troubles, such as bellyaching, nausea, flatulence, frequent defecation, and sometimes even imperative diarrhoeas or faecal incontinence. On the other hand, an appropriate diet does not induce such adverse effects. In sensitive subjects, orlistat may cause malabsorption of lipid soluble vitamins. This requires vitamin supplementation in approximately 10% of the patients chronically treated with orlistat.

Low doses of orlistat are currently available as OTC preparations with only a slightly lower effect than the prescribed dosing. This is a suitable treatment for obese patients whose main problem is a high fat diet. However, for patients who eat too many carbohydrates, orlistat does not have a substantial benefit. Orlistat may be prescribed to patients with type 2 diabetes as it was shown to suppress insulin resistance and lower glycaemia. It may also normalize total and LDL cholesterol levels.

Patients' body weight can be influenced by many other medications. Drugs which tend to increase body weight are psychotropic drugs (e.g., especially antipsychotics), hormones, and some antidiabetic drugs (while other antidiabetic drugs induce weight loss).

7.3.3 Pharmacotherapy of eating disorders

Treatment of eating disorders (e.g., anorexia nervosa, bulimia, etc.) is always based on psychotherapy. Adjuvant pharmacotherapy may be initiated after analysis of psychiatric history and diagnosis. Every centre usually recommends a different approach based on the local experience. Importantly, the benefits of pharmacotherapy are highly variable among patients.

Anorexia nervosa can be treated with antidepressants from the **SSRI** class, low doses of **antipsychotics** (neuroleptics), or **anxiolytics** administered before meals.

Patients with bulimia may have benefit from treatment with different antidepressants – tricyclic, SSRI, SARI or MAO inhibitors (for details about antidepressants see Chapter 3.1.1 Treatment of affective disorders (antidepressant drugs)).

7.4 Pharmacology of hypothalamic and hypophyseal hormones

The hypothalamus and pituitary gland (hypophysis) represent the junction point between the endocrine system and CNS. Together, they produce hormones that regulate metabolism, growth, and partially, reproductive functions. Hypothalamic neural cells directed to the pituitary stalk release regulating hormones which manage the secretion of hormones in anterior pituitary gland (adenohypophysis).

Hypothalamic hormones, which increase hormonal secretion in the anterior pituitary, are called **liberins** (releasing hormones); those which reduce hormonal secretion are called **statins** (release inhibiting hormones).

7.4.1 Hypothalamic hormones

7.4.1.1 Hormones regulating release of somatotropin

Somatostatin (somatotropin release-inhibiting hormone, SRIH) and **somatoliberin** (growth hormone-releasing factor, GHRH) are hormones that control secretion of the growth hormone, **somatotropin**. The synthetic analogue of somatoliberin is called **somatorelin**, and it is used to assess growth hormone secretion in children with delayed growth or growth failure. Apart from the hypothalamus, somatostatin is produced in other parts of the CNS as well as in the periphery; namely in pancreas, where it reduces the secretion of insulin, glucagon, and most of the gastric hormones. Moreover, it also reduces venous blood flow within the splanchnic area.

Octreotide and **lanreotide** are synthetic analogues of somatostatin with prolonged half-lives. They are indicated for acute pancreatitis, bleeding from oesophageal varices, and therapy of hormonally active gastrointestinal tumours. **Pasireotide** is used for the treatment of Cushing's disease.

7.4.1.2 Hormones regulating release of thyrotropin

Thyroliberin (thyrotropin-releasing hormone, TRH) regulates the secretion of **thyrotropin** (thyroid-stimulating hormone, TSH) in the anterior pituitary. Synthetic thyroliberin is called **protirelin**, and it is used as a diagnostic agent to assess the hypothalamic-pituitary-thyroid (HPT) axis or prolactin secretion and in patients with acromegaly.

7.4.1.3 Hormones regulating release of adrenocorticotropic hormone

Corticoliberin (corticotropin-releasing hormone, CRH) regulates the release of corticotropin from the adenohypophysis. Its synthetic derivative, **corticorelin**, is applied in the differential diagnostic test of Cushing's syndrome (see Chapter 8.5 Glucocorticoids).

7.4.1.4 Hormones regulating release of gonadotropins

Gonadoliberin (gonadotropin-releasing hormone, GnRH) or **gonadorelin** controls the secretion of two basic adenohypophyseal gonadotropins, **follitropin** (**follicle-stimulating hormone**, **FSH**) and **lutropin** (**luteinising hormone**, **LH**). Their synthetic analogues include **goserelin**, **triptorelin**, **nafarelin**, and more. The effect of GnRH analogues depends on the duration of their administration. Short-term use has a stimulating effect on FSH and LH, whereas long-term administration inhibits their secretion; thus, it inhibits the secretion of sex hormones.

Short-term administration is used for the stimulation of sexual development in delayed puberty and to promote ovulation in assisted reproduction programs.

Long-term administration that decreases levels of sex hormones is used in psychiatric and sexological programs for the chemical castration of men, which is an alternative to the equally effective surgical castration (orchiectomy). It is performed on patients who have committed violent sexually-motivated crime. In women, long-term application of GnRH agonists may be used for the treatment of endometriosis or uterine fibroids. The medications are administered either intravenously, subcutaneously, or intranasally. GnRH antagonists such as **cetrorelix** and **ganirelix**, which are useful in reproductive medicine, are available, as well.

7.4.1.5 Hormones regulating prolactin secretion

Prolactin-inhibiting hormone (prolactostatin, aka dopamine, a well-known neurotransmitter) and **prolactin-releasing hormone** control prolactin secretion in the adenohypophysis.

Compounds that act positively on the dopaminergic system (e.g., some ergot alkaloids and their derivatives - **bromocriptine, pergolide**, etc.) have a negative effect on the release of prolactin. This phenomenon can be used for the treatment of hyperprolactinemia-induced infertility or to supress lactation if needed.

Conversely, drugs that act negatively on the dopaminergic system (e.g., **antipsychotic drugs**) may increase prolactin levels and lead to fertility disorders, gynecomastia in men, and unwanted galactorrhea in both men and women. There is also evidence for off-label use of **domperidone** (i.e., a D_2 and D_3 receptor antagonist, originally a prokinetic) to promote lactation. However, regarding safety or evidence-based medicine, this application is not well-documented and cannot be recommended to lactating women.

7.4.2 Hormones of anterior pituitary

7.4.2.1 Somatotropin

Somatotropin (growth hormone, GH) is the hormone whose main function is the stimulation of normal growth. It acts on several levels via direct and indirect mechanisms and interacts with other hormones, especially thyroid, sex, and adrenal hormones. It directly affects the

metabolism of lipids and carbohydrates; however, it affects growth indirectly via **somatomedins** or **insulin-like growth factors** (**IGFs**), of which, production in the liver is supported by somatotropin. Through IGF, somatotropin prevents the closure of epiphyseal plates and promotes the incorporation of purine and pyrimidine bases into DNA.

The secretion of somatotropin is highest in neonates and gradually decreases during development, with the lowest levels in adults. The secretion is pulsed, and the highest levels are attained at night because the deep sleep phase is an incentive for its secretion. Lack of endogenous growth hormone causes dwarfism (Mulibrey nanism), for which substitution treatment with recombinantly produced somatotropin is needed. Indications for growth hormone therapy in adults are catabolic states, severe burns, and severe fractures to accelerate healing. Supplementation with IGF-1, recombinant **mecasermin**, is possible, too. It can be given in the form of injections in growth disorders from two years of age and up.

Overproduction of somatotropin results in a disease with different phenotypes according to the age of onset – gigantism in children (i.e., excessive secretion occurs before the end of longitudinal growth) and acromegaly in adults. The cause of these diseases is usually a benign tumour of the adenohypophyseal somatotropic cells. In acromegaly therapy, **pegvisomant**, an antagonist of growth hormone receptors, is usually applied.

7.4.2.2 Thyrotropin

Thyrotropin (TSH) stimulates thyroid activity, increases iodine uptake, and elevates the synthesis of thyroid hormones. It induces thyroid gland hypertrophy and stimulates its vascularization. TSH secretion is pulsed and circadian, the highest production occurring in the deep sleep phase. Therapeutically, TSH is used to treat thyroid carcinoma metastases.

7.4.2.3 Corticotropin

Corticotropin or **adrenocorticotropic hormone** (ACTH) stimulates the synthesis and secretion of adrenal steroids, such as glucocorticoids, mineralocorticoids, and precursors of androgens (e.g., androstenedione and dehydroepiandrosterone). The synthetic analogue of ACTH is **tetracosactide**, which is used for the differential diagnosis of adrenal insufficiency.

Addison's disease, which is caused by the atrophy of the adrenal cortex, is one of causes of primary adrenal insufficiency. In this case, the application of tetracosactide does not induce a response due to destruction of the cortex. Secondary adrenal insufficiency is caused by insufficient ACTH secretion in the anterior pituitary; thus, administering its precursor induces excretion of steroid hormones from the adrenal cortex. This substance has been misused as a doping agent in sports (e.g., cycling).

7.4.2.4 Gonadotropins

Gonadotropic hormones, which regulate the function of the gonads, are **follicle-stimulating hormone (FSH)**, **luteinising hormone (LH)**, and **human chorionic gonadotropin (hCG)**. Unlike the others, hCG does not belong to hormones produced in the anterior pituitary gland. FSH increases gametogenesis, and along with LH, stimulates the development of follicles in women and spermatogenesis in men. FSH induces follicular maturation and the development of ovum. It also promotes the conversion of androgens to oestrogens. The main therapeutic

use of FSH is to induce ovulation in infertility. LH in male Leydig cells stimulates the secretion of testosterone; therefore, it is indicated for disorders of spermatogenesis. The main indication of LH in women is ovulation induction.

7.4.2.5 Prolactin

Prolactin (PRL) is structurally related to growth hormone. Its regulation has some differences compared to other hormones of anterior pituitary: Under normal circumstances, inhibition by prolactostatin (dopamine, see above) predominates; its secretion has no feedback regulation, and prolactin does not stimulate synthesis and secretion of other hormones in target tissues. The main stimulus of its production is breastfeeding. Furthermore, oestrogens, GnRH, and TRH increase its secretion. The main function of prolactin is milk production and ejection. It is also responsible for proliferation and differentiation of breast tissue during pregnancy. Its function in men is unclear.

7.4.3 Hormones of neurohypophysis

Hormones of the posterior pituitary lobe, unlike the adenohypophyseal hormones, are formed in the hypothalamus and are only transported to posterior lobe at neurosecretory nerve terminals. Only then can they be released into systemic circulation from the neurohypophysis.

7.4.3.1 Oxytocin

Oxytocin is a polypeptide structurally related to vasopressin, and besides synthesis in brain tissue, it is also synthesised in the ovaries and testes. Its receptors are found in mammary glands and in the smooth muscle cells of the uterus. Their amount and sensitivity to oxytocin significantly increase toward the end of pregnancy. In the mammary gland, when oxytocin binds to its receptors, it induces the milk ejection reflex. The main stimulus for its release is cervical dilation before birth and nipple stimulation during breastfeeding. In the myometrium, oxytocin induces rhythmic contractions, increases resting tone and contractility, and stimulates the production of prostaglandins important for physiological labour. In men, it affects sexual behaviour and accelerates sperm transport through the urogenital system during ejaculation.

In obstetrics, oxytocin is used to induce birth and stimulate contractions as well as for involution of the uterus after birth and the treatment of postpartum bleeding. For these indications, it is only given parenterally through intravenous application. A lesser effect is achieved with nasal or buccal administration. These application routes are suitable for increasing milk ejection.

One long-acting oxytocin receptor agonist is **carbetocin**. It is applied orally, mainly for the atony of the uterus after delivery by caesarean section. The effect of a single intravenous dose is comparable to an oxytocin infusion lasting several hours. **Atosiban**, an antagonist of oxytocin receptors, can be injected as a tocolytic (anti-contraction medication) in the 3rd trimester of pregnancy (see Chapter 11.2 Tocolytics).

7.4.3.2 Vasopressin

Vasopressin, or **antidiuretic hormone** (**ADH**), plays an important role in the maintenance of optimal water volume in the body. In addition to antidiuretic action, it also acts as a vasopressor. Plasma osmolality is an important regulatory factor for its secretion. A rise in osmolality leads to a pronounced feeling of thirst and increased ADH in the bloodstream. Therefore, diuresis is reduced. Certain medications can also affect ADH. Morphine, barbiturates, and nicotine support its secretion and thus block diuresis. Conversely, in a manner dependent on its blood concentration, alcohol decreases the secretion of ADH and increases the amount of urine produced.

There are three types of specific receptors for ADH: V_1, V_2, and V_3. V_1 receptors are found in the smooth muscles of blood vessels, and they are responsible for vasoconstriction. V_2 receptors are located in renal tubules and are responsible for the antidiuretic effect. The impairment of ADH secretion is defined as diabetes insipidus. It manifests as a great thirst and vast production of hypotonic urine.

Desmopressin and **terlipressin** exhibit a prolonged biological half-life compared to natural vasopressin. Desmopressin is administered perorally, and besides diabetes insipidus, nocturnal polyuria in older children and adult nycturia are other indications. Terlipressin is strongly vasoconstrictive and is most commonly used parenterally to treat bleeding in the GIT and urogenital system.

7.5 Pharmacology of adrenocortical hormones

The adrenal cortex is divided into three functionally and histologically distinct entities. The zona glomerulosa is the outer layer, and it produces mineralocorticoids. The middle zone is the zona fasciculata, which is the site of glucocorticoid production. In the inner layer, the zona reticularis, synthesis of sex hormones takes place. The inner, middle, and partially the outer zone are controlled by pituitary and hypothalamic hormones (i.e., ACTH and CRH). Glucocorticoids and sex hormones are described in detail in separate chapters (Chapters 8.5 Glucocorticoids and 7.8 Sex hormones).

Aldosterone is the primary mineralocorticoid hormone. To a lesser extent, the adrenal gland also produces another mineralocorticoid, **deoxycorticosterone**. Aldosterone binds to specific mineralocorticoid receptors that are located intracellularly, similar to glucocorticoid receptors. Unlike the glucocorticoid receptors found practically in all cells, mineralocorticoid receptors are located only in some tissues (i.e., distal tubules, colon epithelium, urinary bladder, salivary and sweat glands, hippocampus).

The aim of aldosterone production is to increase the resorption of sodium in the distal tubules and collecting ducts while increasing the excretion of potassium and hydrogen ions. Excessive secretion of mineralocorticoids (e.g., in kidney adenoma) induces significant retention of water and sodium ions, hypertension, hypokalaemia, and alkalosis.

Decreased secretion of mineralocorticoids is typical for Addison's disease. It is accompanied by an increased loss of sodium, resulting in decreased osmotic pressure of extracellular fluid and its transfer into cells. This causes a significant decrease in the volume of extracellular

fluid. Furthermore, the hyposecretion of mineralocorticoids is characterized by hyperkalaemia.

Mineralocorticoid supplementation is indicated as a replacement therapy in primary or secondary hypoaldosteronism. The most commonly used agent is **fludrocortisone**, which is given perorally.

7.6 Pharmacotherapy of thyroid diseases

The thyroid gland is the site of synthesis, storage, and secretion of the hormones, **thyroxine (T4)** and **triiodothyronine (T3)**. These are iodinated tyrosine-derived amino acids, which play an important role in the regulation of growth, development, energy metabolism, and adaptation to the environment. The secretion of thyroid hormones is regulated by adenohypophyseal TSH. The second most important regulating factor for synthesis to occur is the concentration of iodides in plasma. Reduced iodine intake leads to decreased T3 and T4 production and increased secretion of TSH. Long-term increase of TSH secretion due to iodine deficiency leads to hypertrophy of the gland (i.e., goiter). Another hormone produced by the thyroid gland is **calcitonin**, a hormone which plays an important role in maintaining calcium homeostasis (see Chapter7.7.1.2 Calcitonin).

95% of T3 and T4 are bound to plasma proteins. Their main transport protein is **thyroxine-binding globulin (TBG)**, approximately one quarter of which is bound to albumin. T4 is metabolized by deiodinase enzymes in the periphery to produce the T3 form. T3 is up to 10 times more efficient; therefore, T4 may act as a prohormone for T3. Metabolites are excreted in bile and partly in urine.

In most tissues, T3 and T4 stimulate the basal metabolism of carbohydrates, lipids, and proteins. However, these effects are mostly indirect due to the modulatory effect of other hormones (e.g., insulin, glucagon, glucocorticoids, and catecholamines). They directly affect only some enzymes of carbohydrate metabolism, which is reflected by increased oxygen consumption and a calorigenic effect (e.g., increased heat production, increased basal metabolism). A strengthened metabolic rate manifests mainly within the cardiovascular and renal systems, liver, and skeletal muscles. The effects of thyroid hormones listed above are similar to the effects of catecholamines.

7.6.1 Therapy of hypothyroidism

Thyroid hormones are indicated for substitution therapy when the function of the thyroid is reduced (hypothyroidism) or completely missing. The differences between primary and secondary (central) hypothyroidism can be distinguished. **Primary hypothyroidism** arises on a congenital basis due to autoimmune disorders, but it can also be caused by iodine deficiency, the malfunction of the thyroid gland due to goitrogens, medicaments, or radiation. **Secondary hypothyroidism** is the outcome of hypothalamo-pituitary malfunction with reduced TSH production. Clinical signs of hypothyroidism include bradycardia, sensitivity to cold, hoarse voice, weight gain, constipation, fatigue.

Substitution therapy is based on the administration of hormones in low doses. Most often **levothyroxine (T4)** is administered, which is converted to T3 in the periphery (on demand). It

is given orally once a day on an empty stomach 30 minutes before any meal or medication to avoid lowered absorption in the GIT. The onset of action proceeds slowly over time (weeks to months). The dose is gradually titrated and slowly increased to avoid undesirable side effects on the cardiovascular system.

Liothyronine (**T3**), unlike levothyroxine, has a faster onset of action and is given 2-3 times a day. It is reserved for emergencies only and is not intended for long-term therapy. Adverse effects occur only after higher doses, and they match the symptoms of hyperthyroidism, a disease caused by the overproduction of thyroid hormones.

Hyperthyroidism manifests as an increase in body temperature, increased oxygen consumption in the tissues, sweating and sensitivity to heat, tachycardia followed by arrhythmias, nervousness, tremors, and increased appetite with simultaneous body weight loss. The striking feature is often exophthalmos, which is caused by abnormal connective tissue deposition in the orbital and extraocular muscles.

7.6.2 Therapy of hyperthyroidism

The most common cause of hyperthyroidism is Graves-Basedow disease. It arises on an autoimmune basis wherein antibodies are formed due to a genetic aberration. They bind to TSH receptors on thyroid cells and activate them, resulting in an overproduction of hormones. There are three possible approaches for the treatment of hyperthyroidism:

- pharmacological treatment,
- radioiodine therapy, and
- surgical removal of thyroid (thyroidectomy).

7.6.2.1 Thionamides

This group of antithyroid agents, also called thyreostatics, includes **carbimazole**, **thiamazole** (**methimazole**), and **propylthiouracil**. Their mode of action lies in the competitive inhibition of the enzyme, thyroperoxidase, which contributes to the synthesis of T3 and T4 in thyroid cells. In addition, propylthiouracil can inhibit the degradation of T3 and T4 in the periphery. Thionamides are taken orally, but the clinical response occurs within 1-2 months due to the relatively large pool of synthesized hormones in the thyroid gland and the periphery. The most common side effects associated with thionamide administration are granulocytopenia and allergies.

7.6.2.2 Iodides

Different pharmacological treatment involves the administration of iodides. Higher doses inhibit synthesis and secretion of thyroid hormones. The onset is fast, but application of iodides cannot be used as a long-term therapy. The maximum effect is achieved within 10-15 days, but then it wears off. Iodides are most often taken by mouth in the form of **potassium iodide** or **Lugol's iodine,** which is an aqueous solution of 1% iodine and 10% potassium iodide that can be administered intravenously (e.g., in thyrotoxicosis).

Another approach in hyperthyroidism treatment is the administration of **radioiodine**, more precisely, its radioactive isotope, I^{131}. After oral administration, it is absorbed by the thyroid gland and incorporated into thyroglobulin, where it emits β and γ rays. β rays are short-ranged and cytotoxic to thyroid follicles; this induces destruction of thyroid parenchyma.

Currently, other drugs, which are used more often as diagnostic tools or in toxicology, are called anionic inhibitors, including **perchlorates** and **thiocyanates**. They act as competitive blockers of the iodide transport system. The indirect sympatholytic, **guanethidine**, is used in the form of eye drops to treat exophthalmos.

7.6.3 Therapy of thyroid storm

Thyrotoxicosis is a sudden, life-threatening condition that exacerbates all the symptoms of hyperthyroidism – from fever, nausea, vomiting, sweating, and increased heart activity to delirium and coma. The therapy in this state also includes, in addition to the above-mentioned **iodides** and **thionamides**, the administration of **β-blockers** and **glucocorticoids**.

Corticoids are applied to prevent shock and as inhibitors of T4 conversion to T3.

β-blockers (e.g., **metipranolol**), the main indication for which is hypertension, alleviate the symptoms of hyperthyroidism that essentially mimic sympathetic stimulation.

7.7 Pharmacology of bone metabolism

7.7.1 Physiological regulation of bone metabolism

Bone metabolism is closely related to the maintenance of calcium, phosphorus, and magnesium homeostasis. For their systemic regulation, the following calciotropic hormones play a major role: **parathormone**, **calcitonin**, and **vitamin D**. Other hormones partly involved in maintaining calcium homeostasis are oestrogens, glucocorticoids, thyroid hormones, prolactin, insulin, and growth hormone.

7.7.1.1 Parathormone

Parathyroid hormone (**PTH**) is formed and stored in parathyroid glands. With decreased calcium ion concentration in plasma, PTH is released from the vesicles. It raises the concentration of Ca^{2+} by several mechanisms:

- by increasing calcium reabsorption in the kidneys,
- increasing calcium absorption from the GIT,
- mobilising bone calcium (i.e., activates bone resorption by osteoclasts and inhibits osteoblasts responsible for bone remodelling), and
- stimulating calcitriol synthesis, which also increases calcium absorption from GIT.

7.7.1.2 Calcitonin

Calcitonin is a natural opponent of PTH. It is formed in the parafollicular C cells of thyroid gland, and its effects are as follows:

- It reduces osteoclast activity through specific receptors, and thereby, inhibits bone resorption.
- In kidneys, it reduces the reabsorption of calcium, phosphates, and other ions.
- In the GIT, it reduces secretion of HCl and gastrin.

The release of calcitonin is regulated by the plasma concentration of Ca^{2+}, such that higher levels of Ca^{2+} increase the secretion of calcitonin. Moreover, calcitonin possesses an analgesic effect which is mediated through the activation of the endogenous opioid system and the inhibition of prostaglandins. The side effects were considered only mild, most often an unpleasant feeling in the mouth and reddening of the face occurring. For therapeutic purposes, synthetic salmon calcitonin (dosage form being a nasal spray) was previously used for the prophylaxis and treatment of osteoporosis and in Paget's disease, but due to a higher incidence of tumours and its limited efficacy in long-term treated patients, the preparations were withdrawn from the market. Currently, no preparation is registered in the Czech Republic.

7.7.1.3 Vitamin D

The term, vitamin D, refers to a complex of compounds with a steroid structure. Clinically, preparations containing **ergocalciferol** (**D2**) or **cholecalciferol** (**D3**) are used. The most effective of their derivatives is a metabolite of cholecalciferol, **calcitriol**.

Vitamin D plays an important role in calcium and phosphorus homeostasis and maintains a constant concentration of Ca^{2+} in extracellular space:

- It increases the absorption of calcium from the intestines by inducing the synthesis of new transport proteins (Calcium-binding protein).
- It mobilizes calcium deposited in bones and reduces its excretion by pronounced resorption in renal tubules.
- It accelerates maturation of osteoclasts and stimulates their activity.
- It acts as an immunomodulator as it supports the proliferation of some cells primarily involved in innate immunity.

7.7.2 Bone metabolism disorders

The most common bone disease is **osteoporosis**. It mainly manifests in women after menopause due to reduced production of oestrogens; this occurs in elderly men, as well, but to a lesser extent. In younger individuals, incidences of osteoporosis are less common. Osteoporosis is characterized by abnormal bone mass loss, malformed bone microarchitecture, and increased fragility (i.e., increased risk of fractures). The prophylaxis for osteoporosis consists of the administration of calcium and vitamin D, sufficient physical activity, and a healthy lifestyle.

7.7.2.1 Osteoclast-inhibiting drugs

The so-called antiresorptive drugs include **raloxifene**, which is a selective oestrogen receptor modulator (SERM). It acts similarly to oestrogen on bone tissue (see 7.8 Sex hormones).

Another group, **bisphosphonates**, induces apoptosis of osteoclasts by disrupting their synthesis of cholesterol. Representatives are **alendronic**, **zoledronic**, **ibandronic**, and **risedronic acid**. They are usually taken orally once a week or once a month depending on the specific drug. In oncology, they are applied to treat bone metastases resulting from some tumour types. The dosages administered are higher than those in osteoporosis. The route of administration differs as these substances are generally given parenterally. A serious adverse effect of high dose administration is osteonecrosis of the jaw. Less severe nausea and pyrosis are common after oral administration.

Denosumab is a human monoclonal antibody which binds to specific receptors on the surface of osteoclasts, thereby reducing their lifetime. It is given as a single subcutaneous injection once in a six-month period. Simultaneous supply of calcium and vitamin D is necessary.

Salmon calcitonin would belong to this group of drugs, but its registration was cancelled in the Czech Republic (see Chapter 7.7.1.2 Calcitonin).

7.7.2.2 Drugs increasing osteoblast activity

Among the anabolic drugs supporting osteoformation, strontium ranelate, fluorides, and teriparatide stand out. The mechanism of action of **strontium ranelate** is an increase in osteoblast activity and the promotion of collagen synthesis in bone cells while reducing osteoclast activity. Nowadays, its use is restricted due to the development of undesirable cardiovascular effects.

The administration of **fluorides** is perceived as an adjuvant therapy and must be combined with calcium supplementation. High fluoride intake may stain dental enamel and long-term administration for osteoporosis is not recommended due to an increased risk of fractures.

Teriparatide is a recombinant version of parathyroid hormone administered in the form of an injection. Phasic changes of PTH stimulate osteoblast synthesis of bone matrix.

7.8 Sex hormones

7.8.1 Sex hormones and their derivatives

Sex hormones are produced in men and women by gonads and the adrenal cortex (zona reticularis). Female sex hormones include **oestrogens** and **progestogens**; male hormones are called **androgens**. These steroids are involved in the development and maintenance of reproductive functions; they also have significant metabolic effects.

7.8.1.1 Release of female sex hormones and the menstrual cycle

Gonadoliberin (GnRH) released from the hypothalamus stimulates secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. The LH and FSH being intertwined in their production is essential for proper synthesis of ovarian hormones. FSH activates follicular growth in the ovaries. One of the follicles is transformed into the Graafian follicle, which can produce oestrogens. These oestrogens promote endometrial proliferation, and through a negative feedback mechanism, they inhibit the release of FSH from the pituitary gland.

Oestrogen concentration reaches its peak at approximately the 14th day of the cycle. This high concentration and subsequent sharp reduction causes a short-term increase in FSH concentration followed by a rise in LH levels (i.e., on the 14th-15th day of cycle).

This short-term increase in pituitary gonadotropins results in the rupture of the mature ovarian follicle, the ovum being released, and ovulation following.

Two days after the ovulation, the Graafian follicle is turned into a corpus luteum, which produces a large amount of progesterone. The secretory phase begins, in which the endometrium undergoes preparation for the implantation of the ovum. If fertilization does not occur, the production of progesterone decreases, the endometrium undergoes thinning and sheds its lining with the consequent menstrual bleeding.

7.8.1.2 Oestrogens

Physiologically produced oestrogens are **estradiol**, **estrone**, and **estriol**. In pharmacotherapy, **estradiol hemihydrate** can be used, but more common is the use of semi-synthetic esters (e.g., **estradiol valerate, estradiol dipropionate**, and **estradiol benzoate**) and synthetically prepared oestrogens (e.g., **ethinylestradiol**). They can be administered orally, intramuscularly, or as a transdermal therapeutic system. For topical (e.g., vaginal) application, natural estriol is a preferred choice.

Physiological effects
Oestrogens participate in the proliferative phase of the menstrual cycle as well as in maintaining libido, sexual behaviour, and preventing ovulation. They also affect the maintenance of pregnancy and the growth of the mammary glands. Oestrogens interfere with a relatively wide range of metabolic processes. They are involved in increasing bone mass density (i.e., by increasing calcium resorption and reducing bone resorption); they also cause retention of Na^+ and water and significantly affect the synthesis of some proteins in the liver (e.g., they cause an increase in production of coagulation factors and fibrinogen, but contrarily, decrease the level of antithrombin III). They also interfere with lipid metabolism by increasing the concentration of serum triacylglycerols and reducing the level of total cholesterol while establishing higher HDL and lower LDL levels.

Pharmacological effects
Due to the negative feedback mechanism, oestrogens block the release of gonadotropins, thus preventing ovulation. Monotherapy with oestrogens leads to endometrial hyperplasia with possible irregular bleeding, and long-term administration increases the risk of endometrial carcinoma. For this reason, it is necessary to administer oestrogens in combination with progestogens in women with an intact uterus. For women who have undergone a

hysterectomy, oestrogen monotherapy is possible. In men, by inhibiting the production of gonadotropins, oestrogens block spermatogenesis, suppress prostate proliferation, cause atrophy of the testicles, induce impotence, and reduce libido.

Pharmacokinetics
After oral administration, oestrogens are well-absorbed through the intestinal mucous membrane. During the first pass through liver, they are subjects of significant metabolic transformation. Their metabolites are conjugated with sulfuric and glucuronic acid. These metabolites undergo enterohepatic recirculation; along with the bile, they enter the intestine where the conjugates are cleaved by bacterial enzymes and about 80% are reabsorbed into the bloodstream. This recycling prolongs their presence in the body.

Side effects
Oestrogens may induce oedema due to increased retention of Na^+ and water. Furthermore, breast tension or pain, hyperpigmentation of the skin, and cholelithiasis are often reported.

The most serious undesirable effect of oestrogens is increased thrombogenesis and hence, an elevated risk of thromboembolic diseases. Oestrogens given as monotherapy lead to endometrial hyperplasia (see above).

Indications
Oestrogens are used as replacement therapy in case of their deficiency during sexual development as well as during sexual maturity and the postmenopausal period. Indications include, above all, primary and secondary amenorrhea, hypoestrogenic conditions associated with developmental disorders (e.g., Turner syndrome, etc.), premature menopause, and climacteric syndrome (see Chapter 7.8.3 Hormone replacement therapy). Combined with progestogens, they can be applied for recurring irregularities of the menstrual cycle. Synthetic ethinylestradiol is the most common component of combined hormonal contraceptives.

7.8.1.3 Selective oestrogen receptor modulators (SERMs)

SERMs are a heterogeneous group of drugs whose common property is the so-called **tissue-selective effect** and the ability **to modulate functions of oestrogen receptors**. Agents of this group act as either antagonists or agonists of oestrogen receptors depending on the target tissue.

The nature of their mode of action is explained by the existence of two isoforms of oestrogen receptors – α and β. α receptors are found primarily in vascular endothelial cells. Activation of this subtype of oestrogen receptors induces direct effects in the vascular wall, such as the release of nitric oxide (NO) and vasodilation. Oestrogen β receptors are present in many tissues (e.g., uterus, ovaries, lungs, CNS, prostate) as well as in arteries and veins, where they complement the effects mediated by the α receptors. In myocardial cells, they regulate the expression of NO-synthase. Natural oestrogens are agonists of both isoforms, whereas SERMs act agonistically mainly with the β isoform (i.e., an oestrogenic effect on bones causing increased density, conversely having an anti-oestrogenic effect on the breasts and uterus).

Clomiphene is an oestrogen receptor antagonist in the hypothalamus and anterior pituitary. It blocks the binding of oestrogens to these receptors, thereby blocking negative feedback.

Consequentially, the production of gonadotropins is increased, and ovulation is stimulated. Its main therapeutic indication is infertility due to anovulation.

Tamoxifen and **toremifene** act as antagonists of oestrogen receptors in breast tissue. They are indicated for long-term treatment of breast cancer after surgical removal of the breasts (as adjuvant therapy).

Raloxifene binds to α and β receptors with high specificity. It induces oestrogenic effects regarding bone mass and the lipid spectrum as well as an anti-oestrogenic effect in the endometrium and mammary glands. It is suitable for long-term therapy of osteoporosis in postmenopausal women, and it has been proven that it can reduce the risk of breast cancer development.

7.8.1.4 Selective tissue oestrogenic activity regulator (STEAR)

Tibolone is a special compound metabolised to three active metabolites after oral administration. Two of the metabolites have oestrogenic effects, and the third has gestagenic and weak androgenic effects. The metabolites have an affinity for oestrogen receptors in bone tissue; they reduce bone resorption and, moreover, moderately stimulate osteogenesis. Tibolone is indicated for the treatment of postmenopausal osteoporosis and to alleviate typical problems experienced in climacteric syndrome.

7.8.1.5 Antioestrogens

The only agent included in the category of direct antioestrogens is **fulvestrant**, which blocks oestrogen receptors in all target tissues. In metastatic and resistant breast carcinoma, intramuscular application of fulvestrant is used.

Aromatase inhibitors (e.g., **anastrozole**, **letrozole**, and **exemestane**) are indirectly anti-oestrogenic. They are given orally for oestrogen-dependent breast cancer therapy in postmenopausal women. Aromatase is responsible for the formation of oestrogens in the periphery and serves as the primary source of these hormones during the postmenopausal period.

7.8.1.6 Progestogens

The only natural agent of progestogens (e.g., progestins, gestagens) is **progesterone**. In women, it is produced by the corpus luteum, and during pregnancy, it is also produced by the placenta; in men, it is produced in the interstitial tissue of testes and in the adrenal cortex. Significant progesterone production in women commences in the luteal phase of the menstrual cycle.

Physiological and pharmacological effects
Progesterone prepares the female organism for pregnancy and then ensures its maintenance (e.g., the endometrium is led to the secretory phase, contractility of the myometrium is dampened, etc.). It suppresses ovulation and the menstrual cycle, and it changes the properties of cervical mucus. By stimulating cervical glands to increase production, the mucus becomes more viscous and impenetrable for sperm. It also increases the body temperature by 0.2-0.5 °C and has a negative effect on the metabolism of carbohydrates and lipids. Moreover, many

progestogens are able to compensate for the oestrogenic effects of sodium and water retention.

Pharmacokinetics

The biological half-life of progesterone in the body is short (about five minutes). There is a significant metabolic transformation in the liver during the first passage (i.e., a strong first-pass effect, almost 100% metabolized). Metabolites are excreted by the kidneys.

Side effects

Progesterone has an unfavourable effect on the lipid spectrum - it reduces HDL and increases LDL cholesterol. It also suppresses libido, and breast tension is often present due to the stimulation of mammary gland proliferation.

Indications

Progestogens are administered primarily perorally, intramuscularly, and transdermally. Indications are irregularities of the menstrual cycle, anovulation, and imminent abortion in the absence of endogenous production of progesterone (luteal insufficiency). They are also used to treat endometriosis, premature ovarian failure, as assisted reproductive treatment, contraceptives, and hormone replacement therapy (HRT) in menopause.

Progestogens

Synthetic progestogens can be divided (according to their chemical structure) into four groups:

- progesterone derivatives: medroxyprogesterone, chlormadinone, dydrogesterone, and others;
- 19-nortestosterone derivatives: norethisterone, dienogest, and others;
- third generation progestogens: levonorgestrel, desogestrel, norgestimate, and others; and
- atypical progestins: drospirenone, tibolone.

It is also possible to classify individual progestogens based on their residual androgenic activities:

- those with mild androgenic effects: norethisterone, levonorgestrel;
- those without both androgenic and antiandrogenic effects: desogestrel, gestodene, norgestimate;
- those with antiandrogenic effects: cyproterone, dienogest, chlormadinone; and
- those with antiandrogenic and antimineralocorticoid effect: drospirenone.

Substances with mild androgenic activity may aggravate acne and hirsutism; progestogens with an antiandrogenic effect can improve the condition of acne, but may, for example, lower libido.

Levonorgestrel is the most common component of combined contraceptives, HRT, and it is also used as emergency post-coital contraception.

Norethisterone is a component of combined contraceptives and HRT preparations, and it is also used as a treatment for menstrual cycle disorders.

Dienogest is a part of combined contraceptives and used for the monotherapy of endometriosis.

Cyproterone is a progestogen with antiandrogenic activity. Previously, it was used as a combined oral contraceptive, but this indication has been abandoned due to the suspicion of serious side effects. It is currently indicated for the treatment of severe androgen-sensitive acne and for the treatment of hirsutism in women. In men, it is favoured for its combined antiandrogenic action in various sexological indications (see Chapter 7.8.1.8 Androgens).

Another representative is **drospirenone**, which has a prominent antimineralocorticoid effect.

7.8.1.7 Antigestagens

Antigestagenic drugs may act either as inhibitors of steroid hormone synthesis or as progesterone receptor antagonists. Nowadays, only the second group is used therapeutically, with its core representative being **mifepristone**. In health care facilities, it is the preferred choice for the pharmacological termination of pregnancy as a combination therapy including prostaglandins (e.g., misoprostol). Common side effects of this treatment include uterine contractions, GI smooth muscle contractions, uterine bleeding, and blood pressure disorders.

7.8.1.8 Androgens

Natural male sex hormones are **testosterone** and **dihydrotestosterone**. For therapeutic purposes, semi-synthetic derivatives of testosterone, such as its esters (e.g., **testosterone propionate**, **testosterone decanoate**, etc.) and synthetic androgens (e.g., **mesterolone** and **dehydroepiandrosterone**), are commonly used.

Managing the release of male sex hormones
Hypothalamic GnRH stimulates the production of adenohypophyseal LH and FSH. Under the influence of LH, which is called interstitial cell-stimulating hormone in men, interstitial (Leydig) cells develop and produce androgens. FSH stimulates the maturation of germ cells in the seminiferous tubules of the testes, and the process of spermatogenesis is initiated. Sertoli cells under the influence of FSH also participate. They transform a portion of testosterone produced in Leydig cells to estradiol with the aromatase enzyme. Estradiol, along with testosterone, contributes to sperm maturation.

Physiological and pharmacological effects
Testosterone ensures the maturation of reproductive organs, the development of secondary sexual characteristics, physical growth, physiological spermatogenesis, the maintenance of libido, increases protein synthesis, and has an anabolic effect on muscle and bone mass. Therapeutic doses of testosterone, its esters, and synthetic androgens can cause the retention of salts, calcium, and water in the body; they can also induce or exacerbate the symptoms of acne (so-called steroid acne) and increase blood pressure. Androgen administration during childhood can lead to premature puberty and growth disorders. Higher doses in adulthood can lead to disorders of spermatogenesis (oligospermia) and prostatic hyperplasia.

Indication
Testosterone supplementation is needed in men with primary or secondary hypogonadal disorders, both innate (e.g., developmental disorders) and acquired. It is used in women, as well, but only rarely. After an ovariectomy and/or hysterectomy, it is combined with oestrogens to stimulate bone mass density or if libido is reduced. Other indications are of sexological character (e.g., transsexuality).

Pharmacokinetics
After oral administration, testosterone is absorbed in the GIT, but due to a strong first-pass effect, it is subject to nearly complete metabolic degradation. For this reason, testosterone is applied in its ester forms intramuscularly. The muscular depot releases testosterone into systemic circulation gradually. Metabolites are excreted via urine.

7.8.1.9 Anabolic Steroids

Nandrolone was the only drug registered in the Czech Republic. It was used in cachectic states involving excessive loss of muscle mass to speed up recovery after severe surgical procedures and as a short-term treatment for osteoporosis induced by corticosteroids. Nowadays, nandrolone and other synthetic androgens are often abused by professional and recreational athletes (especially in bodybuilding and fitness) and are among the list of forbidden substances due to this doping phenomenon.

7.8.1.10 Antiandrogens

Antiandrogens are drugs that reduce the effect of androgens either by interfering with their biosynthesis and/or by antagonising their effects on androgen receptors.

A) 5α-reductase inhibitors
The 5α-reductase enzyme converts testosterone to dihydrotestosterone, which is a strong androgen receptor agonist and the main physiological androgen. 5α-reductase inhibitors are indicated for the treatment of benign prostatic hyperplasia (BPH) and are taken orally. In addition to BPH, **finasteride** is also used in the early stages of androgenic alopecia for younger male patients. **Dutasteride** is reserved for the treatment of moderate to severe BPH.

B) Androgen receptor antagonists
Drugs from this group block the effect of androgens in target tissues. They can be classified into two groups: the group with steroidal structures (e.g., spironolactone, cyproterone) and those which have non-steroidal structures (e.g., flutamide, bicalutamide).

Spironolactone is also an aldosterone receptor antagonist, but it primarily acts as a potassium-sparing diuretic (Chapter 5.1.3.3 Potassium-sparing diuretics). Its antagonistic effect on androgen receptors is helpful for the treatment of acne and hirsutism.

Cyproterone acts as an antagonist at androgen receptors as well as by reducing testosterone production in the testes. Its antiandrogenic action is used for the therapy of sexual deviations, precocious puberty, and prostate cancer. Moreover, it also shows progestogen activity (see above), and in combination with oestrogens, it is a part of the peroral therapy of acne or hormone replacement therapy for climacterium.

Flutamide and **bicalutamide** are antagonists of androgen receptors used to treat advanced prostate cancer along with GnRH antagonists (see Chapter 7.4.1.4 Hormones regulating release of gonadotrophins).

C) Androgen biosynthesis inhibitors
This group includes the azole antimycotic, **ketoconazole**. This substance inhibits some of cytochrome P450 enzymes involved in steroid hormone synthesis. This inhibition is not specific to androgens; glucocorticoid biosynthesis is inhibited, as well.

7.8.2 Hormonal Contraception

The most common method of preventing unplanned pregnancy is through the use of hormonal contraceptives. 2.5 billion women of reproductive age worldwide, around 30% in Europe and about 40% in the Czech Republic, use hormonal contraceptives.

Based on the route of administration, hormonal contraceptives (HC) are categorized as being administered in either an oral and parenteral form. Furthermore, contraceptives can be divided according to the content of the individual hormones. They can be further subdivided based on their duration of use (e.g., continuous, after sexual intercourse).

7.8.2.1 Combined HC: oestrogens with progestogens

The mechanism of action of combined preparations is mediated mostly through negative feedback in the hypothalamus. Gonadotropin secretion is reduced; thus, ovulation is prevented.

The oestrogen component is most often **ethinylestradiol** at low (15-30 μg), medium (35-40 μg), or an exceptionally high (50 μg) dose. **Estradiol valerate** is a prevalent choice.

The progestogen component is usually **levonorgestrel**, **etonogestrel**, **desogestrel**, **drospirenone**, or any other synthetic analogue, from which there are numerous options to choose based on the most suitable pharmacokinetic profile for the individual dosage form.

Oral preparations are commonly referred to as combined oral contraceptives (COC). Depending on the oestrogen and progestogen ratios, monophasic, biphasic, triphasic, and sequential COC can be distinguished. In **monophasic COC**, the dose of oestrogen and progestogen is constant in all pills. In **biphasic** and **triphasic COC**, tablets are divided into two and three phases, respectively, with the possibility of varying the doses of both the oestrogen and progestin components. **Sequential preparations** are designed similarly with more phases; in some, progestin can be completely absent. The aim of these complicated combinations is the most precise imitation of the physiological cycle while maintaining anovulation.

Combined HC also exist in the parenteral form of a transdermal patch or vaginal insert (ring).

7.8.2.2 Progestogen-only HC

This form of HC only contains a progestogen component without any oestrogen. The mechanism of action lies in the inhibition of endometrial proliferation, thickening of cervical mucus, and in about 70% of women, ovulation suppression, as well.

Oral progestogen-only HC, so-called progestogen-only pills (**POP**) or mini-pills, need to be taken with strict regularity every 24 hours and preferably continuously and long-term (without a pause for pseudomenstruation).

Progestogen-only HC are also available as a depot injection, subcutaneous implant, or intrauterine device (IUD). This type of contraception is suitable for women who cannot be treated with oestrogens (e.g., with history of thromboembolic disease, advanced age, smoking, or in a lactation period).

A very common side effect is irregular bleeding. A decrease in libido and consequential deterioration in the quality of one's sex life, weight gain, and the development of acne may occur, as well. A crucial factor for the manifestation of these side effects is the nature of the progestogen administered (residual androgenic activity). The most commonly used representatives are **desogestrel**, **etonogestrel** (in implants), **medroxyprogesterone** (intramuscularly, injection.), and **levonorgestrel** (in IUDs).

7.8.2.3 Post-coital contraception

Nowadays, two compounds are registered in the Czech Republic for this indication, namely ulipristal and levonorgestrel.

Ulipristal is a selective progesterone receptor modulator (SPRM) capable of preventing conception if used orally within 120 hours after unprotected sexual intercourse mediated via inhibited or at least disrupted ovulation.

Levonorgestrel is a progestogen. Its mechanism of action is not entirely clear. However, its effects are carried out by delayed transport of fertilized ovum through Fallopian tubes and changes in the endometrium, making occurrence of proper implantation of the ovum difficult. The use of this tablet is effective if taken within 72 hours after unprotected sexual intercourse.

Emergency post-coital contraceptives often affect the upcoming menstrual cycle. Unusual pain in the breast and abdomen and irregular bleeding are frequent.

7.8.2.4 Positive effects of HC

It has been shown that HC use reduces the risk of endometrial and ovarian cancer. Furthermore, HC regulates dysmenorrhea, reduces the incidence of ovarian cysts, and the risk of developing osteoporosis.

7.8.2.5 Side effects of HC

For HC containing an oestrogen, incidence of thromboembolism is increased (i.e., 3-4 x more frequent), and the risk of myocardial infarction and stroke rises, as well. This is especially true for women over 35 years old, particularly if they are obese or smoke tobacco. Less serious side effects, such as presence or worsening of migraines, changes in libido, tendency to swell and gain weight, and pigment spots on the skin may be encountered. In the first few months of HC use, bleeding may be irregular or it may be even absent. This condition should recede, otherwise a preparation with different progestogen constituent should be taken into consideration.

7.8.2.6 Therapeutic indications of HC

In addition to controlling conception, HC products can be used for therapeutic indications such as dysmenorrhoea and hypermenorrhoea. Likewise, they may be used to moderate very serious acne that does not respond to local therapy.

7.8.2.7 Interaction of HC with other drugs

Drug interactions may affect the plasma concentrations of individual hormone components, hence the effectiveness of the contraceptive method. **Absorption** interference can occur if intestinal adsorbents (e.g., medicinal charcoal) and lipid-lowering ion-exchange resins (e.g., bile acid sequestrants) are concomitantly administered. These compounds adsorb or directly bind to molecules present in the GIT, and therapeutic drugs are no exception. Thus, HC should be taken at least three hours before or after co-therapy susceptible to interaction. Absorption of oestrogens and progestogens may be compromised by vomiting and diarrhoea, in which case it is not recommended to rely on the contraceptive effect for the next seven days.

On the level of **enterohepatic circulation**, HC preparations may interact with broad-spectrum antibiotics (e.g., particularly broad-spectrum penicillins, tetracyclines, macrolides, and others). These antibiotics can cause a breakdown of the intestinal microflora causing the production of hydrolytic enzymes important for the deconjugation of hormone metabolites in the second phase of biotransformation. Deconjugated hormones are resorbed via the intestinal mucous membrane into the bloodstream. If, due to the effect of the antibiotics, deconjugation is blocked and drugs do not undergo enterohepatic circulation, then their persistence in the body and their plasma concentrations fall below the levels necessary to block the ovulation.

On the level of **biotransformation,** inhibitors or inducers of CYP enzymes are of great importance. Inductors induce more extensive metabolism of steroid hormones; thus, they reduce the effectiveness of contraceptives. In contrast, CYP inhibitors may increase plasma concentrations of hormones. Ethinylestradiol is an inhibitor of the CYP family of enzymes, so it can increase plasma concentrations of other drugs.

7.8.3 Hormone replacement therapy (HRT)

HRT (or hormonal substitution therapy, HST) is a preventative therapeutic method for managing the symptoms of climacteric syndrome in women during perimenopause. It can prevent metabolic and organic pathological changes (e.g., osteoporosis, cardiovascular disease, atrophy of the urogenital tract) caused by the reduced production of endogenous oestrogens. The main aim of HRT is to maintain approximately the same plasmatic levels of female sex hormones during menopause as were produced while of fertile age.

Natural and semi-synthetic **oestrogens** (e.g., estradiol, estriol, estradiol valerate) are commonly used for this purpose. Unintended proliferation of the endometrium (in women with intact uterus) is avoided by use of a combined preparation with a **progestogen** component (e.g., medroxyprogesterone, dienogest, drospirenone, cyproterone, etc.). The

oestrogen-only form of HRT is acceptable only in women after a hysterectomy. Representatives of selective tissue estrogenic activity regulators (**STEAR**), like **tibolone** (see 7.8.1.4 Selective tissue oestrogenic activity regulator (STEAR)), show clinical potential for use in HRT, too.

There are many different dosage forms of HRT: oral, transdermal, vaginal, intramuscular depot injection, and topical forms (e.g., via vaginal globules and creams). Topically applied preparations affect mainly the vaginal mucosa and alleviate urogenital atrophy, but they do have a major systemic effect, too.

Adverse reactions include an increased risk of hormone-dependent tumours (e.g., breast cancer), a negative effect on lipid metabolism (i.e., in HRT containing progestogen), a higher risk of thromboembolic events, and risk of cholelithiasis.

In women who refuse or are contraindicated for HRT, the administration of food supplements containing **phytoestrogens** may be considered. Phytoestrogens are naturally occurring compounds that have a non-steroidal chemical structure while exhibiting weak oestrogenic activity (e.g., isoflavones and lignans). Significant concentrations are found in soybeans *(Glycine max)*, red clover leaves (*Trifolium pratense*), and black snakeroot (*Cimicifuga racemosa*).

8 Substances affecting pain, inflammation and functions of the immune system

8.1 Local anaesthetics

Local anaesthetics (LA) are agents used to block pain sensations through the inhibition of conduction of sensitive stimuli along axons. After their penetration into nerve fibres, they block sodium channels, thereby inhibiting depolarisation and the action potential spreading (AP propagation). However, their mechanism of action is not specific to sensitive nerve fibres; therefore, we can expect side effects in other excitatory tissues and organs, mainly in the CNS and cardiovascular system.

LA are bases with the amphiphilic chemical structure of the molecule consisting of a lipophilic aromatic part and a hydrophilic ionized part connected by amide or ester binding (corresponding to the amide and ester classification of LA).

The effect of the LA is dependent on the ratio of its fat to water solubility and the pH of the environment. Their efficacy is higher in an alkaline environment, wherein most molecules exist in their non-ionized form; therefore, the local anaesthetic can better penetrate via the membrane into the axon. In contrast, they have limited efficacy in an acidic environment (e.g., in inflamed tissue) because the ionized molecules cannot penetrate intracellularly.

Absorption of LA is also dependent on their physical and chemical properties, drug dose, site of administration (e.g., local perfusion of the tissue), and whether a vasoconstrictive agent is present. Vasoconstrictive agents (as additives) decrease the LA distribution to systemic blood circulation, reduce local bleeding, prolong the anaesthetic effect, and decrease consumption of LA (i.e., a lower amount of LA are required). Among commonly used vasoconstrictive agents belong catecholamines (**adrenaline**, **noradrenaline**), alpha1 agonists (**naphazoline**), and derivatives of vasopressin (**terlipressin**). Vasoconstrictive agents are contraindicated for use in acral (distal) parts of the body due to risk of ischemic necrosis. Biotransformation of ester LA occurs in plasma via esterase enzymes, while amide LA are metabolized in the liver via the cytochrome P450 system. Hepatic diseases (hepatopathy) can lead to a prolongation of the biotransformation of amide LA.

Side effects

Most frequent local side effects include:
- pain and burning sensations shortly after injection (drug administration),
- haematomas (i.e., a localized collection of usually clotted blood outside the blood vessels),
- traumatic nerve injury, and
- tissue necrosis (gangrene).

Most frequent systemic side effects (most frequently referred):

- topical allergic reaction;

- adrenergic effects owing to the use of vasoconstrictive agents (e.g., adrenaline), such as palpitation, redness, asthenia, hypertension, tachycardia, and anaphylaxis;

- cardiotoxicity (i.e., decreased conduction rate of the action potential in the myocardial conducting system (apparatus) leading to bradycardia, vasodilation, decreased myocardial contractility, and hypotension with the risk of cardiac arrest); and

- CNS toxicity (i.e., metallic aftertaste (dysgeusia), muscle tremor, cramps, respiratory depression, loss of consciousness, and vertigo).

Rarely, Quincke's oedema can occur, which is a rapid non-inflammatory angioneurotic swelling of the face including lips, eyes, and cheeks. It also often affects the mucosal and submucosal tissues of the larynx causing airway obstruction and putting the patient at risk of suffocation.

8.1.1 Local anaesthesia techniques

Superficial (**topical**) anaesthesia includes topical administration of LA on the skin surface, the mucosa of the GIT (e.g., pharynx, oesophagus, and rectum), the respiratory tract (e.g., nasal cavity), the urinary tract (e.g., catheterization), and eye cornea. For these types of LA, the drug is usually incorporated into a pharmaceutical form of spray, solution for topical use, gel, cream, patches, eye drops, etc. An example of a special type of topical anaesthesia is the EMLA cream preparation. This contains a combination of lidocaine and prilocaine administered on the skin under an occlusion bandage for better penetration of LA through mucosa and skin to the nerve endings in subcutaneous tissues. (See the Chapter 8.1.2.2 Amides.)

Infiltration anaesthesia is a form of parenteral administration of local anaesthetic subcutaneously via an infiltration of the tissues in the intended area (i.e., at the surgical site) close to nerve endings (presumed). Only small volumes and very low concentrations of LA and vasoconstrictive agents are used.

Regional anaesthesia includes central and peripheral techniques involving LA; they may be combined with general anaesthesia (see the Chapter 8.2 General anaesthetics).

Peripheral conduction anaesthesia (sometimes called a "**peripheral nerve block**") is the direct administration of a small volume of LA by a syringe (1-2 ml) to the exit area of the sensitive nerve (i.e., area nervina) or along the nerve itself. A larger volume of local anaesthetic is injected to anaesthetize a stronger nerve plexus (e.g., brachial or lumbar plexus) to block pain around a specific group of nerves.

Central conduction anaesthesia is a regional blockade wherein a shot of local anaesthetic is administered near the spinal cord and the nerves that connect to it. **Epidural** and **spinal anaesthesia** can be distinguished in accordance with the site of local anaesthetic

administration; either the shot will be administered to the epidural or to the subarachnoid space, respectively, to block pain from that entire region of the body. The dose of local anaesthetic for spinal blocks is much smaller than that for epidural blocks. There is no use of vasoconstrictive agents for central types of the conduction anaesthesia.

8.1.2 Classification of local anaesthetics

When classified according to their intensity of action, anaesthetics are categorized as follows:

- weak: procaine, benzocaine;

- intermediate strength: lidocaine, trimecaine; and

- strong: tetracaine, bupivacaine, levobupivacaine, articaine, ropivacaine, mepivacaine.

According to the chemical structure of local anaesthetics, they can be divided into two groups:

- esters: cocaine (historical meaning, with a strong addiction potential, used only occasionally by ORLs for local anaesthesia of the eardrum), procaine, tetracaine, benzocaine; and

- amides: trimecaine, lidocaine, mepivacaine, bupivacaine, prilocaine, ropivacaine, cinchocaine, and articaine.

8.1.2.1 Esters

Esters are structural analogues of para-aminobenzoic acid (PABA). Therefore, they have a higher allergenic potential. A crossed allergic reaction (i.e., cross-reactivity) occurs in the ester group of anaesthetics.

Procaine is a typical representative of ester LA. It is an older synthetic anaesthetic compound with low toxicity and a short effect. Procaine has limited transmucosal and transdermal penetration. Therefore, it must be administered by injection.

Tetracaine, is an ester with high toxicity. Thus, it can only be used as a topical local anaesthetic like **benzocaine.** They are used mainly for mucosal anaesthesia of the oropharynx (oral cavity and pharynx) in combination with antiseptics.

8.1.2.2 Amides

Amides are used more frequently than esters. Allergic reactions are less common and are most often caused by an antimicrobial agent (e.g., methylparaben). Caution is required when they are used in patients with hepatopathy (biodegradation of amides occurs by liver enzymes). Amides penetrate cytosol well via the cytoplasmic membrane.

Lidocaine has a fast onset of action, intermediate duration of action, and antiarrhythmic effect. Lidocaine is suitable for all kinds of local anaesthesia techniques.

Trimecaine has a longer onset of action and intermediate duration of action. Like lidocaine, it is also used intravenously in cardiology for its potent antiarrhythmic effect.

Bupivacaine has a long onset of action and a long duration. The main side effect of bupivacaine is cardiotoxicity.

Articaine has a fast onset and intermediate duration of action. The ready-made preparations available on the market contain articaine combined with a vasoconstrictive agent, thus the local anaesthetic effect is significantly prolonged in such a combination. Articaine is frequently used in dentistry as well as **mepivacaine**.

A eutectic mixture of local anaesthetics (EMLA) is a mixture of **lidocaine** and **prilocaine** for topical use on unbroken skin. EMLA is often applied in paediatric patients for about 90-120 minutes prior to invasive techniques such as blood withdrawal, cannulation, and punctures.

8.2 General anaesthetics

General anaesthetics induce reversible unconsciousness without significant reactions from the autonomic nervous system or reflexes of skeletal muscles. They inhibit pain sensations and lead to amnesia (i.e., lack of memory of events) for the time required for the surgical procedure.

8.2.1 Stages of general anaesthesia

Stages of general anaesthesia (GA) can be best described after ether administration, which is no longer used in clinical anaesthetic practice.

1. Analgesic stage (pre-anaesthetic stage): This state can be characterized by decreased pain perception; the patient is still conscious, but sedated.

2. Excitatory stage ("vagus stage"): This translates to increased somatic and autonomic reflexes as well as the loss of consciousness, motoric restlessness, irregular breathing, and activation of the vagus nerve functions. During this stage, there is a risk of bronchospasm, laryngospasm, emesis, and cardiac arrest.

3. Stage of surgical anaesthesia: This stage is recommended for undergoing the surgical procedure. The patient has regular breathing and corneal reflexes and movement of the eyeballs is not present. It continues with the onset of the loss of consciousness, analgesia takes effect, somatic reflexes are not present, and myorelaxation occurs.

4. Stage of the spinal medulla paralysis: This leads to inhibition of the vasomotor and respiratory centres, relaxation of sphincter muscles, and coma. This stage is induced by an overdose of a general anaesthetic and should never be reached.

8.2.2 Premedication before the general anaesthesia

Premedication of the patient is a specific pharmacological preparation before the general anaesthesia and surgical procedure. It prevents adverse reactions in the organism and reduces the number of drugs used for general anaesthesia. **Benzodiazepines** (e.g., midazolam, diazepam) are used for their anxiolytic and sedative effect. **Opioids** (e.g., morphine, fentanyl) are used for their analgesic effect. An **anti-ulcer** agent (e.g., ranitidine) is used for its inhibitory effect on gastric secretion. A **parasympatholytic** (**antimuscarinic**) drug (e.g., atropine) stabilizes the autonomic nervous system; however, atropine use is considered obsolete in premedication in modern medicine due to its side effects. A **prokinetic** agent (e.g., metoclopramide) is used to promote stomach emptying. And finally, a neuroleptic agent (e.g., droperidol, which is not registered in the Czech Republic) is used as an antiemetic and for central sedative effects.

8.2.3 Inhalational anaesthetics

An equilibrium between the blood and inhaled air is required to reach the optimal concentration of general anaesthetic in the CNS. The mechanism by which the anaesthetic agent carries out its effect depends on its liposolubility and a nonspecific influence on ion channels in the cytoplasmic membrane of neurons (i.e., reversible impairment of its fluidity). The main parameter monitored is the minimal alveolar concentration (MAC), which reflects the anaesthetic concentration in the inhaled air; the value of the MAC determines the concentration needed to reach the stage of surgical tolerance in 50% of patients.

Liquid inhalational anaesthetics

Diethyl ether (ether) has become obsolete in clinics because it is combustive and induces a long excitatory stage of anaesthesia. The advantage of ether anaesthesia is its simple use in a field setting as it does not require special anaesthetic apparatus. Therefore, it is often used as anaesthesia in laboratory animals.

Halothane is a volatile halogenated hydrocarbon anaesthetic that provides relatively rapid induction of anaesthesia; however, with it, comes the risk of cardiac and respiratory failure. Due to the hepatotoxicity of its metabolites and the risk of malignant hyperthermia, halothane is currently limited to use only in special situations.

Some volatile anaesthetic ethers are **isoflurane**, **sevoflurane**, and **desflurane**. Isoflurane belongs to agents with a favourable anaesthetic profile. It is non-toxic, with vasodilator properties. Isoflurane induces respiratory depression. Isoflurane, as well as desflurane, are not used for the induction of anaesthesia, but only for maintenance due to irritation of the respiratory tract and risk of laryngospasm and bronchospasm. Sevoflurane has a pleasant odour and it does not irritate respiratory tract. Therefore, it is suitable for the induction of general anaesthesia in paediatric patients.

Gas inhalation anaesthetics

Nitrous oxide N$_2$O ("laughing gas") is a colourless gas, which is used to induce anaesthesia and sedation during ambulatory procedures and childbirth (e.g., dentistry, gynaecology, and obstetrics). It has mild anaesthetic and strong analgesic effects. Side effects include arrhythmias, euphoria, live dreams, and impaired haematopoiesis after long-term use (i.e., anaesthesia exceeding six hours).

A modern, but expensive, inhalation anaesthetic gas is xenon.

8.2.4 Injection anaesthetics

Barbiturates with ultra-short action (**thiopental**; methohexital - not registered in the Czech Republic) are suitable for the induction of general anaesthesia and sedation. In obese patients, there can be a delayed awakening from anaesthesia; due to anaesthetic lipophilicity, agents easily accumulate in adipose tissues wherein they create deposits from which they are slowly released into systemic circulation.

Nonbarbiturate anaesthetics include ketamine, propofol, and etomidate.

Ketamine is an NMDA-receptor antagonist in the CNS, and it induces a dissociation type of anaesthesia wherein patients experience marked depersonalization or an "out of the body experience" and a detachment from reality. It is suitable for use as induction and conduction anaesthesia in short surgical procedures and urgent ambulatory care for short procedures, such as the repositioning of dislocated joints. It increases blood pressure; therefore, it is contraindicated in patients with hypertension and cardiac insufficiency. Ketamine has significant psychotropic properties (i.e., it induces intense visual and auditory hallucinations).

Propofol and **etomidate** are short-acting intravenous anaesthetics with a rapid onset of action and without analgesic properties. Etomidate is used as an initial anaesthetic agent. It has a safe hemodynamic profile, but it suppresses corticosteroid synthesis in the adrenal cortex. Propofol is the only intravenous general anaesthetic suitable as both induction and conduction anaesthesia. It can be used as part of a general anaesthesia maintenance technique called total intravenous anaesthesia (TIVA).

8.2.5 Complications of general anaesthesia

During the induction anaesthesia, the most frequently occurring complications include hypotension, arrhythmias, laryngospasm, and aspiration of gastric content.

Over the course of general anaesthesia, there can be significant blood pressure changes, arrhythmias, hypoxia, hypothermia, and blood coagulation disorders.

After anaesthesia, hypotension, confusion, tremor, delayed awakening from anaesthesia, prolonged myorelaxation, nausea, and vomiting may occur.

Malignant hyperthermia is a rare, but dangerous, side effect following the administration of a peripherally depolarizing neuromuscular blocking agent (e.g., suxamethonium, syn. succinylcholine), usually in combination with a general anaesthetic (e.g., halothane). Genetic abnormality of the receptor controlling calcium release from the sarcoplasmic reticulum in the skeletal muscles (i.e., the ryanodine receptor gene) leads to a sudden excess of free Ca^{2+} in myocytes followed by muscle fasciculations and twitches with an uncontrolled increase in oxidative and anaerobic metabolism in skeletal muscles. As a result of this hypercatabolic state, progressive hyperthermia develops, and lactic acidosis is induced.

This condition can be treated by **dantrolene**, a blocker of calcium release from the sarcoplasmic reticulum (see the Chapter 12.1 Muscle relaxants), which simultaneously lowers the body temperature of the patient through a cooling mechanism. Early treatment of hyperkalemia is desirable. Calcium-channel blockers should be avoided if dantrolene is used because they may worsen hyperkalemia.

8.3 Opioid analgesic drugs (anodynes)

Opioid analgesic drugs have been used for therapeutic purposes since the ancient world, and they are a very effective means of pain treatment. The oldest written mention of these substances dates back to between 8000-5000 B.C. They are sometimes referred to as anodynes, as well. Administration of opioids can manage strong acute pain as well as cancer pain. Substances belonging to this group are of natural origin (e.g., morphine), semi-synthetic origin (e.g., heroin, buprenorphine), or synthetic origin (e.g., pethidine, piritramide, fentanyl).

8.3.1 Effects of opioid analgesics

Effects of opioid analgesic drugs are mediated by opioid receptors, which are found both in the central nervous system and peripheral tissues (e.g., in enteric nervous system). Presently, various types of opioid receptors are recognized. All are specified by Greek letters and the three of the most prevalent are used to represent opioid receptors: μ (mu), κ (kappa), and δ (delta).

Effects of opioids can be classified as central and peripheral. The main **adverse effects** of opioid analgesics are depression of the respiratory centre, nausea, vomiting (particularly at the beginning of therapy), dependence, constipation, urinary retention, and difficulties with bile and pancreatic fluid outflow. Fortunately, for most of these effects, apart from constipation, **tolerance** develops following long-term therapy. Withdrawal of opioids after long-term administration must be gradual.

The **central effects** are as follows:

- The main central effect of opioids involves the **analgesic effect**. The principle of this effect consists of the inhibition of painful stimulus transmission and a change of its processing in the CNS, particularly in thalamus and limbic system.
- **Depression of respiratory centre** is dose dependent. Thus, higher doses can lead to intoxication and respiratory paralysis. For many people, this represents an effect limit

for the use of these substances, particularly with new-borns and small children because their respiratory centre is very sensitive.

- Stimulation of receptors in the area postrema in the medulla oblongata provokes irritation of vomiting centre. Nausea and vomiting can occur following administration of therapeutic doses of opioids.
- The formation and development of dependence is another problematic effect, especially following chronic administration. Heroin (diacetylmorphine) is a frequently abused opioid following chronic clinical administration of legal opioids. It is not prescribed therapeutically in most countries nowadays; however, in the past, it was commonly used for therapeutic purposes.
- **Miosis** is a significant diagnostic symptom of opioid use, particularly for people abusing opioids.

The **peripheral effects** include:

- Peripheral effects involve an increase in the tone of smooth muscles and can, in the case of GIT affection, lead to **constipation**, which occurs with high frequency in patients treated with strong opioids. Large numbers of patients also experience nausea and vomiting at the beginning of therapy.
- **The tone of both urinary bladder sphincters** (i.e., causing urine retention) and the **sphincter of Oddi** (i.e., causing difficulty in bile and pancreatic juice outflow) is increased.
- Opioids have **histamine-liberating effects** on mast cells, which causes skin itch due to the stimulation of histamine H_1 receptors on the free nerve endings by histamine.

8.3.2 Classification of opioid analgesics

Opioids can be classified according to their action on receptors (e.g., agonists, agonists-antagonists, antagonists) and according to their effectiveness (i.e., weak and strong). Agonists stimulate all types of receptors agonists-antagonists act on different receptors, sometimes as agonists and sometimes as partial agonists or antagonists. Antagonists inhibit all types of opioid receptors. Atypical opioids affect opioid receptors as well as other neurotransmitter systems.

8.3.2.1 Strong opioids

Strong opioids are pure, strong agonists of opioid receptors. This group includes, for example: morphine, pethidine, methadone, piritramide, fentanyl, alfentanil, and sufentanil. Unlike weak opioids, they do not have a ceiling effect on analgesic action; thus, in the case of tolerance development, it is possible to continually increase the dose.

Morphine is a natural opioid substance and represents reference drug used as a basis of comparison to the effects of other opioid drugs. It is the main alkaloid of opium (dry juice from the poppyheads – *Papaver somniferum*). Morphine characteristically has high pre-systemic elimination; only 15-25% of the given substance will reach the blood in an unchanged form following oral administration. The main indication is very strong pain, which cannot be affected by other means.

Pethidine has, compared to morphine, a smaller analgesic effect. Following pethidine administration, smooth muscle tone is increased to lesser extent than morphine, thus this substance is indicated for use in colic pain (i.e., biliary and renal colic).

Methadone is used as an analgesic drug and as an oral substitute for individuals dependent on opioids. Orally administered methadone penetrates the CNS slower, does not produce euphoric feelings, and in dependent persons, it prevents development of withdrawal syndrome.

Fentanyl is approximately 100 times stronger than morphine. It can be used in the form of transdermal plasters for severe chronic pain. Furthermore, it is used as part of a special general anaesthesia type called neuroleptanalgesia, which consists of fentanyl given in combination with a neuroleptic drug.

Alfentanil and **remifentanil** have a very short effect, lasting up to only 10 minutes. **Sufentanil** is the strongest analgesic drug, at about 1,000 times stronger than morphine.[5]

8.3.2.2 Weak opioids

Weak opioids are known as substances with a so-called **ceiling effect**. This means that we reach the maximum effect ("ceiling") after dose increase, and further increase will not bring a more effective therapeutic effect. The advantage of these drugs is the smaller risk of dependence development. Codeine and dihydrocodeine are examples of weak agonists.

Codeine is an opioid agonist and a derivative of morphine. Its analgesic potency is very attenuated. It is combined with paracetamol for a stronger analgesic effect. However, an inhibitory effect on the cough centre is present, and for this reason, codeine alone is used in small doses, particularly as antitussive drug.

8.3.2.3 Agonists-antagonist

The group of agonists-antagonists involves, for example: buprenorphine, pentazocine, nalbuphine, and tramadol.

Buprenorphine is a weak partial agonist at μ receptors and an antagonist at κ receptors. It is used as an analgesic drug and for substitution therapy for persons dependent on opioids.

8.3.2.4 Atypical opioids

Tramadol acts predominantly as an agonist at μ receptors, and at the same time, it inhibits reuptake of serotonin at synapses. Its analgesic effect is also mediated by acting at α_2 receptors. For these reasons, some authors refer to tramadol as a so-called atypical opioid. It has approximately 1/6 of morphine's analgesic effect, and its adverse effects are experienced to smaller extent. It is combined with paracetamol to increase efficacy.

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[5] An interesting drug is carfentanil, which is 10,000x stronger than morphine. It is used in veterinary medicine for immobilization of large animals (e.g., elephants or rhinos).

8.3.2.5 Antagonist

The most frequently used antagonists of opioid receptors are represented by naloxone and naltrexone.

Naloxone acts as antagonist on all types of opioid receptors. It is indicated, for example, for the therapy of respiratory centre depression, which is caused by overdosing with an opioid agonist, or to terminate the effect of fentanyl during neuroleptanalgesia.

Naltrexone has similar antagonistic effects to naloxone. It is possible to use it for individuals with a dependence on opioids after opioid substance(s) withdrawal as part of relapse prevention.

8.4 Non-opioid analgesic drugs

This group of non-opioid analgesics is comprised of substances with analgesic effects that are not mediated by binding to opioid receptors; therefore, they do not have the typical adverse effects of opioid analgesics (e.g., dependence, constipation, depression of respiratory centre, etc.). Some of the substances have, besides analgesic effects, antipyretic effects (e.g., analgesics-antipyretics), and others have both antipyretic and antiphlogistic effects (e.g., non-steroidal anti-inflammatory drugs). Classification of a substance into one of these groups can often be complicated because their effects partially overlap.

Choosing an opioid analgesic drug versus a non-opioid analgesic drug is accomplished through the evaluation of the nature and severity of the pain. The combination of these two types of pain-killers, for instance, a combination of paracetamol and codeine or the use of so-called adjuvant analgesics, is also possible (see Chapter 8.4.3 Analgesic ladder).

Adjuvant analgesics (co-analgesics) are a group of substances intended primarily for indications other than pain management. They potentiate the analgesic effects of analgesic drugs and may have also their own analgesic or other useful effects (e.g., antiemetic). The following groups of drugs can be used as adjuvant analgesics: antidepressants, neuroleptics, antiepileptic drugs, central muscle relaxants, anxiolytics, corticosteroids, and local anaesthetic drugs.

8.4.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

Besides having an **analgesic** effect, substances in this group also have an **antiphlogistic** and **antipyretic** effect. Some of these substances also have an **antiaggregatory** effect; acetylsalicylic acid (ASA) is a prime example of one such drug.

NSAIDs are the most widespread group of substances used for pain treatment, but their high consumption is probably also associated with the fact that many of these drugs are sold as OTC drugs without a prescription being necessary for purchase. Different drug dosage forms are available: tablets, capsules, suppositories, injections, syrups, gels, ointments, etc.

8.4.1.1 Mechanism of action

The common mechanism of action in this group occurs by inhibiting the enzyme, cyclooxygenase (COX). This enzyme is responsible for the production of prostanoids, which

participate in whole range of physiological and pathophysiological processes. Prostaglandins, prostacyclin, and thromboxanes are classified as prostanoids.

- Prostaglandins are important mainly for optimal blood circulation in kidneys. They also have protective effects on the gastric mucous membrane, induce contractions of uterus, and are also responsible for the origin of pain, inflammation, and fever (i.e., setting of the thermoregulatory centre to a higher value).
- Prostacyclin induces vasodilatation and inhibits the aggregation of thrombocytes.
- The primary function of thromboxanes is to promote platelet aggregation and induce vasoconstriction.

It is confirmed that COX exists in at least two isoforms:

- **COX-1** is referred to as the **constitutive** (physiological) form. It is present in almost all cells of the organism and is responsible for the production of the prostanoids that ensure physiological and homeostatic functions.
- The **COX-2** isoform is called the **inducible** form. It is synthetized because of the presence of pro-inflammatory mediators (cytokines, IL-1, IL-6. TNF-α, etc.) at the site of inflammation. It is responsible for production of the prostanoids that play an important role in the pathogenesis of inflammation, pain, and fever.

Existence of a third isoform, COX-3, which may play a key role in paracetamol effects, is still under investigation (see below).

8.4.1.2 Adverse effects

It is not useful to combine the individual NSAIDs because it not only causes an increase in the therapeutic effect, but also an increase in the adverse effects. Commonly occurring adverse effects result primarily from inhibition of the physiological isoform, COX-1:

- gastrointestinal difficulties (e.g., dyspepsia, vomiting) to erosions, ulceration, and gastroduodenal ulcers,
- increased bleeding,
- impairment of renal functions, and
- eventual prolongation and complication of delivery (inhibition of uterine contraction).

Extremely high plasma protein binding of NSAIDs can cause clinically significant drug interactions, for example, an increase in oral anticoagulant and antidiabetic effects. NSAIDs also significantly decrease the antihypertensive effect, particularly of diuretics, β-blockers, and ACE inhibitors.

8.4.1.3 Classification

NSAIDs can be classified according to their chemical structure or according to their affinity for specific COX isoforms and subsequent adverse effects:

- non-selective (COX-1 and COX-2): ASA, derivatives of propionic acid, derivatives of acetic acid, derivatives of pyrazolone, and piroxicam;
- preferential (COX-1 < COX-2): nimesulide and meloxicam; and
- specific (COX-1 <<< COX-2): coxibs.

8.4.1.4 Acetylsalicylic acid (ASA)

ASA is one of the oldest used NSAIDs and is a derivative of salicylic acid. ASA is the only NSAID that can block COX in an irreversible manner, and aside from having analgesic, antipyretic, and antiphlogistic effects (at higher doses), it also has an antiaggregatory effect.

ASA is indicated for mild to moderate pain (e.g., headache, pain of muscles, dysmenorrhea, etc.), in febrile diseases, in inflammatory diseases (e.g., rheumatoid arthritis), and as an antiaggregant to be used, for instance, as a prophylaxis for myocardial infarction (e.g., in lower doses, such as 30-100 mg; see Chapter 5.2.2.1 Cyclooxygenase inhibitors).

Adverse effects of ASA involve the typical adverse effects of NSAIDs mentioned above. In addition, development of an allergy can cause aspirin-induced asthma to occur; moreover, salicylism and liver impairment followed by brain damage (Reye syndrome) are possible effects. Salicylism can arise after long-term administration of ASA in high doses and manifests as tinnitus and dizziness. ASA is contraindicated for children up to 12 years because of the so-called Reye syndrome appearing following its administration for febrile viral infections. Symptoms of this syndrome involve hyperpyrexia, metabolic acidosis, convulsions, vomiting, neurological and mental changes, and hepatopathy. ASA is also contraindicated in patients with peptic ulcer disease, those set to have surgery, in women in the third trimester of pregnancy, and for people suffering from asthma or coagulation disorders.

8.4.1.5 Derivatives of propionic acid

These substances are structurally derived from propionic acid; they have good analgesic, antipyretic, and antiphlogistic effects and are well-tolerated. The following drugs from this group are used: ibuprofen, naproxen, ketoprofen, tiaprofenic acid, and flurbiprofen.

Ibuprofen has, if used correctly and not excessively, a small number of adverse effects, and it is well-tolerated by both adults and children (e.g., in the form of suppositories, syrups). It is used particularly for treatment of acute pain, to decrease fever, and for symptomatic treatment of inflammatory joint diseases.

Naproxen has similar indications to ibuprofen, but it cannot be administered to children younger than 12 years of age.

Ketoprofen is used mainly for the treatment of inflammatory, degenerative, and metabolic rheumatic diseases. Preparations for topical administration are strongly phototoxic.

Tiaprofenic acid penetrates synovial fluid well; thus, it is used for treatment of joint diseases.

Flurbiprofen is presently registered only in the form of lozenges, which are intended for local treatment of throat pain in inflammatory and infectious diseases.

8.4.1.6 Derivatives of acetic acid

This group involves substances derived from acetic acid, such as diclofenac and indomethacin. Both are very strong drugs, but also cause frequently occurring adverse effects.

Diclofenac has significant analgesic and antiphlogistic effects as well as a milder antipyretic effect. It penetrates synovial fluid well, and it is effective for painful posttraumatic and postoperative inflammations and oedemas. It has fewer adverse effects compared to indomethacin, but recent clinical studies showed an increased risk of arterial thrombotic events, particularly after the long-term use of higher doses.

Indomethacin is, due to frequent and severe adverse effects, only intended for short-term administration for acute conditions. Aside from embodying the classical effects of NSAIDs, it also has an uricosuric effect, which is utilized during a gout attack.

8.4.1.7 Derivatives of pyrazolone

Only two substances in this group are presently available here: propyphenazone and metamizole. They are not intended for chronic use due to the risk of the development of typical NSAID adverse effects. Moreover, disorders of haemopoiesis can occur, but fortunately, only rarely.

Propyphenazone is only available in combined preparations with paracetamol and caffeine. This combination is especially useful for the treatment of headache, tooth pain, dysmenorrhea, and lumbago as well as a few other ailments.

Metamizole is frequently classified as an analgesic-antipyretic drug. It has significant antipyretic properties, but it also has analgesic, antiphlogistic, and mild spasmolytic effects. It is contained in registered preparations either alone or in combination with spasmolytic drugs (e.g., with fenpiverinium or pitofenone).

8.4.1.8 Oxicams

All these drugs have a common feature: a long biological half-life. Thanks to this property, they can be administered, for example, in one daily dose, but at the same time, there is a risk of their accumulation in the organism. For this reason, the group is not recommended for older patients (i.e., over 65 years). This group involves substances with names that always contain the same ending, "-oxicam".

At present, preparations containing **piroxicam, lornoxicam**, and **meloxicam** are registered here in the Czech Republic. Meloxicam is frequently classified as a preferential COX-2 inhibitor – it shows fewer typical adverse effects than those of NSAIDs – and it penetrates synovial fluid well, which is why it is generally indicated for treatment of degenerative diseases.

8.4.1.9 Nimesulide

Nimesulide, along with meloxicam, are classified as preferential COX-2 inhibitors. This means therapeutic effects comparable with non-selective COX inhibitors should be accompanied with a lower risk of typical NSAID adverse effect development. Nimesulide is indicated for short-term administration for acute pain and is also an effective treatment for inflamed tissue. Its administration is limited to 14 days because longer exposure can lead to liver damage.

8.4.1.10 Coxibs

Coxibs are classified as specific COX-2 inhibitors and substances of this group have the common ending, "-coxib".

These drugs inhibit, up to 100-fold, the COX-2 isoform rather than the COX-1 isoform, which is associated with fewer typical NSAID adverse events. Notably, the impairment of the gastroduodenal mucous membrane is reduced. However, administration of coxibs is associated with a **risk of thrombotic complications**, particularly cardiovascular and cerebrovascular, which has been described extensively in controlled clinical studies. Therefore, some of the first introduced substances have already been withdrawn.

Prescription of these substances is restricted to rheumatologists and orthopaedists because individual examination of the patient is necessary, and indications include, for example, rheumatoid arthritis, ankylosing spondylitis, and short-term treatment of postoperative pain. Registered substances in the Czech Republic are **celecoxib**, **etoricoxib**, and **parecoxib**.

8.4.2 Analgesics-antipyretics (AA)

Analgesics-antipyretics (AA) are drugs with predominantly **analgesic** and **antipyretic** effects (i.e., they can decrease pathologically increased temperature). As mentioned above, some of the NSAIDs, that in certain doses show only analgesic and antipyretic effects with insignificant anti-inflammatory action, can also be classified as AA (e.g., ASA, metamizole, or ibuprofen). The only substance, which shows no anti-inflammatory effects at all, is **paracetamol** (acetaminophen). However, it possesses excellent analgesic and antipyretic effects.

8.4.2.1 Paracetamol (acetaminophen)

Paracetamol is a well-tolerated substance; therefore, it is used for children, adults, and older patients.

The mechanism of its analgesic and antipyretic effects has not yet been fully elucidated. It is assumed that both a central and peripheral mechanism are involved. One of the central mechanisms could be, according to some scientists, inhibition of **COX-3**, which is concentrated in the CNS.

Since its mechanism of action is different from most NSAIDs, paracetamol is better tolerated in the GIT and does not affect coagulation of the blood. Unlike other NSAIDs, it seldom binds to plasma proteins. Paracetamol is metabolised in the liver and converted to some inactive metabolites, but also to a small number of toxic metabolites, which are, under normal conditions, decomposed by glutathione. However, after overdosing or in patients with liver diseases toxic metabolites can accumulate, which may result in severe liver impairment. In such case, **acetylcysteine** can be used as an antidote.

Paracetamol is indicated for fever and pain of various origins (e.g., headache, tooth pain, neuralgia, etc.). It is very frequently combined with weaker opioid analgesic drugs such as tramadol and codeine or with other NSAIDs.

8.4.3 Analgesic ladder

The therapy of pain is usually carried out according to a three-step ladder put forth by the World Health Organization (WHO):

- The first step involves treatment of mild to moderate pain, for which non-opioid analgesics (NSAIDs) are used as monotherapy. If there is no pain relief and a bearable level of pain is still not achieved after a maximum dose of these substances over the course of 36 hours, it is necessary to apply the second step of the WHO ladder. A combination of more substances within the group of NSAIDs makes no sense because it serves solely to increases the risk of adverse effects.
- The second step of the ladder involves therapy of moderate to severe pain, and weak opioids are used. It is generally suitable to combine the opioids with NSAIDs or adjuvant analgesics (co-analgesics). If, after a maximum dose of these substances (combined with NSAIDs) is administered, and no pain relief to a bearable level of pain is still achieved after 72 hours, it is necessary to apply substances listed in third step of the WHO program.
- Strong opioids are used in this third step. It is possible to combine these opioids with substances of the NSAID group and co-analgesics. Combination of weak and strong opioids is not suitable.

In the treatment of chronic pain, we proceed step by step and a higher dose is only used when the lower dose does not produce sufficient analgesic efficacy. In the case of very strong pain (e.g., breakthrough pain in cancer), it is possible to use a so-called "**lift**", which means administration of opioids immediately.

8.5 Glucocorticoids

Glucocorticoids (GC), also known as corticoids or corticosteroids, are substances with a very wide spectrum of effects. They significantly interfere with the metabolism of lipids, proteins, and carbohydrates. In medicine, they are used primarily due to their strong anti-inflammatory and immunosuppressive effects. The main hormone of endogenous production is called **cortisol**, when exogenously administered, it is called **hydrocortisone**.

GC are physiologically released from the adrenal cortex owing to stimulation by corticotropin (adrenocorticotropic hormone, ACTH), which is a hormone produced in the anterior pituitary gland. Its secretion is not only regulated by the hypothalamic hormone, CRH (corticotropin-releasing hormone), but also by the current concentration of GC and ACTH in the blood (i.e., negative biofeedback). GC are not stored in the cells of the adrenal cortex in their finished form and are synthetized as late as after the secretory stimuli of ACTH.

Secretion of GC is dependent upon pulse, circadian rhythm, and it reaches its maximum concentration in the morning (between 6-8 AM). It is increased under stress conditions up to 10-fold.

GC involve a whole range of substances; hydrocortisone is used for replacement therapy and can serve as an example. Likewise, other compounds, such as **prednisone** (the active

metabolite is called **prednisolone**), **methylprednisolone**, **dexamethasone**, **triamcinolone**, and **betamethasone**, are examples of commonly prescribed GC.

They are easily absorbed both from the GIT and other sites of administration. Endogenously produced hydrocortisone has biological half-life of nine minutes; synthetic GC have biological half-life up to several hours. GC bind in plasma to corticosteroid-binding globulin (75%) and to albumin (15%). They are metabolized in the liver and excreted in urine. Synthetic derivatives are metabolized slower than endogenous hormones.

8.5.1 Effects of glucocorticoids

GC have a lipophilic nature; thus, they penetrate very easily through the cytoplasmic membrane. They bind in cytoplasm to specific **glucocorticoid receptors**. These receptors are found in all tissues. Following glucocorticoid binding, a receptor-GC complex is formed; this complex enters the cellular nucleus, binds to the DNA segment of a certain gene, and affects protein biosynthesis.

However, because of the complexity of the GC genomic mechanism, their more expedient effects must be attributed to other mechanisms. These effects of GC are mediated by specific **membranous receptors**, which after interaction with a certain GC, cause fast intracellular changes through interference with membrane fluidity and via modulation of the sensitivity of other receptors (e.g., GABA).

The effects of GC are as follows:

1. **Metabolic effects:** Physiologically, GC maintain normal glycaemia, and following long-term lack of glucose, they stimulate gluconeogenesis from amino acids (i.e., they support amino acid release peripherally, which leads to the breakdown of muscle mass and generally to increased catabolism of proteins). GC facilitate the absorption of fats from meals, they increase lipolysis, and cause redistribution of fat (Cushing's syndrome).
2. **Anti-inflammatory effects:** GC inhibit the synthesis of inflammatory mediators through interference with the arachidonic acid cascade in that they catalyse synthesis of lipocortin-1, which inhibits phospholipase A_2. Phospholipase A_2 is a key enzyme necessary for the synthesis of inflammatory mediators such as prostaglandins, prostacyclins, leukotrienes, and thromboxanes. Furthermore, GC inhibit the production of cytokines (e.g., IL, TNF) as well as synthesis of their receptors. They affect both chronic and acute inflammation.
3. **Immunosuppressive effects:** GC inhibit antigen recognition, exposition of antigen on the cell surface, activation of T-lymphocytes, and phagocytosis. Also, they block cell cycle progression (i.e., creating an anti-proliferative effect).
4. **Mineralocorticoid effects:** these effects appear when exogenously administered GC are taken to different extents. In these cases, sodium retention and potassium loss occur, which can carry the risk of blood pressure increase leading to hypertension.
5. **Effects on blood and the lymphatic system:** GC significantly decrease the number of circulating lymphocytes and eosinophils; conversely, they increase number of thrombocytes, erythrocytes, and haemoglobin.

6. **Effects on the kidneys and the cardiovascular system:** GC have a permissive effect for the maintenance of normal kidney function, and they decrease sensitivity to catecholamines and angiotensin II.
7. **Effects on the CNS:** GC participate in mood regulation; they induce feelings of well-being thanks to directly acting on the CNS and indirectly influencing metabolic effects. However, in predisposed individuals or after high doses of GC, psychotic disorders can occur.
8. **GIT:** GC increase gastric secretion of pepsin and HCl. However, GC themselves do not cause gastroduodenal ulcers; they just worsen them.
9. **Bone metabolism:** GC produce a negative calcium balance; they decrease its absorption in the gut and increase its secretion in kidney, which leads to increased risk of osteoporosis.
10. **Effect on foetus development:** GC are important for the maturation of the lungs and the stimulation of surfactant production. They are administered in case of premature birth risk.

8.5.2 Adverse effects

Most adverse effects of GC are associated with their physiological functions. The determinants of the effects is dependent upon the type of GC administered as well as the duration of administration and the dosage. The longer glucocorticoids are administered, the larger the risk of iatrogenic Cushing's syndrome. Adverse effects can be classified into various groups:

- **Decreased immune response to infection:** Sensitivity to infections (e.g., bacterial, viral, and mycotic) is increased, the course of infectious diseases worsens, and latent infections can be exacerbated (e.g., tuberculosis).
- **Decreased ability of the adrenal cortex to synthesize hormones:** Long-term GC administration leads to adrenal gland atrophy (i.e., the hypothalamic–pituitary–adrenal axis becomes depressed), whereby the ability of GC synthesis is decreased, and thus abrupt withdrawal can result a shock condition (i.e., GC must be withdrawn slowly!). Also, the ability of an organism to cope with stressful situations is limited.
- **Metabolic effects:** Following prolonged treatment with GC, Cushing's syndrome may develop, the symptom of which is fat redistribution. Fat accumulates in the region of trunk and neck (i.e., moon face, buffalo neck); contrastingly, limbs stay thin. Hyperglycaemia occurs and there is a risk of so-called steroid diabetes. Loss of muscle mass occurs in the musculoskeletal system, and there is a risk of retardation or even stunting growth in children. In adults, there is a risk of osteoporosis, and as a result of decreased blood supply, the development of avascular bone necrosis may occur. Furthermore, retention of water and electrolytes occur, thereby increasing the risk of hypertension.
- **Other adverse effects:** Psychotic disorders, gastroduodenal ulcers, increased blood coagulation, disorders of menses in women, loss of supportive tissue in the skin, and subcutis (i.e., subcutaneous tissue), striae (i.e., stretch marks), and worsening of wound healing may occur.
- **Adverse effects after local administration:** Skin - acne, telangiectasia (i.e., localised accumulation of dilated blood vessels); eye - cataracta, glaucoma; oral cavity -

mycosis and hoarseness (this may be prevented by rinsing mouth following application).

Prevention of the development of adverse effects consists of the administration of the lowest possible doses, for the shortest possible period, and preferably in the morning (with respect to physiological secretion). If the patient's condition allows it, local application of GC rather than systemic is preferable. Following long-term administration, GC must be withdrawn slowly with a gradual decrease of doses. Adherence to dietetic measures should also be observed during the therapy; in general, it is advised to increase intake of proteins and, decrease intake of fats and saccharides.

8.5.3 Indications and dosage schemes

Using **physiological doses**, hormones are substituted in case of their insufficient secretion (e.g., Addison's disease).

Pharmacological doses are particularly used for anti-inflammatory and immunosuppressive therapy for diseases such as bronchial asthma, allergic reactions, anaphylactic shock, autoimmune diseases, as prevention of transplantation rejection, in oncologic diseases (e.g., Hodgkin's disease, acute lymphoblastic leukaemia, and brain tumour), and for dermatologic indications (locally).

Contraindications for GC administration include hypertension, bacterial infections without ATB treatment, vaccination with live vaccine, heart insufficiency, chronic renal failure, gastroduodenal ulcers, psychosis, diabetes mellitus, and glaucoma.

Dosage schemes during GC therapy include:

- **Single mega doses** which are administered in "polytrauma" (multiple trauma) or shock conditions. It is important to administer GC at the beginning of disease onset (i.e., at the beginning of pathological condition development). For example, two to four grams of methylprednisolone can be administered in a short infusion.
- **Short-term administration of high doses** has numerous indications, for example brain oedema, thyrotoxic crisis, anaphylactic shock, and hypoglycaemic coma can be treated effectively. It consists as a 500 mg dose given over 24 hours intravenously for a maximum of 5-7 days, then GC can be withdrawn without risk of adverse consequences.
- **Pulse therapy**, which means administration of pharmacological doses in short-term infusions over several consecutive days. This form of application is suitable for diseases with immune conditioning, for example, those which are resistant to standard treatment. The advantage of this approach is that it involves a low risk of adverse effects, and there is no suppression of the hypothalamic-pituitary-adrenal axis.
- **Prolonged treatment** is used in majority of cases, during which the need for employment of anti-inflammatory, immunosuppressive, or anti-allergic effects is necessary.

8.6 Therapy of allergies

An allergy can be defined as an inadequate immune system response in the organism to substances that are a common part of our environments. Allergies can manifest as, for example, allergic rhinoconjunctivitis, atopic eczema, and contact dermatitis, but more severe reactions, such as bronchial asthma and anaphylaxis, can occur.

Etiological agents of allergic reactions (allergens) can be diverse, for instance, poles, grasses, dust, some food, medical products, and many other substances. These allergens activate IgE antibodies on the surface of mast cells (mastocytes) and basophiles, which results in the release of allergic reaction mediators (e.g., histamine, bradykinin, prostaglandins, leukotrienes, etc.) and induction of the characteristic **symptoms of allergic reaction**. The symptoms exhibited range from pruritus to pain, including flush and oedema. Other symptoms include difficulty breathing, dyspnoea (bronchoconstriction), and increased secretion from glands (e.g., aqueous secretions from nose and mucus in airways).

Histamine

Endogenous amine histamine is the most important mediator of allergic reactions and is formed in an organism from the amino acid, histidine. Aside from the aforementioned function as a mediator of inflammatory and allergic reactions, it can regulate secretion of HCl in the stomach (i.e., it increases its release) and acts as neurotransmitter in CNS. It occurs in almost all the tissues of human body, and its concentration is largest in the lung, GIT, and skin.

Histamine is stored in granules in mast cells and basophiles, it is also found in histaminocytes in the stomach and CNS. It acts through specific receptors (H_1-H_4), which have different localisations, and histamine activation exerts a variety of effects based on these distinguishing factors. Activation of H_1 receptors, which play crucial role in allergic reactions, induces following effects:

- Contraction of smooth muscles of the bronchi, uterus, and GIT;
- Vasodilation of smaller vessels (e.g., causing decrease in blood pressure, flush);
- Increased permeability of postcapillary venules (oedema); and
- Irritation of peripheral nerve endings (i.e., symptoms of which include itchiness to pain) and the CNS.

8.6.1 Pharmacotherapy of allergies

For the treatment of allergic conditions, not only is targeted pharmacotherapy important, but also measures which prevent the development of the reaction in the first place, such as preventing initial contact with allergens. For pharmacological treatment, substances blocking the effects of histamine on H_1 receptors are used (**H_1 antihistamines**); furthermore, **stabilisers of mast cells**, **antileukotrienes**, **glucocorticoids** are administered, and **allergen immunotherapy** is carried out.

The aim of **allergen immunotherapy** is to decrease the hypersensitivity of the organism to the causal allergen through intervention in the regulatory actions of T lymphocytes. Over the course of a long period of time and at regular intervals, the patient is administered (subcutaneously or sublingually) the actual allergen (i.e., the allergy-causing allergen) at very low concentrations (that are gradually increased). Therapy may be accompanied by adverse effects, which can be both local (e.g., flush, itch, etc.) and systemic (e.g., increased temperature, sniffles, asthmatic dyspnoea, etc.); however, if good medical practices are followed, these occur only rarely.

Glucocorticoids are administered locally or systemically depending upon the type of allergic disease. For example, in the case of allergic rhinitis, nasal sprays are used; for skin allergies, ointments, emulsions, and solutions are administered; for bronchial asthma inhalation drug dosage forms are preferred to oral forms. In case of more severe or life-threatening conditions, glucocorticoids can also be administered parenterally.

Mast cells stabilisers are substances intended for prophylactic therapy, but not for treatment of acute difficulties. They can be given to patients with bronchial asthma (e.g., inhalation forms), allergic rhinitis (e.g., sprays), and conjunctivitis (e.g., drops).

Antileukotrienes are indicated for the therapy of bronchial asthma, for which they can also be combined with inhaled glucocorticoids.

H_1 antihistamines belong to the most frequently used substances used to treat allergic diseases; therefore, they are described in the following text in a more detailed way.

8.6.2 H_1 antihistamines

The mechanism of action by which H_1 antihistamines work consists of inhibiting histamine effects on the level of H_1 receptors through reversible competitive antagonism. Effects of these drugs involve the inhibition of increased vascular permeability, blocking the vasodilation of smaller blood vessels, and inhibition of bronchoconstriction. They also prevent irritation of free nerve endings, thus reducing itch.

H_1 antihistamines are indicated for both the prevention and treatment of allergic rhinitis, conjunctivitis, urticaria (i.e., hives), atopic eczema, pruritus, and so on. They are also used as adjuvant substances to treat the allergic form of bronchial asthma, migraine, and vomiting, and they have an extremely important role in the treatment of anaphylactic shock.

Medical products are available in different, practical drug dosage forms for both local and systemic use; for example, tablets (e.g., classical and orodispersible), drops (e.g., for internal use and locally into the eye), solutions, injections, ointments, and gels. H_1 antihistamines can

be divided into three generations according to their pharmacokinetic and pharmacodynamic properties; although, some substances may be classified differently in various related literature.

8.6.2.1 H$_1$ antihistamines – 1st generation

This group involves substances that, owing to their chemical structure, penetrate the CNS and have significant damping effects. These drugs do not have a selective effect only toward H$_1$ receptors, they can also affect other receptors and induce several adverse events involving antimuscarinic, antiserotonergic, or antiadrenergic effects. Some substances can block Na$^+$ channels, thus possessing a local anaesthetic effect, which can be used in cases of allergically conditioned itch. Generally, their effects last 4-6 hours; therefore, they must be administered several times a day. Single application or short-term application is preferred.

These substances show more adverse effects than the next generation, particularly because of their non-selective action. Aside from sedation (a problem for patients who have jobs requiring attentiveness!), the following effects can also occur: orthostatic hypotension, antimuscarinic effects (e.g., dry mouth, urine retention, etc.), digestive disorders, and in rare cases, hematopoietic disorders and skin affections. Rarely, particularly in children, paradoxical excitation may occur. Combining these drugs with substances damping the CNS is not recommended (e.g., alcohol, anxiolytics, hypnotics, etc.).

Today, clinically used drugs are dimetindene, promethazine, bisulepine, antazoline, moxastine, dimenhydrinate, and ketotifen.

Dimetindene is available in drug dosage forms for both systemic and local use and has a significant antipruritic effect.

Promethazine can be used for the treatment of allergic conditions, nausea, vomiting, for premedication prior to surgical and diagnostic treatments, and for sleep disorders.

Bisulepine is used in acute allergic conditions as well as for allergic reactions following an insect sting, etc.

Antazoline is in the form of nasal drops most often used for treatment of hay fever.

Moxastine and dimenhydrinate are used especially for prophylaxis and therapy of motion sickness. Moxastine also has an anti-vertigo effect.

Ketotifen is an interesting substance, which besides its antihistaminic effects, also stabilizes the membrane of mast cells. Ketotifen is indicated for long-term prevention of asthmatic attacks and for prevention of other allergic conditions, for instance, hay fever. It is not suitable for treatment of acute conditions, and it can be given locally in the form of ear drops in seasonal allergic rhinoconjunctivitis.

8.6.2.2 H$_1$ antihistamines – 2nd generation

Drugs of the 2nd generation are newer substances which, when compared to the antihistamines of the 1st generation, show higher selectivity for H$_1$ receptors and have minimal sedative effects because they do not penetrate the CNS. They have a longer biological half-life; therefore, it is possible to administer them one time per day and eventually two times per day.

The anti-allergic effect is broader because they affect, not only the early phase of an allergic reaction, but also its late phase (i.e., they prevent activation and migration of inflammatory cells to the site of inflammation).

Adverse effects only occur only rarely (e.g., nausea, headache, and rash, and following higher doses, fatigue and sleepiness may occur). These substances are also suitable for long-term administration, and they are intended for prophylaxis and therapy of all sorts of allergic conditions: urticarial, seasonal, and perennial allergic rhinoconjunctivitis as well as adjuvant therapeutics in asthma.

Substances intended for systemic administration include **cetirizine**, **loratadine**, and **fexofenadine**. Cetirizine and loratadine are available in the form of tablets, drops, syrups; fexofenadine only comes in the form of tablets.

Azelastine and **levocabastine** and other drugs (see Chapter 17.2 Anti-inflammatory, Anti-allergic and Immunosuppressive Drugs) are intended for local administration in the form of eye drops.

8.6.2.3 H$_1$ antihistamines – 3rd generation

This generation is sometimes referred to as H$_1$ antihistamines with an immunomodulatory effect. It involves the newest substances, which influence both the early and late phase of an allergic reaction in various ways. Their effect is highly selective for H$_1$ receptors and affinity to these receptors is also higher compared to the substances of the 1st and 2nd generations. Thus, these substances are more effective and safer.

Medical products are available in different drug dosage forms including orodispersible tablets, which facilitate therapy in patients with deglutition problems.

This group involves levocetirizine, desloratadine, **rupatadine**, and **bilastine**.

Levocetirizine is the left-handed enantiomer of cetirizine, and owing to its high affinity for H$_1$ receptors, it has up to a two-fold higher antihistaminic effect than cetirizine. Moreover, it has anti-inflammatory properties because it inhibits the migration of eosinophils at the site of inflammation and inhibits expression of adhesion molecules.

Desloratadine is an active metabolite of loratadine, and its immunomodulatory effect consists of, for instance, decreased production of leukotrienes, cytokines, and chemokines.

Rupatadine, aside from H$_1$ receptor inhibition, stabilizes the membranes of mast cells and antagonizes receptors for PAF (Platelet Activating Factor), which is an important mediator of allergic reactions.

Bilastine, when compared to other substances, is metabolized in the organism and is excreted in its unchanged form. Therefore, it can also be administered to patients with kidney or liver disorders.

8.7 Immunomodulatory substances

The main function of the immune system is to remove dead, impaired, or cancerous cells as well as to protect against infections and inorganic substances and to adequately react to these stimuli. Inadequate reaction may lead to impairment of the organism and to development of disease.

Immunomodulatory substances are drugs which act on components of immune system by a direct or indirect mechanism. In principle, function of the immune system can be either potentiated (i.e., immunostimulation) or supressed (i.e., immunosuppression). On this basis, we divide substances affecting immune system into immunostimulants and immunosuppressants.

8.7.1 Immunosuppressants

Immunosuppressants are substances which are used to treat autoimmune diseases (i.e., disorders of immunity caused by pathological reactivity to internal antigens); furthermore, in severe allergic conditions (i.e., pathological hypersensitivity to external antigens) and in transplantation medicine, they can be used as prevention of transplantation rejection.

8.7.1.1 Non-specific immunosuppressants

Glucocorticoids

Glucocorticoids are the main substances used for immunosuppressive treatment. They cause immunosuppression in higher doses as compared to their anti-inflammatory doses, which, when in need of long-term administration, lead to an increased occurrence of adverse effects.

However, their immunosuppressive effects are very different. They suppress production of leukotrienes, prostaglandins, and thromboxanes through inhibition of phospholipase A_2 in monocytes. Furthermore, they decrease chemotaxis, secretion of pro-inflammatory cytokines (e.g., IL-1, IL-8, TNF, etc.), and decrease activity of NO-synthase. They decrease the ability of T lymphocytes to produce IL-2 as well as decreasing serum levels of immunoglobulins. Glucocorticoids have an inhibitory effect on allergic reactions because they inhibit the release of histamine from basophiles and suppress functions of eosinophils.

Main features of glucocorticoids are described in a separate chapter (see Chapter 8.5 Glucocorticoids).

Cytostatic drugs with an immunosuppressive effect

The following substances are described in more detail in the chapter dealing with cytostatic drugs (see Chapter 10.3 Overview of cytostatic agents):

- **Methotrexate** acts as an antimetabolite of folic acid. In doses used for the treatment of autoimmune diseases (e.g., rheumatoid arthritis, psoriasis), the main effect is anti-inflammatory.
- **Cyclophosphamide** is an alkylating agent and acts primarily on B lymphocytes. It decreases antibody response to new antigens as well as decreasing the number of

immunoglobulins. Its immunosuppressive effect does not occur until after several weeks to months of consistent administration.

- **Azathioprine** is a purine analogue of guanine, and unlike the previous two substances, its indication is solely to induce immunosuppression; it is not a cytostatic drug. It inhibits both T and B lymphocytes.

Substances that bind to immunophilins:

- **Cyclosporine A** is a cyclic polypeptide acquired from soil bacteria. It affects primarily Th1 lymphocytes by decreasing the production of IL-2. It is strongly lipophilic, and its absorption from the GIT is very variable. Following absorption, it binds to plasma lipoproteins or cell membranes of blood corpuscles. It is metabolised in the liver via cytochrome P450, thereby having significant interactive potential with substances inhibiting CYP450. It is nephrotoxic as well as hepatotoxic, and neurotoxicity and hypertension have been described after its administration. Therapeutic drug monitoring (TDM) is recommended during the therapy.
- **Tacrolimus** is a macrolide antibiotic and its mechanism of action is similar to the action of cyclosporine A. It is 10-100 times more effective than cyclosporine A, but also more nephrotoxic. After oral administration, it is thoroughly spread throughout the entirety of the GIT; once in the blood, it is transported bound to erythrocytes and plasma proteins. It is metabolised in the liver by CYP450 enzymes and eliminated via bile. Adverse effects are the same as with cyclosporine A; additionally, it also causes alopecia.

Other substances:

- **Mycophenolate mofetil** intervenes with the synthesis of guanosine nucleotides and inhibits the proliferation of T and B lymphocytes. Adverse effects involve diarrhoea, nausea, and leukopenia. It is used in combination with cyclosporine A and glucocorticoids.

Targeted therapy

This group of substances is sometimes referred to as biological drugs (for more details see Chapter 10.6 Principles of targeted therapy). They affect immunocompetent cells by acting as antibodies against T and/or B lymphocytes or IL-2. They are polyclonal antibodies of animal origin (e.g., anti-lymphocyte serum or monoclonal antibodies):

- **Alemtuzumab** is a monoclonal antibody against T and B lymphocytes and mature granulocytes. It is indicated for the treatment of acute leukaemia and is sporadically administered during therapy for autoimmune diseases (e.g., multiple sclerosis) as well as for transplantation medicine to prevent of xenograft rejection.
- **Basiliximab** is a monoclonal antibody against receptors for IL-2 on activated T lymphocytes. It is used for the prevention of acute rejection after kidney transplantation, treatment of multiple sclerosis, and in myasthenia gravis.
- **Rituximab** is a monoclonal antibody against B lymphocytes. It is indicated for the therapy of autoimmune diseases (e.g., rheumatoid arthritis, lupus erythematosus, etc.) as well as in oncology.

8.7.1.2 Specific immunosuppressants

The use of **specific allergen immunotherapy** is widespread in practice. The aim is to evoke immunologic tolerance to an allergen, which induces a pathological response from the organism. Gradually increasing doses of a specially modified allergen are given for a period of 3-5 years. Preparations are administered sublingually or as injections. Specific allergen immunotherapy is indicated for pollen allergies, mite allergies, mould spore allergies, pet allergies, and bronchial asthma mediated by IgE antibodies.

8.7.2 Immunostimulants

8.7.2.1 Specific immunostimulants

Vaccination against infectious disease

Vaccines are modified, in so far as that they can induce an immune reaction with immunological memory, which will prevent the development of an infectious disease. Vaccines are derived from live, attenuated strains of microorganisms, modified bacterial toxins, and vaccines containing only a certain immunogenic part of a microorganism.

Anti-tumour vaccines

These vaccines consist of activated dendritic cells, which provoke an immune response against tumour antigens. They are in the phase of clinical testing.

8.7.2.2 Non-specific immunostimulants

Non-specific immunostimulants are of synthetic or bacterial origin or they can be products of the immune system, which are acquired by, for example, recombinant techniques. They are referred to as immunomodulators. They are indicated for disorders of cellular immunity.

Synthetic immunomodulators

- **Levamisole** was originally an anthelmintic drug (acting against parasitic worms), and it is not currently registered in the Czech Republic.
- **Isoprinosine** is a purine derivative, which besides immunostimulant properties also has an antiviral effect. It is indicated for repeated herpetic infections. However, today it has been replaced by specific antiviral drugs against herpes viruses.

Bacterial immunomodulators

Bacterial immunomodulators are extracts from bacteria or bacterial lysates. Their application activates macrophages. They are indicated for repeated infections of airways and the urinary tract.

Products of the immune system

- **Transfer factor** is a dialysate of homogeneous leucocyte mixture that has been acquired from healthy blood donors. It activates both specific and non-specific immunity.
- **Cytokines** have biological effects, which is why they are used. Presently, the following cytokines are used:
    - **Interleukin 2 (Il-2)** is used for antitumor therapy and under certain conditions after bone marrow transplantation.
    - **Interferon alpha** (**INF-α**) interferes with large number of viruses in the cell and has an antitumor effect. It is indicated for infectious hepatitis B and C and oncologic diseases.
    - **Interferon beta** (**INF-β**) has similar effects to interferon alpha. It is used to treat multiple sclerosis, hepatitis B and C, and for oncologic diseases.
    - **Interferon gamma** (**INF-γ**) has the same basic biological properties as other interferons. It is indicated for immunodeficiency disorders and antitumor therapy.

9 Anti-infective drugs

9.1 Disinfectants and antiseptics

Some places in the public space, especially medical and sanitary facilities, need an intensive decontamination protocol. To reach and sustain a relatively bacteria-free environment, there are several procedures, chemicals, and physical processes (e.g., heat, UV light) which may be used.

Sterilization is any process which leads to the elimination of all forms of microorganisms. Medical devices or tools used to prepare eye drops or for parenteral preparation must be sterilized.

Disinfection is any process which kills all pathogenic microorganisms. Substances used for the treatment of air, floors, furniture, and tools are called **disinfectants**.

Pathogenic microorganisms can sometimes be found on living tissue. Substances which are used to kill microorganisms on/in an organism are called **antiseptics**. They are used for the skin, eye, gastrointestinal tract, etc. Antiseptics are meant to be highly effective, and thus, they have an impact on a broad spectrum of microorganisms while not being absorbed into systemic circulation. Additionally, antiseptics should have low systemic toxicity and should not cause local irritation where applied.

Disinfectants and antiseptics have a non-specific mechanism of action and are placed into classes depending on their chemical structure, mechanism of action, or clinical use:

- Heavy metals and their derivatives,
- Oxidisers:
    - Ozone and peroxides,
    - Halogens and their derivatives, and
    - Others,
- Alcohols and phenols,
- Aldehydes,
- Boric acid and borates,
- Quaternary ammonium salts,
- Antiseptic dyes, and
- Oral antiseptics.

9.1.1 Heavy metals and their derivatives

Heavy metals' cations bind to important biomolecules in the cell, such as proteins (e.g., enzymes, structural proteins) with sulphur in their molecular structure or to nucleic acids.

The disinfection properties of **silver** have been known since ancient times. Compounds with a silver cation ($AgNO_3$, silver sulfadiazine) or nanoparticles of elementary silver (Ag^0) are used. They are used for skin infections (e.g., creams, concentrated solutions for warts) and

poorly healing wounds (e.g., special silver-impregnated dressings). $AgNO_3$ used to be given to treat eye infections in neonates; however, they can cause damage to the conjunctiva and are not used anymore.

Silver is also a component of **amalgam** (i.e., an alloy with mercury, and even other metals), which is a material used for dental fillings. Other products may contain silver microparticles (e.g., colloidal silver). However, these products are not registered as drugs or food supplements, and their oral administration is controversial due to doubts about their quality and the risk of silver accumulation in the body (i.e., argyrosis). Products such as face wash, sprays, and skin creams can be used as skin antiseptic cosmetics.

Other heavy metals with antiseptic and disinfectant properties are **mercury** and **bismuth**. Thiomersal (containing mercury) has previously been used as a preservative in vaccines and eye drops. Bismuth subgallate is a part of wound powder and gastrointestinal antiseptics.

9.1.2 Oxidisers

Endogenous oxidative agents such as hydrogen peroxide or superoxide radicals are part of innate immune system mechanisms and are produced during innate immunological response. Living systems have limited protection against oxidative damage (e.g., degrading enzymes, low molecular antioxidants). When exhausted, cell structures (e.g., biomembranes, nucleic acid, structural proteins, and enzymes) become damaged.

9.1.2.1 Ozone and peroxides

The strongest oxidiser is ozone, which is used in stomatology to treat dental caries (i.e., no need to drill) or to clean an infected root canal.

Peroxides are used as antiseptics and disinfectants. **Hydrogen peroxide** (3% H_2O_2 solution) is commonly used for superficial wounds. At a 6% solution, H_2O_2 is used to treat oral lesions. A concentrated solution (30%) is also used in stomatology to treat gingiva issues. Hydrogen peroxide should not be applied in deep wounds. It is also unstable when stored in an unsuitable environment (e.g., presence of light, heat, and some ions); therefore, the manufacturer instructions about expiration and storing must be followed (e.g., store in a cool place).

Dibenzoyl peroxide is used topically in dermatology for acne treatment.

Another peroxide disinfectant is **peroxyacetic acid** (also known as peracetic acid), which can be used to disinfect surfaces, tools, or hands.

9.1.2.2 Halogens

Halogens and their derivatives are strong oxidative agents. For medical use, derivatives of iodine and chlorine are most commonly agents utilized.

Iodine tincture (i.e., ethanolic iodine solution) and **glycerol-based iodine solution** are applied to skin or mucosa, for instance to treat an area before surgery. **Lugol's iodine solution** (i.e., a solution of iodine in aqueous solution of KI) is used as an antiseptic, as well. Although, iodophors, organic polymerous complexes, are more frequently used. Iodophors

incorporate molecules of iodine and release them as free iodine in solution. An example of an iodophor is **Povidone-iodine** (polyvinylpyrrolidone–iodine). Products with iodine should not be applied to a large area because of the ready absorption of iodine by the skin which may result in suppression of the thyroid.

Derivatives of chlorine are mostly used for the disinfection of surfaces, examples include: **chloramine B**, **chloramine T**, and **sodium hypochlorite**. Sodium hypochlorite is also used in stomatology to clean an infected root canal.

9.1.2.3 Others

Potassium permanganate is also an oxidative agent. Its diluted solution (light pink colour) can be applied to skin, for example, as a wash for foot mycosis.

9.1.3 Alcohols and phenols

Alcohols and phenols cause the denaturation of proteins by the removal of water from the protein's hydration layer. They do not affect spores. Concentrated solutions of **ethanol**, **propanol**, and **isopropanol** (often combined) are used to disinfect the hands before and after contact with a patient's body or before surgery. Alcohols are volatile; hence, their effect is short-term. They were used to disinfect medical tools, but that practice has been recognized as insufficient now.

Phenol (carbolic acid), in a 1-4% aqueous solution, was the first ever and most widely used disinfectant. Although, because there is a risk of absorption through the skin, which results in systemic toxicity as well as a risk of acid burns, it is not used anymore.

Cresols are methylated derivatives of phenol. In the past, a 2% mixture with soap and water was used to disinfect surfaces; higher concentrations were used to disinfect medical tools in medical facilities. Chlorine and bromine derivatives are also very effective (e.g., p-chlorocresol) disinfectants. Amylmetacresol can be found in some lozenges for sore throat and oral infections. It primarily affects gram-positive bacteria.

Thymol and **eugenol** are substances found in the essential oils of some herbs, such as thyme and clove, respectively. They are antiseptic and may be used in stomatology or be applied on skin or mucosa.

Hexachlorophene is an antimicrobial compound, which was used for acne treatment (e.g., antibacterial soaps, cosmetics). However, it is absorbed and is neurotoxic. Its derivatives, such as **triclosan**, are less toxic while still being effective. Triclosan is common component of toothpastes, deodorants, mouthwashes, and soaps.

9.1.4 Aldehydes

Formaldehyde is used for the disinfection of rooms and floors in the form of either a solution or as vapour. It is irritating to skin and mucosa; therefore, it is not used as an antiseptic. Previously used formaldehyde gargle (i.e., a solution of menthol, rhatany root extract, and an ethanol-based solution of formaldehyde, also named *Kutvirt gargle*) is now obsolete. Formaldehyde also serves as fixative for the preservation of biological material (e.g., 40%

aqueous solution, formol, and formalin). Formaldehyde causes the denaturation of proteins and fragmentation of nucleic acids.

9.1.5 Boric acid and borates

Boric acid is an antiseptic, which can be applied to both skin and mucosa (e.g., conjunctiva). Its 3% aqueous solution and 2% aqueous solution with glycerol (also known as *Solutio Jarisch*) are used as skin antiseptics, and its 1.7% aqueous solution is used as an eye wash.

Sodium tetraborate decahydrate is a component of antiseptic eye drops and eye ointments. Vaginal globules with this boron derivate are used in gynaecology to treat and prevent mycotic infections. In children, products with boron should be used with caution and only for a short time because of their ease of absorption and consequent potential systemic toxicity.

9.1.6 Quaternary ammonium salts

Quaternary ammonium compounds are used as antiseptics; they act as detergents and eliminate the microorganism by damaging its cytoplasmic membrane, which is due to their physical and chemical properties. They are most effective against bacteria, but may also influence fungi and viruses. It is necessary to apply these compounds on clean skin or mucosa; because of the contact with soap containing quaternary ammonium, purulence or proteins can inactivate these antiseptics. They are very well-tolerated, non-irritable, and cannot cause systemic toxicity. They are widely used to treat superficial wounds and mucosal infections (e.g., mouth, nasopharynx, vagina, and conjunctiva).

The most widely used quaternary ammonium salts are carbethopendecinium bromide, benzododecinium bromide, and benzalkonium chloride. Dermal solutions and sprays, eye and nose drops, and eye washes are examples of available forms. Benzalkonium is a component of antiseptic lozenges and vaginal preparations. It also is a spermicide. Another antiseptic compound used for skin and mucosa is octenidine dihydrochloride.

9.1.7 Antiseptic dyes

Antiseptic dyes were very popular in the past. Now, they are used either as a second choice or only for special indications.

Brilliant green (V*iride nitens* in Latin) is the most common of the antiseptic dyes. It is a component of a local antiseptic used on stitches, a liquid bandage named Solutio Novikov.

Crystal violet (gentian violet, *Solutio methylrosanilinii chloridi* in Latin) is sometimes used on mycotic infections of the skin or mucosa, mostly for children. Although, there is a concern about its toxicity and carcinogenicity; therefore, long-term usage of the concentrated solution is not recommended.

Other antiseptic dyes are **methylene blue** (e.g., administered as nose drops, also used to treat methemoglobinemia when given intravenously as a reducing agent), **ethacridine**, and **acriflavine** (both used in dermatology and stomatology).

9.1.8 Oral antiseptics

Hydrogen peroxide is not the only antiseptic used for the treatment of lesions of the oral cavity and gingiva. Below are some other oral antiseptics worth mentioning. Natural oral antiseptics are listed in Chapter 16.4 Herbal therapy in dentistry.

Chlorhexidine acts similarly to quaternary ammonium salts even though they differ in structure. It is available as lozenges, toothpaste, gargle, and mouthwash. Chlorhexidine binds to the surface of the mucosa and is gradually released into oral cavity. Low concentrations (i.e., up to 0.05%) are meant for everyday oral hygiene. More concentrated solutions of chlorhexidine (i.e., 0.1-0.2%) are used for the treatment of infectious lesions, but for no more than 14 days. Use of these chlorhexidine solutions may lead to an alteration in taste perception, tongue and teeth discoloration, and desquamation of the oral mucosa. There is also a dermal solution containing chlorhexidine.

Benzydamine is an antiseptic with anti-inflammatory and local anaesthetic effects. It is used to treat painful oral wounds or wounds due to dental surgery (e.g., spray, lozenges, gargles). There is also a vaginal douche available which contains benzydamine.

Hexetidine is an antiseptic structurally similar to thiamine, blocking the production of one of the essential coenzymes in microorganisms. It affects a broad spectrum of microorganisms including both Gram positive and Gram negative bacteria as well as fungi. Hexetidine also has a local anaesthetic effect. It is available in the form of lozenges and gargles for oral infections.

Aminotridekan has effects similar to hexetidine and can be found in lozenges. It is a good choice for sore throat in pregnant women.

Antiseptics used preferentially in stomatology and gynaecology are listed in Chapter 16 Drugs used in dentistry and Chapter 11.3 Therapy of vulvovaginal infections.

9.2 Fundamentals of the rational therapy of infectious diseases

The drugs used for the treatment of infectious disease have historically been divided into antibiotics, drugs derived from natural substances (e.g., mainly fungi), and chemotherapeutics, substances of synthetic origin. Often, both groups are included under the general term antibiotics.

It is also important to realize that "chemotherapeutics" have nothing to do with "chemotherapy"; the term, chemotherapy, refers to the use of cytostatics for the treatment of cancer.

The effect of antibiotics is generally divided into two groups:
 • **Bacteriostatic** (i.e., reduction of bacterial growth and proliferation) and
 • **Bactericidal** (i.e., directly killing microbes).

The effect may depend on several factors:
- • The duration of administration (the so-called **time-dependent effect**, e.g., penicillins); such antibiotics should be administered for at least 7-10 days, and
- • The concentration of the drug (the so-called **concentration-dependent effect**, e.g., aminoglycosides); these drugs may be administered for a shorter period, but at a higher dose.

The antibiotic dose directly correlates to the **minimum inhibitory concentration** (MIC), which is the lowest concentration of antibiotic that inhibits the growth of the observed bacteria, or to the minimal bactericidal concentration (MBC), which corresponds to the lowest concentration of drug that is effective at killing the selected microorganism. Therefore, antibiotic dosing should be chosen so that a concentration over the MIC is reached for a sufficient time at the site of action. If this principle is violated, for example, if the patient does not follow the dose interval, the treatment of the infection can be prolonged and the selection of resistant strains can happen. The patient should always be instructed on the correct use of antibiotics. These principles should also be followed in hospitals.

Some antibiotics have a so-called **post-antibiotic effect**. This is a condition in which the continued inhibition of bacterial growth or continued killing of bacteria occurs despite the plasmatic concentration of antibiotics being no longer measurable in the human body.
This effect is caused by severe damage to bacterial organelles or their metabolism; because of which, the microorganism is unable to adapt quickly enough to survive. The aminoglycosides irreversibly bind to a ribosomal subunit that then cannot perform its function, and the cell must synthesize this cellular component *de novo*, which depletes the microorganism energetically.

This antibiotic treatment is either based upon the direct detection of a specific pathogen by a culture or other techniques (**the causal treatment**), or in the case of common infections, it is possible to deploy the antibiotics **empirically** based on the patient's clinical condition and the laboratory findings.

The unwarranted overuse of antibiotics and their misuse by patients leads to an increase in microbial resistance. For this reason, antibiotic centres oversee antibiotic treatment policy and the conditions under which a physician can prescribing antibiotics are also regulated:
- • So-called **bound antibiotics** may only be prescribed by the physician after approval with an antibiotics centre and
- • Other, so-called **the free antibiotics**, may be prescribed by the physician according to her/his discretion as well as according to any prescription/indication restrictions without the need for consultation.

An antibiotic centre, in addition to the inspection of selected drugs, also records the total consumption of antibiotics and contributes to the monitoring of nosocomial infections, performs specialized tests, and provides consultations on the bacteriological findings. It also prepares various recommendations on the use of antibiotics (e.g., in surgical prophylaxis, etc.).
Antibiotic centres are mostly located in the large hospitals, and for example, four such centres have been operating in Brno since August 2013. The antibiotics policy is detailed by the

National Antibiotic Program at the national level. (For more information, see the website of the State Health Institute: http://www.szu.cz/cile-a-principy-nap)

The correct choice of antibiotic depends primarily on the specific clinical findings of the patient, on the condition of the pathogen resistance at a specific site, on the health condition of the patient and any other possible comorbidities (e.g., kidney function, liver function, etc.), and the pharmacokinetics of the considered drug (e.g., bioavailability, distribution, biological half-life, drug excretion) and its possible adverse effects.

In common practice for uncomplicated infections, it is preferable to first choose **narrow spectrum antibiotics**, and when they are ineffective, to choose **broad-spectrum antibiotics**.

Another scenario is the treatment of severe multi-resistant infections, sepsis, or infections in hard-to-reach areas of the organism (e.g., in bones) that are progressing vigorously; in which case, antibiotics are often combined.

Not all combinations of antibiotics are rational. Suitable combinations include aminoglycosides with β-lactam antibiotics or sulfonamides with trimethoprim. These combinations increase drug penetration into the bacterial cell or cause a bactericidal sequential blockade of bacterial metabolic processes. Generally, the combinations of bacteriostatic and bactericidal drugs (e.g., penicillins with tetracyclines or macrolides) are unsuitable due to the antagonism, and this combination can lead to a reduction of the antimicrobial effect more so than individual drugs administered alone.

9.2.1 Mechanisms of action of antibiotic resistance

Antibiotics act on different levels of the bacterial cell:

> • The synthesis of **cell wall components** is affected by the β-lactam antibiotics, glycopeptides, and the polypeptide, bacitracin.
> • The integrity of the **cytoplasmic membrane** is disturbed by other polypeptide antibiotics.

Other substances primarily target microbial proliferation:

> • The sulfonamides and trimethoprim interfere with the **metabolism of folic acid**, which is necessary for *de novo* nucleotide synthesis.
> • The quinolones inhibit the **bacterial topoisomerase II (gyrase)**, which is necessary for superhelical double strand windings of DNA to be created (i.e., initiating DNA replication).
> • The nitrofurans and nitroimidazoles inhibit the **replication** of DNA by covalently binding to proteins bound to the DNA strands as well as the DNA strands themselves.
> • The ansamycins inhibit the **transcription** (i.e., the transcription of the DNA sequence into the mRNA structure by RNA polymerase).
> • The largest group of antibiotics inhibits **translation** on ribosomes. The macrolides, aminoglycosides, amphenicols, lincosamides, and tetracyclines interfere with translation due to linkage to specific sites on the ribosome structure.

Bacterial resistance to antibiotics is naturally present in the bacterial genome, for example, certain staphylococcal genes can account for tetracycline resistance. Moreover, bacterial cells are capable of flexible adaptation to the new conditions. Especially regarding antibiotics that work bacteriostatically, which produce a selective pressure for microbes, this leads to the survival and further multiplication by only the more resistant microbes possessing some mechanisms of **secondarily obtained resistance**:

> • The bacteria can alter the construction of their **cellular packaging** to make them less of a target for antibiotics.
> • The bacteria can also synthesize **transporters** that can actively withdraw antibiotics from the intracellular space utilizing ATP.
> • A well-known mechanism of resistance is also the formation of **degradative enzymes** for antibiotics (e.g., synthesis of different β-lactamases).
> • Further, the bacterial cell may also slightly **alter the site where the antibiotic binds**. For example, methylation will occur at certain sites of rRNA forming the ribosomes, which does not affect the functionality of organelles, but prevents the binding of antibiotics.

Microorganisms often combine the above mechanisms, and secondary resistance genes can transmit to each other, for example, in the case of plasmids and transposons. The result is that microorganisms are *de facto* always a step ahead with regards to antibiotics.

9.3 Antibiotics

9.3.1 β-lactam antibiotics

Penicillins, cephalosporins, monobactams, and carbapenems are the β-lactam antibiotics affecting peptidoglycan synthesis in the cell wall. They bind to the specific proteins - **penicillin-binding proteins (PBPs)** - and inhibit cross-linking of the cell wall layers with transpeptidases.

The dysfunction of the cell wall is recognized by the bacteria, which triggers a cascade of autolysins in an attempt to repair the enzymes breaking down the poorly assembled cell wall. This process will cause the total destruction of the cell wall and the bacteria will die. Thus, the β-lactam antibiotics have **bactericidal** action.

Penicillins and cephalosporins belong to the class of relatively safe antibiotics, which are also suitable for children and pregnant women. The most common adverse effect is an occurrence of an allergic reaction (e.g., urticaria, anaphylactic reaction).

Diarrhoea caused by GIT dysbiosis can occur with the use of broad-spectrum β-lactams. Rarely, reversible blood disorders (e.g., leukopenia, thrombocytopenia) can occur.

The β-lactam antibiotics share similar pharmacokinetic characteristics: They are well-distributed into tissues and body fluids, usually do not affect intracellular pathogens, and are

excreted renally. Their biological half-life and plasma protein binding vary from one representative to another depending on the antibiotic administration interval (e.g., peroral (p.o.) amoxicillin is given for otitis therapy every eight hours). In patients with renal impairment, a dosage adjustment is necessary. The absorption of β-lactam antibiotics also differs; while penicillins are more suitable on an empty stomach, cephalosporins should be taken after a meal.

9.3.1.1 Penicillins

The penicillins are distinguished by their spectrum and some other characteristics.

The narrow-spectrum penicillins

Narrow-spectrum penicillins are highly effective against Gram-positive (G +) bacteria. The first of the penicillins to be included in this group is penicillin G (benzylpenicillin), which even today is still used intravenously (i.v.) as an infusion for the treatment of meningococcal meningitis, streptococcal, and pneumococcal infections.

It is used exclusively parenterally because of its acid-lability, its minimal plasma protein binding property, and its near immediate renal excretion; thus, the infusion should be long-lasting.

The depot penicillins belong to this group, as well, such as **benzylpenicillin** or **procaine penicillin.** These are a class of compounds within the **penicillins G** which provide a long-lasting effect. These penicillins are given intramuscularly (i.m.). In the muscular environment, the dissociation of benzylpenicillin is ongoing and released gradually into systemic circulation.

The narrow-spectrum penicillins also include acidostable penicillins for peroral use, such as **penicillin V** (phenoxymethylpenicillin) and **penamecillin**, which are used, for example, to treat streptococcal tonsillopharyngitis.

Another group is a part of the narrow-spectrum penicillins, and they are acidostable and β-lactamase-resistant; examples include **oxacillin**, **cloxacillin**, **dicloxacillin**, and **flucloxacillin**. Oxacillin is administered i.v. or i.m. for the treatment of respiratory, skin, and soft tissue infections. These penicillins have a very narrow spectrum (i.e., streptococci and staphylococci only) and are sometimes referred to as antistaphylococcal penicillins. This group also includes **methicillin**, but this agent is not used for therapeutic purposes anymore; instead, it is only used as a diagnostic reagent in microbiology.

The broad-spectrum penicillins

These are classified according to their chemical structure:

  • Aminopenicillins (e.g., **ampicillin**, **amoxicillin**),
  • Carboxypenicillins (e.g., **ticarcillin**), and

• Ureidopenicillins (e.g., **piperacillin**, **azlocillin**).

These penicillins act against both gram-positive (G+) and certain gram-negative (G-) bacteria (e.g., *E. coli, H. influenzae*). The carboxypenicillins and ureidopenicillins are also effective against pseudomonads. The broad-spectrum penicillins are not resistant to β-lactamase, so it is preferable to combine them with inhibitors of these degradative enzymes.

Clavulanic acid, **sulbactam**, and **tazobactam** are substances without their own antibiotic effect (or with moderate antibiotic effect), which are structurally related to penicillins. They have a higher affinity for β-lactamase, which become inactivated after binding to these inhibitors.

The combination of penicillin antibiotics with β-lactamase inhibitors is termed penicillins potentiation. The most widely used potentiated penicillins include co-amoxicillin (i.e., amoxicillin with clavulanic acid) and sultamicillin (i.e., ampicillin with sulbactam). The aminopenicillins, particularly amoxicillin and co-amoxicillin, belong to the most widely used antibiotics. They are used to treat the respiratory infections, sinusitis, otitis, urinary tract infections, kidney, skin, bone, and joint infections.

9.3.1.2 Cephalosporins

The cephalosporins are structurally similar to the penicillins and share essential characteristics (e.g., mechanism of action, drug safety, some pharmacokinetic properties). These drugs are acidostable and are used both orally and parenterally. Patients allergic to penicillins are at high risk for cross-hypersensitivity; therefore, cephalosporin administration is contraindicated for a patient allergic to penicillin.

Abstinence from alcohol consumption during cephalosporin therapy is necessary because of the possible disulfiram reaction; cephalosporins can interact with the metabolism of ethanol in the body by inhibiting acetaldehyde degradation and can cause severe nausea, vomiting, and headaches.

- The 1st generation of cephalosporins acts primarily on G+ bacteria, but also on some G- (e.g., *E. coli, Klebsiella*) bacteria. **Cefazolin**, is administered parenterally (i.e., via i.v.), and **cefadroxil** or **cefalexin** are administered orally.
- The 2nd generation of cephalosporins is broad-spectrum, effective against both G+ and G- bacteria. **Cefuroxime** is widely used and **cefuroxime axetil**, the ester form, is administered orally.
- The 3rd generation of cephalosporins is broad-spectrum, it affects a wide range of G- bacteria including pseudomonads. For example, **ceftriaxone**, **ceftazidime**, or **cefotaxime** are administered parenterally (i.v.).
- The 4th generation of cephalosporins is equally effective against both G+ and G- bacteria. **Cefepime** or **cefpirome** are two such antibiotics, which should only be used on a very limited basis because they are one of the last resorts used to treat infections caused by multidrug-resistant bacteria.

The 1st and 2nd generations are used for the treatment of infectious diseases of the respiratory tract, urinary tract, otitis, skin infections, and intra-abdominal infections. Representatives of

the 3rd and 4th generation are intended for the treatment of sepsis, complicated or multi-resistant infections of the respiratory and urinary tracts, skin, bones, intra-abdominal infections, etc. They can also be used for the treatment of meningitis because they penetrate the blood-brain barrier.

9.3.1.3 Monobactam

Aztreonam is a β-lactam antibiotic belonging to the group of monobactams. It is only effective against G- bacteria (including pseudomonads), so it does not act on G+ bacteria and anaerobes. It is administered parenterally (i.e., i.v., i.m., or inhaled). Administration via inhalation is intended for the treatment of infections caused by pseudomonads in patients with cystic fibrosis.

9.3.1.4 Carbapenems

The carbapenems are broad-spectrum β-lactam antibiotics effective against G+, G- bacteria, and anaerobic pathogens. They are resistant to β-lactamase. They are administered parenterally and belong among the drugs reserved for serious and complicated infections (e.g., pulmonary, intra-abdominal, skin, diabetic foot syndrome, etc.).

Imipenem is degraded by renal dehydropeptidase; therefore, it should be given in combination with **cilastatin**, an inhibitor of these enzymes, to prolong its effects. Other representatives, such as **meropenem** and **ertapenem**, are unaffected by dehydropeptidase.

9.3.2 Other antibiotics interfering with cellular packaging

9.3.2.1 Glycopeptides

Glycopeptides interfere with the cross-linking of peptidoglycans in the cell wall. **Vancomycin** is administered parenterally (i.v.) for the treatment of severe infections caused by G+ pathogens in the case that other, less toxic antibiotics cannot be used. Vancomycin acts bactericidal with certain strains and bacteriostatic with others (e.g., enterococci), and these bacteria may develop secondary resistance (i.e., VRE - vancomycin resistant enterococci). Vancomycin can also be administered perorally, but it is not absorbed in the gastrointestinal tract and acts locally there. This is optimal, for example, in the treatment of pseudomembranous colitis caused by *Clostridium difficile.*

After i.v. administration, vancomycin is well-distributed in bodily fluids and tissue and can penetrate abscesses, as well. However, it is a very toxic substance - it causes nephrotoxic, ototoxic (i.e., formation of tinnitus, hearing loss), and on rare occasions, blood disorders, general skin reaction, and anaphylactic reaction. The "red man" effect can also occur; vancomycin causes the release of histamine from mast cells followed by vasodilatation in the upper half of the body causing chest, neck, face, itching, hypotension, and tachycardia.

A similar substance is **teicoplanin**, which is intended for parenteral administration only. It has a long biological half-life and is only administered once a day.

9.3.2.2 Polypeptides

Polypeptide antibiotics are used locally in the form of ointments, nasal drops, etc. Because of their molecular weight, they cannot be absorbed into the bloodstream. However, if they were administered systemically, for instance, if administered intravenously, they would endanger the patient through the development of many undesirable effects due to their nephrotoxic and neurotoxic properties. After oral administration, they are not absorbed in the GIT and act locally there.

A typical agent in this group is **bacitracin**. This antibiotic interferes with the synthesis of cell wall components and acts in a bactericidal manner, primarily on G+ pathogens. It is most commonly used in combination with the aminoglycoside antibiotic, neomycin, which acts on G-bacteria, to treat impetigo, pyoderma, and other skin infections as well as bacterial conjunctivitis, sinusitis, purulent rhinitis, ear canal infections, etc. Other polypeptides act through a detergent mechanism, thereby disrupting the integrity of the cytoplasmic membrane. These antibiotics act primarily on G-pathogens.

Polymyxin B is used in gynaecology to locally treat bacterial and mixed vaginal infections in combination with neomycin and the anti-mycotic, nystatin. It is also used in ophthalmology in combination with neomycin and the glucocorticoid, dexamethasone, for the treatment of infectious conjunctivitis and uveitis with oedema as dexamethasone has anti-oedematous effects.

Colistin can be used in for therapy of GIT infections as it is effective against pseudomonads. It is not absorbed in the GIT.

9.3.3 Antibiotics inhibiting protein synthesis

9.3.3.1 Tetracyclines

Tetracycline antibiotics bind to the 30S ribosomal subunit and reversibly inhibit protein synthesis in the bacterial cell. They act bacteriostatically on a broad spectrum of pathogens (e.g., G+ and G-bacteria, intracellular, and anaerobic pathogens, etc.), but streptococci and staphylococci are largely resistant to tetracyclines. The absorption of tetracyclines within the GIT may be complicated by concomitantly administered food and drugs.

Tetracyclines create non-absorbable complexes with the cations: Ca^{2+}, Mg^{2+}, Fe^{2+}, Fe^{3+}, Al^{3+}, and others, which are then excreted from the body without any antibacterial effect. Therefore, it is necessary to avoid or temporally separate the administration of the milk products, the drinking of highly mineralized waters, and the administration of drugs like antacids and other preparations containing calcium (i.e., drugs taken during therapy for osteoporosis), magnesium (e.g., for muscle spasm therapy), and iron (e.g., for therapy of anaemia),

Tetracyclines penetrate the placental barrier, and they are contraindicated during pregnancy, breastfeeding, and until the children's permanent teeth replace all their deciduous teeth. This is due to the possibility of deposition of tetracyclines in bones and teeth, where they primarily affect the developing tissues negatively; they impair the quality of the dental enamel and

affect the growth and fracture of the bones. Because of the wide spectrum of these antibiotics, they often cause diarrhoea, and in women, they can also cause disturbance of vaginal flora and superinfection mostly caused by yeast. Currently, **tetracycline** is only used as local therapy for acne (3% tetracycline alcohol).

Doxycycline is an antibiotic less capable of binding to cations. Therapeutically, it is administered orally to treat many respiratory and urogenital infections including borreliosis, listeriosis, GIT infections caused by *Campylobacter*, *Shigella*, and many others.

Minocycline is reserved for the oral therapy of acne. Other tetracyclines (e.g., **oxytetracycline**) are used in veterinary medicine.

9.3.3.2 Amphenicols
From the group of amphenicols, only chloramphenicol is used clinically. It is a substance with an affinity for the 50S ribosomal subunit. It reversibly inhibits the synthesis of proteins in the bacterial cell and acts bacteriostatically on a broad spectrum of pathogens (e.g., G+, G- bacteria, and intracellular pathogens).

Chloramphenicol is used locally to treat eye infections in combination with the anti-inflammatory glucocorticoid, dexamethasone. It is also used in exceptional cases for systemic infections such as meningitis and infections caused by rickets, etc. It is administered parenterally (i.v.) and passes through the blood-brain barrier. It is a drug that is highly toxic; it causes reversible myelosuppression and neurotoxicity (e.g., causes vision disorder; optic neuritis).

Rarely, an irreversible aplastic anaemia with potentially lethal effects can occur. The aplastic anaemia can occur even after topical administration, when part of the drug is absorbed through the skin or a mucous membrane. For this reason, the 2% solution of chloramphenicol alcohol used for acne therapy has been dropped.

9.3.3.3 Macrolides
Macrolides belong to the most commonly used antibiotics. They are used as first-choice drugs for patients allergic to β-lactam antibiotics. The mechanism by which their bacteriostatic effect functions is through binding to the 50S subunit of the ribosome causing the subsequent inhibition of the proteosynthesis. They have a broad antimicrobial spectrum including G+ and G- pathogens, anaerobic and intracellular bacteria, and they also act against toxoplasmosis.

The pharmacokinetics of macrolides is significantly tissue-oriented; in other words, the tissue concentrations are considerably higher than the plasma concentration. They also penetrate macrophages, but they do not pass through the blood-brain barrier. Some macrolides are potent CYP3A4 inhibitors and exhibit many drug interactions. Dangerously, they may increase, for example, the plasmatic concentration of statins, digoxin, warfarin, and other drugs metabolised by this enzyme. The interaction potential of individual representatives within this group is different: the riskiest being erythromycin and clarithromycin, and by contrast, the least risky being azithromycin, roxithromycin, and spiramycin.

Macrolides are used to eradicate *Helicobacter pylori* in gastroduodenal ulcer treatment and to treat chlamydia infections as well as common respiratory infections. Due to their popularity among physicians and patients, bacterial resistance has recently increased. The typical phenotype is given the acronym, MLSB, which indicates secondary cross-resistance to macrolides, lincosamides, and streptogramin B.

Erythromycin is a drug currently used only locally in dermatology (e.g., acne therapy - solutions, ointments). During its administration, erythromycin diarrhoea occurs as a result of erythromycin binding to intestinal motilin receptors. Other representatives may also have a lesser affinity for these receptors.

Clarithromycin is a commonly used antibiotic for the treatment of *Helicobacter* and is also used to treat respiratory and skin infections.

Azithromycin is indicated for the treatment of respiratory, skin, and some specific sexually transmitted infections. It is only used once a day because it has a long biological half-life and is retained in the tissues for a longer duration than many other antibiotics. For this reason, it is referred to as a "three-days antibiotic" because it is sufficient for three days of use in a common uncomplicated infection. However, it is advisable for the patient to adhere to the standard seven-day treatment regimen.

Spiramycin is used in the treatment of toxoplasmosis in pregnant women.

Another macrolide agent is **roxithromycin**, with similar indications as has azithromycin.

9.3.4 New antibiotics similar to macrolides and tetracyclines

New antibiotics developed for the ongoing increase of the bacterial resistance can be derived from existing antibiotic drugs. Such is the case for macrolide-like antibiotics (e.g., streptogramins, ketolides, and oxazolidinediones) and tetracyclines (e.g., glycylcyclines).

9.3.4.1 Streptogramins

The **streptogramins**, **quinupristin**, and **dalfopristin** bind to two different sites on the 50S subunit of the ribosome and thereby inhibit proteosynthesis. In combination, they act as bactericides and are used for the therapy of infections caused by resistant G+ bacteria (e.g., MRSA, VRE, etc.). These drugs are administered intravenously combined and both drugs have the potential for drug interactions as they are CYP3A4 inhibitors.

9.3.4.2 Ketolides

The ketolides include **telithromycin**. This is a drug that is effective on G+ and G- bacteria, but does not act against pseudomonads. Its mechanism of action is like that of other macrolide-like antibiotics. It is intended for the treatment of pneumonia and other respiratory infections caused by β-lactam- and macrolide-resistant pathogens. It is an inhibitor of CYP3A4.

9.3.4.3 Oxazolidinediones

Linezolid belongs among oxazolidinediones and is an antibiotic effective against G+ aerobic and anaerobic pathogens. It also binds to the 50S subunit of the ribosome. It is given only to hospitalized patients, and it is intended for the treatment of pneumonia and complicated infections of the skin and soft tissues. Linezolid does not affect CYP enzymes. The common side effects of all the above-mentioned antibiotics are the possibility of developing diarrhoea from dysbiosis in GIT, oral and vaginal superinfections, and mild hepatotoxicity (i.e., elevated liver enzymes). Linezolid can also cause reversible myelosuppression.

9.3.4.4 Glycylcyclines

Tigecycline belongs among the glycylcyclines, the tetracycline-like antibiotics. Its mechanism of action is similar to tetracyclines; it binds to the 30S subunit and blocks proteosynthesis. It acts on G+ and G- bacteria as well as some anaerobes. It is administered in an intravenous infusion for therapy of the skin, soft tissue, and intra-abdominal infections, but only when other alternatives are not suitable. Its adverse effects include GIT disturbances, which are standard with regards to antibiotic therapy, including: photosensitivity, mild hepatotoxicity, dental enamel staining, and the possibility of blood clotting (i.e., aPTT prolongation).

9.3.5 Lincosamides

Lincosamides include antibiotics acting on the 50S ribosomal subunit. They act in a bacteriostatic manner on G+, some G-, and anaerobic pathogens, whereas at higher concentrations, they act bactericidally. Lincosamides are another therapeutic option for patients allergic to β-lactam antibiotics.

They are very well-distributed and deliver medication to even the most difficult-to-reach areas (i.e., bones, teeth); therefore, they are used mainly to treat dental infections and as prophylaxis for stomatologic surgery. They are also used in gynaecology, for situations in which antibiotics are suitable for the treatment of various pelvic infections (e.g., salpingitis, endometritis, etc.) as well as for the treatment of bacterial vaginosis of pregnant women. Lincosamides are further used for the treatment of respiratory, skin, and intra-abdominal infections, joint infections, and as a prophylactic against endocarditis in major surgical procedures.

The only clinically used agent from this group is **clindamycin**. It is used orally as well as intravenously. Clindamycin has only very mild side effects such as GIT difficulty and the elevation of liver enzymes.

9.3.6 Aminoglycosides

Aminoglycosides are the last group of antibiotics included with the others that embody mechanisms which block proteosynthesis through ribosomal subunit binding. These antibiotics bind irreversibly to rRNA, and their effect is primarily bactericidal. They act mainly on G- pathogens, aerobic pathogens, less on G+ (e.g., staphylococci) pathogens, and they do not act on anaerobes. Aminoglycosides are substances that are highly hydrophilic;

therefore, they permeate biological membranes, and for example, if they are administered orally, they will not be absorbed during passage through the GIT. They are also applied topically, for example, in the form of ointments and eye drops. Aminoglycosides are characterized by concentration-dependent effects and clinically significant post-antibiotic effects (see chapter introduction).

The toxicity of these antibiotics is considerable; they are nephrotoxic (e.g., they cause a decrease in glomerular filtration, proteinuria, increase serum creatinine, and rarely, they may cause acute kidney failure), ototoxic, and neurotoxic (e.g., can cause vestibular-ocular damage, hearing disorders, hearing loss, balance disturbances, and tinnitus). During the aminoglycoside treatment, the therapeutic monitoring of plasma drug concentrations is necessary to set up the appropriate dose and time interval administration and to avoid irreversible harm to the patient. The systemic therapy is usually for short period because the risk of irreversible side effects increases with prolonged treatment.

The administration of aminoglycosides is contraindicated with other nephrotoxic and ototoxic drugs (e.g., vancomycin, furosemide, cisplatin, etc.). A combination of aminoglycosides with β-lactam antibiotics is preferred, which leads to a potentiation of the antibiotic activity.

The first aminoglycoside was **streptomycin**, which is now used as an antituberculotic, and it is also one of the first drugs to be used to treat this infectious disease. It is administered intramuscularly.

Other systemically administered substances include **gentamicin** and **amikacin**. They are administered intravenously for the treatment of complicated urinary tract infections, pneumonia, intra-abdominal, and postoperative infections. They can also be administered to children at a young age; however, caution must be used due to immature renal function.

Tobramycin and **kanamycin** are primarily administered topically, for the treatment of bacterial infections of the eye. Tobramycin is also available as an inhalable form for the treatment of pulmonary infections in patients with cystic fibrosis.

Neomycin, in combination with bacitracin, a polypeptide antibiotic, is used for topical skin treatment, bacterial conjunctivitis, sinusitis, purulent rhinitis, and ear canal infections, etc.

9.3.7 Antibiotics for a local use

In some cases, for instance, during therapy of infectious foci accessible on local skin and/or mucous membranes, topical application of antibiotics is preferred to systemic treatment. Ideally, these substances are not absorbed from the site of administration and do not cause systemic side effects.

Fusafungine is a substance produced by the fungus *Fusarium*. Structurally, it belongs among depsipeptides, but the mechanism of antibacterial effect is still unclear. It also acts anti-inflammatorily. It is used in the form of an oral or nasal spray for topical treatment of pharyngeal and respiratory tract infections.

The inhibitors of bacterial cell protein synthesis, **retapamulin, fusidic acid**, and **mupirocin**, are the most commonly used for the topical treatment of mastoids for impetigo, pyoderma, and other skin infections.

9.4. Anti-infectious chemotherapeutics

9.4.1 Sulfonamides

The sulfonamides have historically been the first synthetic antimicrobial drugs. They were prepared in the early 20th century. Their antimicrobial effect was discovered in the 1930s, and the first representative of the group, sulfanilamide, already began to be used in clinical practice in the late 1930s. Due to the lack of evaluation of drug safety then, a tragedy linked to this sulfanilamide occurred: The medicinal product caused the poisoning of at least a hundred people in 1937 by diethylene glycol contamination, which was used as a starting reactant to synthesize the sulfanilamide. The mechanism of action of sulphonamides is through interference with the folic acid metabolism, hence with the purine nucleotide synthesis, as well. Microorganisms do not have the ability to take up folic acid from the environment in which they live; thus, they must synthesize it *de novo*.

The sulfonamides interfere with the first step of biosynthesis: competing with p-aminobenzoic acid (PABA) for the enzyme, dihydropteroate synthase. This enzyme converts PABA into dihydropteroate. The blockade of the enzyme creates a **bacteriostatic** effect on a broad spectrum of pathogens, including protozoa.

The sulfonamides are administered orally, and they are excreted by the kidneys. The precipitation, crystalluria, and rarely, renal insufficiency, occur with a fall in pH due to their poor solubility in an acidic pH. Other side effects include GIT difficulty and skin reactions (e.g., exanthema), mild reversible elevations of the liver transaminases, and blood disorder (i.e., myelosuppressive effect). Sulfonamides are contraindicated during pregnancy due to potential teratogenic effects. They are not suitable for nursing women either, but can be given to children from three months of age upward.

Among the most frequently clinically used sulfonamides include **sulfamethoxazole**, which is used in the combination with trimethoprim, a representative of pyrimidine chemotherapeutics, for the treatment of urinary and respiratory infections. This combination is referred to as a **co-trimoxazole**.

Sulfacetamide is locally used for the treatment of ocular infections and **sulfadiazine** for treatment of skin infections.

Sulfasalazine is a drug used for unspecific intestinal inflammation (e.g., Crohn's disease and ulcerative colitis); in the intestine, it breaks down into sulfapyridine (i.e., causing an antibiotic effect on undesirable intestinal microflora and having immunosuppressive action) and 5-aminosalicylic acid, which have anti-inflammatory effects.

9.4.2 Pyrimidines

Trimethoprim is a bacteriostatic chemotherapeutic agent that also interferes with folic acid biosynthesis. It inhibits the dihydrofolate reductase enzyme, which converts dihydrofolate to tetrahydrofolate. In combination with the sulfonamides, the sequential blockade of both enzymes has a bactericidal effect. However, trimethoprim may also be used as monotherapy for uncomplicated urinary, GIT, and respiratory infections. It is not suitable for pregnant and nursing women.

9.4.3 Quinolones

The quinolones are bactericidal chemotherapeutics, which inhibit bacterial DNA gyrase (i.e., topoisomerase II) and topoisomerase IV - the enzymes required to replicate bacterial DNA. These agents are active against the G- bacteria, anaerobes, and intracellular pathogens. They are administered orally or intravenously by infusion. The absorption of quinolones from the GIT may be complicated by concomitantly administered food and drugs. The quinolones form with multivalent cations, like tetracyclines, non-absorptive complexes that are exuded out of the body inertly.

The quinolones are characterized by concentration-dependent effects and by a clinically significant post-antibiotic effect (see chapter introduction). These compounds are CYP1A2 inhibitors. Their most significant side effects are the risk of joint and tendon damage (e.g., tendonitis, tendon tears, cartilage damage), particularly during physical exercise. Phototoxicity, reduction of the threshold for convulsion occurrence, reversible hepatotoxicity, and nephrotoxicity (i.e., crystallization of quinolones during urinary alkalization) may also occur. In addition, they can cause common GIT difficulties. They are contraindicated for children, pregnant, and nursing women due to the possibility of damage to immature cartilage and the baby's ligaments.

- The 1st generation of quinolones is not registered in the Czech Republic anymore, but it is still used abroad. **Nalidixic acid** and **oxolinic acid** are substances that only produce effective concentrations in urine; therefore, they are indicated for urinary tract infections exclusively.
- The 2nd generation has much wider applications; they are the most commonly used quinolones from this entire group. **Ciprofloxacin**, **levofloxacin**, **ofloxacin**, and other agents are used for therapy of the respiratory tract, urinary tract, kidney, skin, joints, bones, in the treatment of certain sexual diseases (e.g., gonorrhoea), and intra-abdominal infections. They can be applied both systemically and locally (e.g., ointments, eye drops).
- The 3rd generation drugs are not registered in the Czech Republic. An example is **sparfloxacin**.
- The 4th generation has an extended spectrum of action against G+ bacteria and mycobacteria. Representatives, such as moxifloxacin, belong to the reserved antibiotics intended for the serious infections. Unfortunately, the resistance to these quinolones is still rising.

9.4.4 Nitrofurans

The nitrofurans are transformed within the bacterial enzymes into an active form that covalently binds to DNA and blocks its proper function. They belong to the broad-spectrum chemotherapeutics that also act against protozoa. Their effective concentration is only formed in the urine; therefore, it is reserved for the treatment of urinary infections. They are GIT irritants (i.e., up to 50% of patients experience nausea and vomiting); they can also cause hepatotoxicity, neurotoxicity (i.e., they are correlated with an increase in peripheral neuropathic complaints), and pneumotoxicity (e.g., lung fibrosis, pneumonitis).

Nowadays, only **nitrofurantoin** is still used in a clinical setting.

Other drugs have been derived from nitrofurans; of these, the antimycotic, nifuratel, and intestinal antiseptic, **nifuroxazide**, are two such examples.

9.4.5 Nitroimidazoles

The nitroimidazoles are chemotherapeutic agents that act against anaerobes and protozoa, so they are used to treat mainly viral infections and GIT infections.

Metronidazole is useful for the eradication of *Helicobacter pylori* in gastroduodenal ulcers. It can cause GIT problems (e.g., nausea, diarrhoea, dry mouth, metallic taste in the tongue) and rarely also peripheral neuropathy. For both local and systemic use, alcohol is contraindicated due to the possibility of a disulfiram reaction (see cephalosporins).

Other agents include **ornidazole** and **tinidazole**, but neither are currently registered in the Czech Republic.

9.5 Antimycotics

Antimycotics are drugs used for the treatment of infections caused by microscopic fungi, especially yeasts and various pathogenic fungi. The most common mycoses are found on the skin, nails, and mucosa (e.g., mouth, vagina), and they are usually caused by the yeast, *Candida*. Systemic mycoses occurs more frequently in immunosuppressed patients, examples include people who have been treated with cytostatics, for AIDS, or with other immunosuppressive agents, etc. These conditions can cause *Candida*, *Cryptococcus*, *Aspergillus*, and other pathogens to proliferate systemically. The antimycotics are divided into groups according to the chemical structure:

• Polyethylene antimycotics,
• Azole antimycotics,
• Echinocandins, and
• Other antimycotics.

9.5.1 Polyene antimycotics

9.5.1.1 Polyene antimycotics for systemic use

Amphotericin B binds to the ergosterol in the cytoplasmic membrane of the pathogenic fungal cell, thereby causing a change in membrane permeability and destroying the ionic homeostasis of the cell. Amphotericin is a wide-spectrum and the most effective antifungal, also acting on some protozoa. It is mainly administered intravenously; during oral administration, it is not absorbed from the GIT, or it may also be applied locally (e.g., for eye infections). It binds strongly to plasma proteins.

The adverse effects are common (i.e., up to 10% of patients experience them) and result mainly from the binding of sterols to human cells. Although amphotericin has a lesser affinity to human cells compared to fungal cells, the drug, nevertheless, is still very toxic. It is considered a nephrotoxic (i.e., causing blood vasoconstriction, electrolyte disturbances, and renal insufficiency) as well as hepatotoxic agent. Other toxicity results from the ability of amphotericin to induce the prostaglandin, PGE2, and the proinflammatory interleukins, IL-1 and TNF, which causes abdominal pain, vomiting and diarrhoea, hypotension, muscle pain, fever, and bronchospasm. It can also cause cardiac arrhythmias and thrombocytopenia.

Today, only amphotericin in phospholipid complexes is used, which has very low affinity for cholesterol and, therefore, is less nephrotoxic. It is used for the treatment of invasive systemic candidiasis and other systemic fungal diseases, such as aspergillosis and cryptococcosis.

9.5.1.2 Polyene antimycotics for topical use

Other representatives of polyene antimycotics have the same mechanism of action, but they are only used locally for the treatment of skin and mucous membranes. These agents are not readily absorbed from the application site.

Nystatin is used for *Candida* infections of the oral cavity and vaginal candidiasis. The ointment is available as an over-the-counter formulation.

Natamycin also acts against *Trichomonas vaginalis*. The adverse effects of both drugs may be irritation at the application site. Both drugs may also be used locally during pregnancy and lactation.

9.5.2 Azole antimycotics

The azole antimycotics inhibit the synthesis of ergosterol, resulting in the loss of functionality of the cytoplasmic membrane of the mould cell. The blockade of synthesis is achieved by an inhibition of the fungal CYP enzyme. Although these drugs have a higher affinity for fungal CYP enzymes, they also inhibit human CYPs (e.g., 2C9, 3A4, and 2C19); therefore, there is a high risk of drug interactions occurring. Some azole antimycotics also act on G+ bacteria and protozoa in addition to fungi and yeasts.

Fluconazole is used systemically (i.e., intravenously and orally). For example, it is used for the treatment of invasive organ candidiasis, chronic mucosal candidiasis, recurrent vaginal candidiasis, and dermatomycosis in the absence of topical treatment.

Similar indications require systemic administration of **itraconazole** and **voriconazole**. Itraconazole is used locally as a gargle, as well. The adverse effects of these antimycotics include GIT difficulties, elevation of liver transaminases, and skin reactions. They are contraindicated during pregnancy and lactation.

Usually, ketoconazole and miconazole are included in the systemic azole antimycotic group, but currently, both substances are only used locally for the treatment of skin and vaginal mycoses. The azole antimycotics are reserved for topical use for the treatment of vulvovaginal mycoses and dermatomycosis, mostly as over-the-counter medications.

Econazole, **clotrimazole**, **fenticonazole**, and **oxiconazole** are also effective against some G+ bacteria (e.g., streptococci and staphylococci). After topical application, these substances are either not absorbed at all or only very limitedly. The risk of drug interactions is minimal. They may also be used with caution during pregnancy.

9.5.3 Echinocandins

The echinocandins are lipopeptide antimycotics that inhibit the synthesis of β-1,3-glucan in the cell wall of the fungi.

Caspofungin acts primarily against *Aspergillus* and *Candida*, and it is administered systemically (i.e., i.v.) for the treatment of invasive mycoses. It can be combined with azole antimycotics and amphotericin; the combination has a synergistic effect. Because of its peptide structure, caspofungin can cause allergic reactions during topical or systemic administration manifesting as oedema at the site of application, fever, chills, pruritus, bronchoconstriction, and rarely, anaphylaxis. In addition, it can cause phlebitis at the application site, blood count disorder, hepatic transaminase elevation, and GIT difficulties. It is not suitable for pregnant and nursing women.

9.5.4 Other antimycotics

9.5.4.1 Other antimycotics for systemic use

Griseofulvin is a lipophilic antimycotic effective against dermatophytes only. Its mechanism of action works by binding to tubulin and blocking mitosis of the fungal cell. After oral administration, it accumulates in the skin and skin adnexa (i.e., nails, hair), and it is excreted by the sweat glands on the surface of the skin. It belongs to the family of CYP inducers. It only causes common, non-serious adverse effects, such as GIT difficulties, headache, skin reactions, etc. Currently, the medicine is not registered in the Czech Republic.

Flucytosine acts as an antimetabolite; it is transformed into 5-fluorouracil in the cell. There, it is incorporated into RNA and inhibits DNA replication. It is effective against *Candida* and

Cryptococcus, when administered either orally or intravenously. It is used primarily in combination with amphotericin or azole antimycotics for the treatment of the systemic mycoses. It has a myelosuppressive effect, it is slightly neuro- and hepatotoxic, and can cause GIT difficulties. Currently, it is not registered in the Czech Republic.

9.5.4.2 Other antimycotics for topical use

Terbinafine belongs to the allylamine antimycotics and is intended primarily for the local (but, can also be used systemically) treatment of onychomycosis and dermatomycosis caused by dermatophytes. Its mechanism of action works through the inhibition of ergosterol synthesis in the cytoplasmic membrane of fungi, but it does not affect fungal CYPs. However, it is an inhibitor of human CYP2D6. If it is administered systemically, its local administration may cause an allergic reaction in the area (e.g., urticaria, redness, pruritus), GIT difficulties, and rarely, hepatotoxicity (e.g., cholestasis). The ointments and creams containing terbinafine are available as over-the-counter preparations.

Amorolfine is also used for the treatment of onychomycosis in the form of a medicinal nail polish. Amorolfine inhibits ergosterol biosynthesis and affects a wide range of fungal infections. From the surface of the nail, it is absorbed into the nail plate without penetrating the skin and winding up in systemic circulation. Discoloration of the nails or irritation of the surrounding skin may occur during administration.

Ciclopirox olamine acts antimicrobially against several bacteria (e.g., G+ and G-), fungi, and protozoa (e.g., trichomonads). It is only used locally to treat onychomycosis, mixed vaginal infections, and seborrheic dermatitis. Its mechanism of action is likely to disrupt the synthesis of cellular packaging components, interactions with DNA, tubulin, and some pathways of the energy metabolism of the fungal cell. It penetrates well into the nail plate and the skin. The most common side effect is irritation at the application site.

9.6 Antiviral drugs

Viruses are pathogens with a simpler cellular structure than prokaryotes (e.g., bacteria) and eukaryotes (e.g., fungi). They also have a different life cycle:

• The virions must adhere to the surface of the host cell; these must then penetrate the cell and shed their coat (i.e., capsids).
• In the host cell, the virion then uses a replication device to propagate its DNA or RNA and ribosomes for the synthesis of proteins (e.g., structural components, enzymes) needed for the formation of a new virion. Viruses also have the ability to integrate their genetic information into the genome of the host cell.
• New virions are either gradually assembled and slowly released by a budding mechanism while maintaining the integrity of the host cell (i.e., lysogenic cycle), or virions replicate rapidly overwhelming the host cell causing its cytoplasmic membrane to rupture (i.e., lytic cycle).

Antiviral drugs can act during different stages of viral infection:

• The inhibition of penetration of the virion into the host cell (e.g., interferons, docosanol),
• The inhibition of viral coat disassembly (e.g., amantadine),
• The inhibition of specific viral enzymes (e.g., reverse transcriptase inhibitors), and
• Inhibition of the release of newly generated virions from the host cell (e.g., neuraminidase inhibitors).

The development of new antiviral agents is associated with the Czech organic chemistry professor, Antonín Holý, DrSc., dr. h.c. mult. (ca. 1936-2012), former employee and director of the Institute of Organic Chemistry and Biochemistry of the Academy of Sciences in Prague, Czech Republic. His team collaborated to develop important anti-herpetic drugs (e.g., cidofovir), antiretroviral drugs (e.g., tenofovir), and drugs used to treat hepatitis B (e.g., adefovir).

Clinically used antivirals are commonly classified according to the indication for which they're prescribed:
• Anti-herpetics,
• Flu medicines,
• Antiretroviral drugs, and
• Drugs used to treat viral hepatitis and other antiviral drugs.

9.6.1 Drugs for herpes viruses

Herpesviruses include HSV-1 (herpes labialis), HSV-2 (herpes genitalis), varicella-zoster virus (herpes zoster), EBV (Epstein-Barr virus), and CMV (cytomegalovirus).

Anti-herpetic drugs are classified according to their chemical structure as being either nucleoside or non-nucleoside analogues. The active form of nucleoside drugs is produced through the action of intracellular host cell kinases or viral kinases. Phosphorylated nucleosides are incorporated into newly formed nucleic acid fibres; this either causes termination of the synthesised chain or the formation of nonsense sequences that subsequently cannot be transcribed. Both nucleoside and non-nucleoside anti-herpetic drugs may inhibit various enzymes, such as DNA-polymerase.

Nucleoside anti-herpetic drugs

Aciclovir is a nucleoside analogue of guanosine that is converted to its monophosphate version by viral thymidine kinase, which is significantly more effective at carrying out phosphorylation than the analogous enzyme in the host cell; therefore, it only becomes activated in infected cells. The host cell kinases then convert the monophosphate to aciclovir trisphosphate, the active form that inhibits viral DNA polymerase, terminating the nucleotide chain. Aciclovir can be given orally, intravenously, or topically.

For the treatment of herpes labialis, it is applied topically in the form of an ointment, preferably at the first signs of herpes (e.g., itching, feeling of warmth). Aciclovir in the form of eye drops is intended for the treatment of herpes infections of the eye. Local administration should be repeated every four hours. Oral therapy is particularly suitable for recurrent herpes labialis, h. genitalis, and h. zoster. Intravenous administration is preferred for severe mucosal

and skin infections and herpes encephalitis.

The most common side effects of systemic therapy include GIT difficulty, hepatotoxicity with increased liver transaminases and bilirubin, and skin reactions (e.g., urticaria). In therapy, good hydration should be maintained to prevent nephrotoxicity by the drug.

Valaciclovir is an aciclovir ester containing L-valine. It is a prodrug of aciclovir that improves its bioavailability after peroral administration. Another drug related to aciclovir is **penciclovir**. It is intended for the topical treatment of herpes labialis. A penciclovir ester with more favourable pharmacokinetic properties is **famciclovir**.

Ganciclovir is similar to aciclovir, but it also acts on cytomegalovirus. Therefore, it is used for the treatment of CMV infections in immunosuppressed patients (e.g., CMV retinitis in AIDS patients). It is only applied parenterally (i.e., i.v.), and systemic therapy can lead to reversible myelosuppression in the patient (e.g., neutropenia, leukopenia, thrombocytopenia, and anaemia) as well as psychiatric disorders (e.g., depression, anxiety, sleep disturbances). Ganciclovir is also nephrotoxic, ototoxic, hepatotoxic, and causes GIT difficulty. Local eye gel therapy is suitable for keratitis caused by herpes simplex viruses.

Trifluridine and **idoxuridine** are the nucleoside analogues of thymidine and uridine, respectively. After intracellular phosphorylation, they are incorporated into both viral and cellular DNA. Due to their non-specific effect, they are used only locally for the treatment of herpes infections of the eye (i.e., conjunctiva, cornea, and eyelid). These substances can irritate the eye locally, causing congestion and swelling of the eyelid.

Brivudine is administered orally in patients with herpes zoster. The mechanism of action of brivudine involves viral kinase activation; therefore, it acts specifically on infected cells. Its most common side effects include GIT disturbances, hepatotoxicity, skin reactions, and myelosuppression.

Cidofovir is a nucleoside analogue of cytidine. It is used to treat CMV infections and aciclovir-resistant herpes infections. Intravenous application is the only form of administration and only after ensuring sufficient hydration.

Vidarabine is a nucleoside analogue of adenosine. It is used locally for herpes keratitis. In practice, intravenous therapy with vidarabine for herpes encephalitis has already been replaced by aciclovir.

Non-nucleoside anti-herpetic drugs

Docosanol is non-nucleoside, anti-herpetic drug, a saturated fatty alcohol, which inhibits fusion of the viral envelope to the cytoplasmic membrane of the infected cell. This prevents the entry of the virion into the cell and its replication. It is applied locally to herpes labialis lesions and is contained in over-the-counter (OTC) products.

Fomivirsen is a chemically modified short RNA that binds complementarily to viral mRNA (i.e., "antisense therapy"). After binding to mRNA, the subsequent transcripts are edited in such a way as to prevent the necessary proteins for construction of new virions from being

produced. Fomivirsen is used for the treatment of CMV retinitis in immunosuppressed patients in the form of an intraocular injection. It is applied once every 2-4 weeks.

Foscarnet inhibits DNA polymerase and reverse transcriptase by binding to the phosphate site. It is given intravenously in high doses for CMV infections.

9.6.2 Influenza treatment

Influenza effects about 20% of the world's population each year. Influenza epidemics and pandemics occur during different seasonal periods. An effective defence is vaccination, but influenza virus antigens often change, mutate; therefore, vaccines are always produced based on a prediction for a defined timeframe. Antiviral drugs against influenza viruses shorten the duration of influenza symptoms and reduce the risk of serious complications, but therapy should begin as soon as possible after the onset of the first symptoms (i.e., within 48 hours). In terms of mechanism of action, two distinguishable groups are: M2 ion channel inhibitors and neuraminidase inhibitors.

9.6.2.1 Inhibitors of M2 ion channels

The first influenza antivirals were adamantane derivatives. Their effects are inhibition of fusion of the host cell membrane and virus, inhibition of viral coat disassembly, and preventing the secretion of newly synthesised virions.

The M2 protein is a viral transmembrane protein that functions as a channel for H+ cations. **Amantadine** and its derivatives block this channel and interfere with the various stages of viral infection by disrupting acid-base processes. However, the resistance of the influenza virus to M2 channel inhibitors is rapid, for example, during the 2009 H1N1 influenza pandemic, all isolates of the virus were resistant to M2 channel inhibitors.

Amantadine may be administered orally and intravenously; parenteral application is reserved for
neurological indications (see the section on Drugs affecting the function of the locomotion system). Oral use may also be prophylactic, such as in patients with immunodeficiency, patients with chronic respiratory disease, health care professionals, etc. The side effects of amantadine are primarily in CNS (e.g., dizziness, insomnia, restlessness, and nervousness), orthostatic hypotension, and GIT problems. A similar substance to amantadine is **rimantadine**. Another adamantane derivative is **tromantadine**, which is used locally in the early stages of herpes labialis and is a component of an over-the-counter formulation.

9.6.2.2 Neuraminidase inhibitors

The influenza virus carries two antigens on its surface, these unique antigens are used to classify the specific influenza viral strain; for example, the recent "swine flu" was caused by the H1N1 virus, so-called due to the specific H and N antigens presented. Label H belongs to **hemagglutinin**, a membrane glycoprotein whose function is binding to sialic acid residues on the surface of the host cell. N is the abbreviation used to denote **neuraminidase**, an enzyme that aids in viral transport through respiratory tract mucus digestion and prevents the

clustering of the newly formed virions. These are enveloped by the cytoplasmic membrane of the host cell, but also have viral antigens on their surface, such as the hemagglutinin described above. Subsequently, neuraminidase cleaves sialic acid residues from the cytoplasmic membrane before coating the new virions to avoid hemagglutinin-sialic acid interaction. Neuraminidase inhibitors, on the one hand, make cell infection more difficult, and on the other hand, cause new virions to clump to the infected cell preventing the spread of infection in the body.

Oseltamivir is a neuraminidase inhibitor suitable for oral administration. It is designed to treat and prevent influenza in adults and children. In addition to common, non-serious side effects (e.g., GIT disturbances, skin reactions), it also causes increased liver transaminases and rarely neuropsychiatric side effects (e.g., confusion, agitation, hallucinations, abnormal behaviour).

Zanamivir has very low bioavailability after oral administration and is, therefore, administered via inhalation (i.e., topical administration to the lungs).

9.6.3 Antiretroviral therapy

HIV viruses are retroviruses equipped with the enzyme, **reverse transcriptase** (RT). This enzyme enables RNA to be transcribed into complementary DNA (cDNA), then double stranded DNA, which, with the aid of the integrase enzyme, integrates into the genome of the host cell. The HIV virus causes AIDS (acquired immune deficiency syndrome). HIV viruses have an affinity for human T lymphocytes and destroy them during the acute infection phase. The infected person becomes increasingly prone to various other infections (e.g., pneumocystis pneumonia, lung tuberculosis, oesophageal candidiasis, etc.). Likewise, their risk developing certain cancers (e.g., Kaposi sarcoma, lymphoma, cervical cancer, etc.) increases.

HIV is transmitted via three main routes: sexual contact, significant exposure to infected body fluids or tissues, and from mother to child during pregnancy, delivery, or breastfeeding (known as vertical transmission). Antiretroviral drugs slow down the course of the disease, prolong survival, and reduce the overall mortality of the patients. It is important to initiate antiretroviral therapy in a timely manner as in later stages of the disease, the prognosis is no longer as favourable. Drugs are often used in combinations, most often in triple combinations. The use of multiple drugs that act on different viral targets is known as highly active antiretroviral therapy (**HAART**).

The following antiviral groups are used:

• Nucleoside reverse transcriptase inhibitors,
• Nucleotide reverse transcriptase inhibitors,
• Non-nucleoside reverse transcriptase inhibitors,
• Protease inhibitors,
• Fusion inhibitors,
• Entry inhibitors, and
• Integrase inhibitors.

9.6.3.1 Reverse transcriptase (RT) inhibitors

Nucleoside RT inhibitors

These substances are administered as prodrugs and their intracellular phosphorylation is required. After attaching phosphate groups, they compete with endogenous nucleosides to bind to RT, which they then block.

Therapy with nucleoside inhibitors carries the risk of several undesirable effects, some of which are potentially lethal. There is myelosuppression with anaemia, neutropenia, and leukopenia, which is the reason for frequent blood counts being taken. Lipodystrophy and redistribution of fat in the body (i.e., visceral fat increases, blood lipid levels increase) occurs, as well. Likewise, serious complications of therapy with RT inhibitors may include the development of lactic acidosis and hepatotoxicity. Sometimes, after the onset of treatment, so-called immune reconstitution inflammatory syndrome (IRIS, also known as immune recovery syndrome), a violent systemic reaction of the immune system to opportunistic pathogens or to its own tissue (the occurrence of an autoimmune disease), can manifest.
Zidovudine is historically the first HIV-antiviral agent to be introduced into clinical practice at the end of the 1980s. It is administered orally or as an intravenous infusion. It is part of treatment regimens for HIV-positive pregnant women and reduces the risk of foetal harm. It is used in combination with other antiretroviral drugs.

Other group representatives include **stavudine**, **lamivudine**, **emtricitabine**, and **abacavir**.

Nucleotide RT inhibitors

The only representative of this group is **tenofovir**, a drug prepared by Prof. Holy (see the introduction of the chapter, Antiviral drugs). Tenofovir has a nucleotide structure similar to adenosine monophosphate. It is given orally and combined with other antiretroviral agents (e.g., emtricitabine). Adverse reactions are similar to nucleoside inhibitors, including the risk of severe lactic acidosis.

Non-nucleoside RT inhibitors

The mechanism of action of these compounds is through the induction of a conformational change in reverse transcriptase, which subsequently loses its ability enable transcription. These substances do not require intracellular phosphorylation and do not compete with endogenous nucleotides.

The spectrum of adverse effects is different from those of the nucleoside and nucleotide type. A rash may develop with a moderate to severe course, lighter rash forms are quite responsive to glucocorticoids and antihistamines; however, if a severe rash with blisters forms, this medication should be discontinued. Various neurological and psychiatric side effects are also common including: depression, suicide attempts, delusions, insomnia, wild dreams, etc. Non-nucleoside inhibitors are not suitable for pregnant women because they may cause defects in neural tube formation of the foetus. Some non-nucleoside inhibitors affect CYPs and have a high risk of drug interactions.

The representatives of this group are **efavirenz**, **rilpivirine**, and **nevirapine**. They are given orally and are also combined as part of some therapeutic regimens. Efavirenz is an inhibitor of CYP2C9 and nevirapine induces CYP3A4.

9.6.3.2 Protease inhibitors

HIV protease is an enzyme necessary to form fully functional virions and to lyse the cell allowing their release. Thereby, protease inhibitors prevent the spread of the virus in the body. Their side effects include GI complications, especially diarrhoea, the onset or decompensation of diabetes, lipodystrophy with redistribution of body fat, and hyperlipidaemia. Rarely, pancreatitis may occur. HIV protease inhibitors are both substrates and inhibitors of CYP enzymes.

Ritonavir is given orally. It is a potent inhibitor of CYP3A4 and 2D6; therefore, it is used in lower doses as a modulator of the pharmacokinetics of other protease inhibitors metabolised by these enzymes.

Other group representatives include **saquinavir**, **indinavir**, **darunavir**, **fosamprenavir**, and **lopinavir**. They are part of combined therapeutic regimens.

9.6.3.3 Fusion inhibitors

The only representative of this group is **enfuvirtide**. Its mechanism of action works by inhibiting the fusion of the viral membrane to the membrane of the host cell. If no fusion occurs, viral RNA cannot be swept into the cytoplasm of the cell, thereby preventing infection as well as the spread of infection throughout the body. The drug is generally given by subcutaneous injection in combination with other drugs to treat HIV when resistance becomes a problem or when the patient has become intolerant of other antiretroviral drugs.

9.6.3.4 Entry inhibitors

These are substances that antagonize the CCR-5 receptor specific to leukocytes. HIV uses this receptor to enter the cell. These are new drug groups; the only representative on our market is **maraviroc**.

9.6.3.5 Integrase inhibitors

This is another modern group of medicines. Integrase, the enzyme necessary for the integration of the HIV genome into the host cell genome, is targeted by these medicines. Registered representatives are **elvitegravir**, **raltegravir**, and **dolutegravir**.

9.6.4 Drugs used to treat chronic viral hepatitis and other antiviral drugs

Other serious viral diseases include hepatitis. The chronic form of hepatitis B and C causes fibrotic remodelling of the liver (i.e., cirrhosis) and increases the risk of malignant reversal. The acute phase of the viral infection is addressed by supportive therapy including bed rest, diet, supplementation with B vitamins, and **hepatoprotective drugs** (e.g., **silymarin**, **essential phospholipids**).

Chronic hepatitis B

Antiviral agents, such as **adefovir** and **lamivudine**, are used to treat chronic HBV infection. In addition, antiviral **immunoglobulin** (i.e., gamma globulin), an IgG-rich human plasma fraction with traces of IgA and IgM, can be used. This preparation prevents viral penetration into host cells and activates complement and cellular immunity. In addition to HBV infection, this preparation is also used to treat herpes infections. It is applied parenterally once every 2-3 weeks. Local and generalized hypersensitivity reactions, and rarely anaphylaxis, may occur after administration.

More often, the use of interferons α and α-2a are used to treat chronic hepatitis B. These cytokines inhibit all phases of viral infection. They are administered subcutaneously (also i.v. and i.m.), and the therapy is long-term, lasting 4-12 months. Frequent side effects include flu-like syndrome, which is a range of flu-like symptoms (e.g., headaches, muscles, increased body temperature, inability to concentrate). However, these effects are soon tolerated over the course of the medication. Interferons can also cause myelosuppression, cardio-, and pneumotoxicity. In pregnant women, these medicines can cause abortion.

In terms of psychiatric side effects, depressive episodes are most common.

Chronic hepatitis C

Treatment of chronic hepatitis type C involves administering **interferon α-2a** or a combination of **interferon α-2b** and **ribavirin**.

In addition, **miravirsen** is in its clinical trial phase. It's a chemically modified oligonucleotide that binds to a short RNA synthesised only by the liver cells the virus uses for its replication. Blockade of this RNA does not affect the virus itself and has a lower potential for resistance. From the clinical trials, the drug appears to be well-tolerated with a suitable pharmacokinetic profile and efficacy.

10 Cancer treatment, principles of targeted therapy

10.1 Principles of cancer treatment

In the Czech Republic, cancer diseases are the most frequent cause of death among adults aged 40– 70 years old. The population of the Czech Republic has a higher incidence of colorectal and renal carcinoma as compared to the rest of the world. Czech men primarily suffer from prostate, colorectal, and lung carcinoma, while Czech women are primarily diagnosed with breast, colorectal, lung, and uterine cancer. Overall cancer mortality has become stagnant, and with some diagnoses, it has even decreased due to innovative therapeutic approaches. A typical example of therapeutic approaches improving disease prognosis is in the case of breast cancer.

Cancer tissue is different from healthy tissue, and these differences can be used as specific pharmacotherapeutic targets. **Unregulated proliferation** (i.e., cell division) in cancer tissue is one of the typical **hallmarks of cancer**. It may be caused by unresponsiveness to intracellular signals that stop the cell cycle or by mutations (e.g., mutation in p53 gene). Cancer cells gain **unrestricted replication potential**, for instance, through the activation of telomerases. Unregulated proliferation can also be triggered by the overproduction of growth factors (e.g., EGF – epidermal growth factor) or by the constitutive activity of their receptors (e.g., EGFR), both of which having been caused by a mutation. The "immortality" of a cancer cell is also caused by impairments in **the regulation of programmed cell death** (i.e., apoptosis). Finally, cancer cells can migrate from the tissue of origin through the blood circulation to distant organs **forming metastases**. Importantly, since oxygen and nutrient supply for the growing tumour is necessary, starving and hypoxic cancer cells produce growth **factors for neoangiogenesis** (e.g., VEGF – vascular endothelial growth factor).

Various **treatment approaches** are combined for the treatment of a cancer. If possible, the tumour is **dissected surgically** along with a portion of the healthy surroundings and/or nearby lymph nodes. Patients often undergo **radiotherapy**, as some cancers are sensitive to irradiation. If the cancer cells express receptors for endogenous hormones, such as oestrogen in the case of breast cancer, it is possible to use **endocrine therapy** (e.g., antioestrogens – see Chapter 10.5 Endocrine therapy of cancer diseases, and 7.8. Sex hormones). In most cancers, **cytostatic therapy** (i.e., **chemotherapy**) represents an effective treatment approach, and it is sometimes combined with **targeted therapy** (see Chapter 10.6 Principles of targeted therapy). All therapeutic modalities should be supported by adequate **compensation for adverse effects** (e.g., skin lesions after radiotherapy, adverse effects of cytostatic agents, etc.) as well as by **nutritional support** for the cancer patient, which can significantly influence his/her prognosis.

10.2 Principles of chemotherapy

Cytostatic agents have cytotoxic and antiproliferative effects, thereby stopping unregulated cell division, which is a typical feature of cancer tissue. These drugs influence the majority of

somatic cells; however, their effect is most pronounced in fast-proliferating tissues. Influence on physiologically fast-proliferating cells leads to the various adverse effects of the therapy (for details, see later in the text). Cytostatic agents can be administered orally (e.g., temozolomide in the treatment of glioblastoma), parenterally by bolus, or more frequently, by infusion. The dose of cytostatics is sometimes stated in mg per square meter of the body surface; for instance, the recommended dose of doxorubicin is $60-75$ mg/m^2. Cytostatic agents can be used as monotherapy or as a combination in specific regimens. Examples of chemotherapy regimens can be found in Table 7. The administration of cytostatics is usually repeated in series and cycles. For instance, doxorubicin is administered every three weeks, meaning the dose is given every 21 days. The interval is chosen to give time to the organism to recover from adverse effects, although it has also another reason. A portion of cancer cells could be in phase G_0 of the cell cycle (i.e., non-dividing, dormant cells), when they are least sensitive to the effects of most the cytostatic agents. After transition to the active cell cycle, these cells can be destroyed.

Table 7: Examples of chemotherapy regimens

Abbreviation	Drugs used	Indication
BEP	Bleomycin, etoposide, platinum derivative	Testicular cancer
FUFA	Fluorouracil, folinic acid	Colorectal carcinoma
FOLFIRI	Fluorouracil, folinic acid, irinotecan	Colorectal carcinoma
CVC	Cisplatin, vincristine, cyclophosphamide	Brain tumours
ABVD	Doxorubicin, bleomycin, vinblastine, dacarbazine	Hodgkin's lymphoma
ECF	Epirubicin, cisplatin, fluorouracil	Gastric and oesophageal cancer
CVAD	Cyclophosphamide, vincristine, doxorubicin, dexamethasone	Lymphoma and leukaemia
XELOX	Capecitabine, oxaliplatin	Colorectal carcinoma

10.2.1 Mechanism of action of cytostatic agents

Cytostatic agents interfere with many intracellular processes. Antimetabolites affect **metabolism of nucleic acids**, for example, by inhibiting nucleotide biosynthesis. Alkylating and intercalating agents, and platinum derivatives **bind to the DNA** double-helix, which is then damaged by forming double- or single-strand breaks; moreover, these drugs also hinder replication enzymes from approaching the DNA strand. **Topoisomerase inhibitors** block the unwinding of DNA supercoiling (i.e., superhelix), which creates DNA strand breaks and hinders replication enzymes. Cytostatic agents can also affect mitosis in that some alkaloids influence the functionality of the **mitotic spindle**. Many cytostatic agents have combined effects.

According to the mechanism of action, cytostatic agents can be divided into the following groups:

- **The following are drugs that damage the structure of DNA**;
  - Alkylating agents
  - Platinum derivatives
  - Intercalating agents
  - Bleomycin
- **Drugs that inhibit key enzymes of DNA metabolism include the following**;
  - Antimetabolites
    - Purine analogues
    - Pyrimidine analogues
    - Folic acid analogues
    - Hydroxyurea
  - Topoisomerase inhibitors
    - Inhibitors of topoisomerase I – camptothecins
    - Inhibitors of topoisomerase II – podophyllotoxins
- **Drugs that alter microtubules include those listed below**; and
  - Inhibitors of tubulin polymerisation – Vinca alkaloids
  - Inhibitors of tubulin depolymerisation – taxanes
- **Others**.
  - Drugs that inhibit protein synthesis – L-asparaginase

With respect to the cell cycle phase in which the specific agent is effective, cytostatics can be phase-specific or phase-nonspecific. **Phase-specific drugs** act primarily on cells in at a particular stage of the cell cycle, for instance, antimetabolites act during S-phase (i.e., replication of DNA) and alkaloids act during M-phase (i.e., mitotic spindle formation). **Phase-nonspecific agents** have an effect during all phases of the active cell cycle (e.g., alkylating agents). Moreover, a few cytostatics even affect cells in the resting, G_0 phase (e.g., melphalan, busulfan, nitrosourea derivatives). These drugs are **cell-cycle nonspecific**.

10.2.2 Toxicity of chemotherapy, adverse effects of cytostatic agents, and their management

Toxic effects common to all groups of cytostatic agents, although they are structurally and pharmacologically different, arise from the preferential effect on **fast-proliferating tissues** like gastrointestinal epithelia (i.e., gastrotoxicity), bone marrow (i.e., myelotoxicity), or spermatogenic cells (i.e., reproduction toxicity). Cytostatics have different potentials to induce **nausea and vomiting**. Distinct mechanisms lead to **other cell and organ damage**: neuron (i.e., neurotoxicity), kidney (i.e., nephrotoxicity), or lung (i.e., pneumotoxicity) damage. Less frequently occurring is urothelial or myocardial damage (i.e., urotoxicity, cardiotoxicity, respectively). All cytostatics are teratogenic. Treatment with cytostatic agents might lead to secondary malignancies, mostly hematologic. A very typical adverse effect of chemotherapy is thinning of hair and alopecia. Based on the death of a large number of tumour cells during chemotherapy, hyperuricemia and secondary gout may also manifest.

10.2.2.1 Gastrointestinal toxicity

Epithelial lesions can occur in the mouth as well as the proximal and distal parts of the GIT. Depending on the localization, they can manifest as painful swallowing, heartburn (i.e., pyrosis), dyspepsia, nausea, or diarrhoea. Lesions on intestinal epithelium are one of the causes of chemotherapy-induced vomiting. The affected GIT is usually associated with the loss of appetite (i.e., anorexia) as well as with possible worsening of the nutritional state of the patient.

Epithelial lesions in the mouth are treated with irrigations or gargles containing **antiseptic**, **anti-inflammatory**, or **astringent agents** such as chlorhexidine, benzydamine, and extracts from medicinal herbs including sage (*Salvia officinalis*), chamomile (*Matricaria chamomilla*), agrimony (*Agrimonia eupatoria*), etc. Tolerability of this treatment is very individual as administration of some antiseptic solutions may be very painful. Therefore, the therapy of mouth lesions should be chosen empirically and in a personalised manner. When candidosis (or candidiasis) occurs in the mouth, **antimycotic agents** should be used locally, preferably azole antimycotics like itraconazole.

Heartburn (i.e., pyrosis) can be managed by **proton pump inhibitors** (e.g., omeprazole) or **antacids** (e.g., hydrotalcite). Diarrhoea is treated best with **antimotility agents** (e.g., loperamide).

With regard to nausea and loss of appetite, specific nutritional support by emulsions and solutions for enteral nutrition is recommended.

10.2.2.2 Myelotoxicity

This type of toxicity affects the hematopoietic cells of bone marrow. At first, damage to white blood cell generation occurs leading to leukopenia. Patients with leukopenia have impaired immune functions and are highly prone to infections. A serious escalation of this condition is febrile neutropenia, when the neutrophil count drops below 0.5×10^9/L and fever rises above 38.5°C. This condition should always be managed by **broad-spectrum antibiotics** (e.g., amoxicillin/clavulanic acid and ciprofloxacin), antipyretics (e.g., acetaminophen = paracetamol), bed rest with some form of isolation, or hospitalization. Patients with sepsis are always hospitalised and treated with cephalosporins of the 3rd or 4th generation (e.g., cefoperazone) in combination with aminoglycosides (e.g., gentamicin).

Leukopenia can be prevented by cytostatic agent dose reduction or by administration of **immunostimulatory factors**, such as filgrastim (i.e., G-CSF, recombinant granulocyte-colony stimulating factor) or molgramostim (i.e., GM-CSF, recombinant granulocyte-macrophage-colony stimulating factor). These factors are administered subcutaneously once or three times per week.

During chemotherapy, an impairment of thrombocyte formation may occur. In this case, blood coagulation is decreased, and the patient is in danger of haemorrhagic complications. This condition can be managed by dose reduction of the cytostatic agent, if possible. In serious thrombocytopenia, **transfusion of thrombocytes** or whole blood can be used.

Higher doses of cytostatic agents, or individual predisposition, can also trigger anaemia. Besides higher rates of fatigue, anaemia is also a negative prognostic factor in some cancer diseases. Anaemia is associated with hypoxia, which stimulates neoangiogenesis in primary tumours and metastasis. Appropriate treatment of anaemia is chosen according to the type of disease: erythrocyte transfusion, recombinant **erythropoietin (EPO)** or its analogues (e.g., EPO α, EPO β, or darbepoetin α), supplementation of B_{12} and B_6 vitamins, or iron in the case of proven deficiency. EPO and its analogues are administered subcutaneously once or three times per week or every three weeks according to the dose and pharmacokinetics of the specific substance. Vitamins and iron are administered orally or by intramuscular injection (e.g., vitamin B_{12}). For details see Chapter 5.8 The treatment of anaemias and haematopoiesis defects.

10.2.2.3 Nausea and vomiting

Cytostatic agents can be highly (e.g., cisplatin), moderately (e.g., doxorubicin), or weakly emetogenic (e.g., Vinca alkaloids). Vomiting is caused by damage to the enterochromaffin cells, which release serotonin causing irritation of the vagus nerve as well as irritation of the chemoreceptor trigger zone in the medulla oblongata. The treatment of chemotherapy-induced nausea and vomiting consists of **5-HT$_3$ receptor antagonists** (e.g., setrons: ondansetron, palonosetron), **prokinetic agents** (e.g., metoclopramide), **D$_2$ receptor antagonists** (e.g., haloperidol, thiethylperazine), and their combination with **glucocorticoids** (e.g., dexamethasone), and **antihistamines** (e.g., promethazine).

The most effective antiemetics within these groups are the setrons. They can be also combined with a relatively new group of antiemetics called **neurokinin (NK$_1$) receptor antagonists** (e.g., aprepitant, netupitant; for details, see Chapter 6.4 Antiemetics). Antiemetic treatment is administered orally, per rectum, or by intravenous bolus or infusion. It is given either before the start of cytostatic infusion as premedication or combined with the cytostatic agents. Delayed vomiting after chemotherapy (i.e., starting 24 h to three days after administration) can be treated by antiemetics given repeatedly for a longer period.

10.2.2.5 Neurotoxicity

Most cytostatics do not cross the blood-brain barrier; thus, potential damage to nervous system mainly manifests as peripheral neuropathy (e.g., paresthesia, dysesthesia, neuromuscular coordination impairment, changes of muscle tone, fine motor skills impairment, etc.). Peripheral symptoms may be accompanied by autonomic neuropathy (e.g., paralytic ileus).

Central symptoms of neurotoxicity can manifest when a cytostatic agent is administered in higher doses or intrathecally. These symptoms include those of encephalopathy (e.g., headache, impairment of consciousness, coma, cognitive impairment), meningitis, and myelopathy (i.e., pathologies of spinal cord along with, for example, limb paresis). Encephalopathy can result in frontal lobe disorders (i.e., cognitive, emotional, and behavioural impairment, aphasia, or movement disorders). Changes of the nervous system induced during chemotherapy may be irreversible.

Signs of neurotoxicity usually lead to a dose reduction of the cytostatic agent or a switch to a drug that is not toxic to the nervous system. There are few reports from clinical studies regarding the effective treatment of neurotoxicity. In peripheral neuropathy, **supplementation of magnesium**, **vitamin B$_6$**, and **B$_1$** is recommended. **Anticonvulsants** (i.e., **antiepileptic drugs**) of the 3rd generation (e.g., gabapentin, tiagabine, pregabalin) and some **antidepressants** (e.g., duloxetine, imipramine) help fight neuropathic pain. **Nootropics** can be added to the therapy when cognitive functions start to decline. In accordance with a psychiatric examination, other drugs may be indicated (e.g., antipsychotics), as well.

10.2.2.6 Nephrotoxicity and urotoxicity

Cytostatic agents may harm the glomerulus, the renal interstitium, and the renal blood vessels. Symptoms of nephrotoxicity vary in intensity from a mild increase in serum creatinine to severe renal failure with the need for haemodialysis. Toxicity can be potentiated by co-medication with other nephrotoxic drugs (e.g., furosemide, aminoglycosides, nonsteroidal anti-inflammatory drugs, etc.).

Distinct mechanisms of renal toxicity are involved. Platinum derivatives cause necrosis in the proximal tubule, constrict renal blood vessels, and increase levels of pro-inflammatory cytokines. Methotrexate precipitates in acidic urine and the crystals cause mechanical damage to the kidneys. When many tumour cells perish during chemotherapy, secondary hyperuricemia can also lead to precipitation of urate calculi (i.e., uric acid stones).

Urotoxicity is associated with cyclophosphamide and ifosfamide, which are transformed to acrolein (i.e., propenal) and other substances irritating the urothelium and causing haemorrhagic cystitis.

As a prevention of kidney and urinary bladder toxicity, **hydration regimens** are commonly used before and after the administration of a cytostatic agent. Hydration is given orally and/or intravenously by so-called **forced diuresis**; a high level of hydration is achieved by infusions of fluids with optimal mineral content. After intense hydration, diuretics may be added.

To prevent haemorrhagic cystitis, the drug **mesna**, formerly a mucolytic agent, is administered intravenously. The thiol groups of mesna react with acrolein and other irritating substances forming non-toxic metabolites.

10.2.2.7 Cardiotoxicity

Myocardial damage is mostly associated with treatment consisting of anthracycline cytostatics (i.e., intercalating agents), but may also be present after administration of drugs such as bleomycin, vincristine, alkylating agents, fluorouracil, etc. Acute damage emerges a few hours after administration and manifests as reversible arrhythmia or angina (i.e., chest pain). Chronic damage of myocardium manifests after years. A typical symptom of chronic chemotherapy-induced cardiotoxicity is dysfunction of left ventricle, which is, at first, asymptomatic and later manifests as (congestive) heart failure.

The molecular mechanism of the chronic anthracycline toxicity is not yet fully elucidated. Most likely, it is a multifactorial process involving reactive oxygen species (ROS). Superoxide radicals ($\cdot O_2^-$) are physiologically processed by superoxide dismutase to less

reactive hydrogen peroxide, which is later catabolised by catalase and glutathione peroxidase. In cardiomyocytes, decreased levels of superoxide dismutase are found, and thus, the superoxide radicals are processed more slowly. The damage could also be triggered by the reactions of hydrogen peroxide catalysed by iron ions, during which a hydroxyl radical ($\cdot$OH) is created. ROS react with lipids in biological membranes and impair their functions. In the cell, apoptosis is triggered once damaged structures have accumulated reaching above a certain threshold.

The prevention of cardiotoxicity includes examination of heart functions before beginning treatment and excluding patients with a high risk of cardiovascular complications. During the treatment, regular checks (e.g., ECG, echocardiography, blood analysis, etc.) are necessary. Cumulative doses of cytostatics should be observed. A **cumulative dose** is the sum of all doses of a drug given during the entirety of the treatment, while the stated cumulative dose (e.g., 550 mg/m^2 for doxorubicin) is the dose limit that is relatively safe. Another cardioprotective possibility is through the administration of **dexrazoxane** intravenously before the infusion of anthracycline. It is suggested that dexrazoxane has a chelation effect and binds to iron in cardiomyocytes, which leads to the inhibition of undesirable reactions catalysed by iron. But, it is also speculated that dexrazoxane could thereby decrease the efficacy of cytostatic treatment, or worse, induce secondary hematologic malignancies. These issues are not yet resolved.

Chronic myocardial damage which is already present is **treated like common heart failure** (i.e., with ACE inhibitors, beta-blockers, calcium channel blockers, diuretics, digoxin, etc.). For details see Chapter 5.1 Antihypertensive drugs, diuretics, and 5.4 Cardiotonics (positive inotropes).

In clinical trials, antioxidant agents (e.g., vitamins C, E, A, coenzyme Q$_{10}$, or *N*-acetylcysteine) were not effective in the prevention of or treatment of cardiotoxicity. Cytostatic liposomal dosage forms were proven less toxic. Liposomes distribute well into the tumour tissue, and because of insufficient lymphatic drainage from the tumour site, liposomes accumulate there. Thus, the drug has less of an effect on healthy tissues as well as a higher possible cumulative dose (e.g., for liposomal doxorubicin: 860 mg/m^2). When combining radiotherapy and chemotherapy, it is necessary to bear in mind the higher risk of cardiotoxicity after irradiation of the mediastinum.

10.2.2.8 Pneumotoxicity

Some of the cytostatic agents, like methotrexate, bleomycin, busulfan, and other alkylating agents, have toxic effects on lungs. Pneumotoxicity is cumulative like cardiotoxicity. Various mechanisms lead to acute pneumonitis with lung oedema or chronic interstitial pneumonitis (i.e., interstitial lung disease) followed by lung fibrosis with worsening respiratory function. As prevention, patients with a high risk (e.g., those who already have lung disease) should not be treated with pneumotoxic drugs. Cumulative doses should be observed.

10.2.2.9 Skin toxicity and damage to the skin adnexa

When injecting some cytostatic agents outside of the blood vessel by mistake, a caustic effect can be seen, and the lesions may be extensive and quite difficult to treat. Healthcare personnel

is endangered when staining with cytostatics while injecting and manipulating infusions. Everyone should treat these drugs with extreme caution.

Many oncologic patients develop alopecia and the thinning of hair, representing a well-known adverse effect of chemotherapy. This condition is reversible, and it is probably caused by vasoconstriction in hair roots. Usually, only the hair on the scalp is affected, but sometimes eyebrows, eyelashes, or hair elsewhere falls out.

10.2.2.10 Secondary malignancies

Some cytostatic agents can act as carcinogens and mutagens affecting the DNA of healthy cells. This is a serious effect that is well-recognised in healthcare after the end of chemotherapy. Thereafter, the patient's state of health should be checked regularly and often. For instance, secondary hematologic malignancies (e.g., leukaemia) may be present after 10 years due to treatment with alkylating agents, and this problem is typical for oncological care in the paediatric population.

10.3 Overview of cytostatic agents

10.3.1 DNA-damaging drugs

10.3.1.1 Alkylating agents

The mechanism of action for this drug group lies in the transfer of the alkyl group to the nitrogen atoms of the nucleobases, mostly to guanine. This alkylation can covalently bind two guanines in either one strand of DNA or between two strands of DNA. The covalent bond of the alkyl group impedes the binding of enzymes and other substances, which interact with DNA. Thus, it interferes with gene transcription and is also recognised as beyond repair in the cell, which triggers cell cycle arrest and apoptosis.

Alkylating agents are phase-nonspecific and some of them also cell cycle-nonspecific (i.e., also affect G_0 cells). All drugs in the group are mutagenic and increase the risk of secondary malignancies (e.g., leukaemia, myelodysplastic syndrome), primarily in patients undergoing long-term treatment. Other common adverse effects are reversible myelosuppression and GI lesions along with diarrhoea and vomiting.

Alkylating agents are classified according to their chemical structure:

Bis(2-chloroethyl)amines

Mechlorethamine (chlormethine) is a nitrogen derivative of sulphur mustard ("yperite" – a gaseous vesicant chemical warfare agent). Substitution of sulphur with nitrogen in the molecule led to the development of the first cytostatic agent, which, since after WWII, has been used for the treatment of Hodgkin lymphoma. In conjugation with oestrogen, **estramustine** was developed and is used to treat advanced prostate carcinoma. Chlorambucil and melphalan are other derivatives of mechlorethamine; their advantage lies in lesser toxicity while maintaining the same anticancer effect. **Chlorambucil** is used orally for the treatment

of lymphoma and chronic lymphatic leukaemia in children and adults. **Melphalan** is used for the treatment of multiple myeloma, advanced breast cancer, and ovarian carcinoma.

Oxazaphosphorines

Cyclophosphamide is a widely-used agent derived from mechlorethamine. It is a prodrug metabolised by CYP enzymes to active cytotoxic substances. Its biotransformation also leads to the formation of urotoxic acrolein causing haemorrhagic cystitis. Cyclophosphamide is used orally and intravenously to treat lymphoma, leukaemia, and solid cancers (e.g., ovarian, mammary, and lung cancer, sarcoma, and neuroblastoma). In lower doses, it is used as an immunosuppressant to treat progressive autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus (SLE), or myasthenia gravis). Higher doses can be combined with busulfan as a premedication before bone marrow transplantation. Higher doses are highly emetogenic. Cardiotoxicity and pneumotoxicity can also occur, but their incidence is lower. **Ifosfamide** is also a prodrug and shares the same indications and toxicity as cyclophosphamide.

Nitrosourea derivatives

These alkylating agents have characteristically high lipophilicity enabling them to cross biological membranes, including the blood-brain barrier. **Carmustine** (often abbreviated as **BCNU**) and **lomustine (CCNU)** are used orally, and **fotemustine** is administered intravenously. This group is used for the therapy of primary brain tumours and brain metastasis of other tumours; carmustine and lomustine can also be used to treat lymphoma. Delayed onset of myelosuppression (i.e., after 6– 8 weeks) is a typical adverse effect of this drug group.

Triazenes

Dacarbazine is a prodrug that is metabolised to alkylating substances (e.g., diazomethane). It is used for the treatment of malignant melanoma, lymphoma, and sarcoma. The related compound, **procarbazine**, can be used for the therapy of glioblastoma. **Temozolomide** is an alkylating agent with high bioavailability (i.e., 100% after oral intake), which is also used for the treatment of glioblastoma.

Alkyl sulfonates

Busulfan is the only representative of this drug group that is used for treatment of haematologic malignancies and in combination with cyclophosphamide as premedication before bone marrow transplantation. High doses are associated with significant toxicity. Besides the common adverse effects of alkylating agents, busulfan is also hepatotoxic and pneumotoxic.

Aziridines

Mitomycin C is a natural substance produced by bacteria of the *Streptomyces* genus. In the organism, mitomycin C is metabolised to the active alkylating agent. The drug is administered mostly intravenously, rarely intra-arterially or intravesically. It is a component of combined chemotherapeutic regimens for the treatment of breast, lung, GI, or urinary bladder cancer.

Unlike mitomycin C, **thiotepa** is of synthetic origin. This drug is used as a premedication before a bone marrow transplant.

10.3.1.2 Platinum derivatives

The mechanism of action of platinum derivatives resembles alkylating agents; however, instead of binding to the alkyl group, the platinum cation is bound to the nitrogen in guanines. Through the central atom of platinum, the double helix of DNA becomes cross-linked. These modifications impede the approach of various enzymes and other substances that would interact with the DNA, thus blocking gene transcription. Topoisomerases are also inhibited.

Cisplatin is administered intravenously as monotherapy or as a component of combined chemotherapeutic regimens. It is an important drug for the treatment of solid tumours (e.g., testicular, ovarian, GI, lung cancer, and head and neck carcinoma). In the case of urinary bladder cancer, cisplatin may also be administered intravesically. It is the most emetogenic cytostatic agent, and it also has nephrotoxic, ototoxic, neurotoxic, and myelosuppresive effects. The rate of adverse effects is dose-dependent; thus, therapeutic drug monitoring (i.e., TDM, measuring of plasma levels) makes it possible to prevent their occurrence. Renal toxicity can be prevented by observing hydration regimens before and after the administration of the drug. **Amifostine** can also be used for the prevention of adverse effects. This drug is transformed by alkaline phosphatase to the active substance, which reduces binding of alkylating agents and platinum derivatives to DNA. In healthy cells, alkaline phosphatase is more abundant. Amifostine is administered intravenously 15 minutes before the cytostatic agent.

Carboplatin is less nephrotoxic, but more myelosuppresive. It is used intravenously for the treatment of ovarian and lung cancer. **Oxaliplatin** is the least nephrotoxic and myelosuppressive drug of all the platinum derivatives. It is one of the components in combined intravenous chemotherapy regimens for colorectal carcinoma.

10.3.1.3 Intercalating agents

Bacteria of the *Streptomyces* genus produce a wide range of pharmacologically active substances. Intercalating agents, also termed "cytotoxic antibiotics", or "anthracyclines", are their semi-synthetic derivatives.

The mechanism of action of this drug group is complex. The molecules are able to intercalate between the planarly arranged base pairs of DNA, which impedes the binding of enzymes and other substances, hence, interfering with DNA replication. Topoisomerase II is also inhibited. ROS are produced and oxidise biological membranes. Lipid peroxidation and overall ROS actions are a part of the cytotoxic effect on both healthy and cancerous cells. Influence on healthy cells is a cause of adverse effects (e.g., cardiotoxicity).

Besides acute and chronic cardiotoxicity, intercalating agents are also myelosuppressive, cause GI mucositis, and increase the risk of secondary malignancies. They are administered intravenously, rarely intra-arterially, or intravesically. After repeated administration into a vein, phlebitis, or even sclerotization, may occur. Therefore, it is necessary to rotate the places

of injection. Extensive necrosis of the skin and subcutaneous tissue can be triggered by extravasation of the cytostatic agent. Intra-arterial administration, which is rarely chosen for the treatment of liver and bile duct cancer, can provoke sclerotization leading to bile duct stenosis and hepatic necrosis. Intravesical use is frequently associated with chemical cystitis.

Doxorubicin (adriamycin) is a part of the therapy for a wide range of haematologic malignancies (e.g., lymphoma, leukaemia, multiple myeloma) and solid cancers (e.g., sarcoma, breast, endometrial, testicular, ovarian, lung, and gastric cancer). A modern drug dosage form is doxorubicin encapsulated in liposomes with molecules of polyethylene glycol (PEG) on the surface of the particle. PEGylated liposomes are not recognised by the cells of the mononuclear phagocyte system (formerly reticuloendothelial system); therefore, they persist much longer in the circulation. Liposomes enter tumour tissue easily, and due to the insufficient lymph drainage, they accumulate there. The liposomal dosage form of doxorubicin has fewer adverse effects on healthy tissues.

Epirubicin is used intravenously and intravesically for indications similar to doxorubicin. Idarubicin is used to treat leukaemia and administered orally. Other drugs (e.g., **daunorubicin**, **mitoxantrone**, **amsacrine**) are gradually being abandoned and are not currently available in the Czech Republic. **Dactinomycin** is an intercalating agent with a polypeptide structure, which blocks gene transcription and inhibits RNA polymerase. It is used to treat sarcoma and some rare solid tumours (e.g., Wilms' tumour, germinal tumours).

10.3.1.4 Bleomycin

Bleomycin is the name given to a mixture of semisynthetic glycopeptides produced by *Streptomyces*. It has complex mechanism of action; through intercalation between DNA base pairs and a blockade of thymidine incorporation into DNA, it creates strand breaks. This resembles the state of DNA after irradiation; thus, bleomycin is sometimes termed a "radiomimetic" agent. It also influences RNA synthesis.

Bleomycin is used intravenously for the treatment of lymphoma as well as cervical and testicular carcinoma. This drug may provoke an allergic reaction because of its peptide structure. It is pneumotoxic and causes hyperpigmentation and hyperkeratosis of the skin along with exanthem and itching.

10.3.2 Drugs that inhibit key enzymes of DNA metabolism

10.3.2.1 Antimetabolites

Antimetabolites are sometimes termed "false substrates" as they are drugs similar in structure to that of the endogenous substances, but minor changes in their molecular structure lead to the inhibition of various biochemical reactions or to the formation of dysfunctional products. This group of cytostatic agents affects uncontrolled proliferation and cell division with as much efficiency as other cytostatics. The biochemical target of antimetabolites is the biosynthesis of nucleic acids. All these agents are prodrugs, meaning the active substances are formed in the cells after biotransformation, for example, after being phosphorylated by various kinases.

Purine analogues

Mercaptopurine is one of the most important purine analogues. Its metabolites inhibit purine metabolism, specifically *de novo* biosynthesis and mutual conversion of purines. Mercaptopurine is used to treat haematologic malignancies in both children and adults.

Metabolism of mercaptopurine may be clinically problematic. The drug is metabolised by thiopurine methyltransferase (TPMT) to biologically ineffective methylmercaptopurine. There is a gene polymorphism in TPMT described in the human population, which may result in the patient's enzyme being less active or entirely inactive in comparison to patients with normal TPMT function. Standard doses in these patients lead to an increase in adverse effects, mainly escalated myelosuppression and hepatotoxicity. Pharmacogenetic examination is now widely used in the posology of mercaptopurine to identify patients at high risk and to determine the proper dose.

Thioguanine is a drug similar to mercaptopurine. **Azathioprine** is a prodrug, which is metabolised to mercaptopurine in enterocytes and the liver. It is used as an immunosuppressant after organ transplantation and for the treatment of autoimmune diseases.

Cladribine is a purine analogue; it is converted to the active substance mainly in lymphatic and haematopoietic cells. Unlike other antimetabolites, cladribine also affects dormant cells (i.e., in G_0 phase). It is used for the treatment of leukaemia.

Fludarabine inhibits replication enzymes (i.e., DNA polymerase, ligase, primase, etc.) and is used for the therapy of lymphocytic leukaemia.

Pyrimidine analogues

Fluorouracil is the most frequently used pyrimidine analogue for cancer treatment. Its mechanism of action lies in the inhibition of thymidylate synthase (or thymidylate synthetase), thus, in the inhibition of nucleic acid biosynthesis. It is effective primarily in the S phase of the cell cycle. Because it has a structure similar to uracil, fluorouracil is able to incorporate itself into RNA and interfere with RNA function. Fluorouracil is a component of many combined chemotherapy regimens for solid tumours (e.g., colorectal carcinoma, pancreatic, gastric, breast, and head and neck cancer).

Fluorouracil is used intravenously, and aside from having myelosuppressive effects and causing GI mucositis, it also has an acute cardiotoxic effect (e.g., changes on ECG, chest pain) and causes alopecia and dysesthesia. It is frequently used in conjunction with **leucovorin** (**folinic acid**), which potentiates the effect of fluorouracil by so-called biochemical modulation. Leucovorin causes an increase in the level of polyglutamates in cancer cells, which prolongs the inhibition of thymidylate synthase.

Tegafur and **capecitabine** are prodrugs of fluorouracil. They are converted to the active substance by thymidine phosphorylase. This enzyme is produced in cancer cells in large amounts as compared to healthy cells.

Gemcitabine is an analogue of cytosine. It inhibits ribonucleotide reductase and incorporates itself into DNA. It is administered intravenously in combined chemotherapy regimens for solid tumours (e.g., urinary bladder, lung, breast, or pancreatic cancer). Gemcitabine has myelosuppressive effect and is hepatotoxic.

Cytarabine (**cytosine arabinoside**) is another analogue of cytosine. Its mechanism of action lies in the inhibition of DNA polymerase. This drug is administered intravenously or intrathecally for the treatment of leukaemia and lymphoma in children and adults along with glucocorticoids and methotrexate. Cytarabine is strongly myelosuppressive, nephrotoxic, and hepatotoxic and could trigger central neurotoxic symptoms (i.e., impaired consciousness, nystagmus, etc.) Cytarabine syndrome is a hypersensitive reaction to the administration of cytarabine. It manifests after 6– 12 hours as fever, myalgia, headache, exanthema, etc. It can be prevented by and/or treated with glucocorticoids.

Folic acid analogues

The active form of folic acid, tetrahydrofolate (THF), participates in nucleobase biosynthesis, mainly one carbon metabolism.

Methotrexate (MTX) is a drug that is structurally similar to folic acid. After entering the cell, a polyglutamate chain becomes bound to it, and this MTX-polyglutamate complex represents the active form of the drug. It inhibits dihydrofolate reductase, which physiologically transforms dihydrofolate to THF and thymidylate synthase, which transform deoxyuridine monophosphate to thymidine monophosphate. Other biosynthetic pathways may also be affected (e.g., the metabolism of adenosine). In summary, the *de novo* biosynthesis of nucleobases and nucleic acids is inhibited.

MTX, without the bound polyglutamate chain, can be forced out of the cell by **leucovorin** (**folinic acid**). In cancer cells, the polyglutamylation is more intensive; therefore, less MTX is displaced from the cell. This "rescue therapy" utilising leucovorin is administered after a calculated time interval to decrease undesired effects on healthy cells.

MTX is used intravenously or intrathecally for various oncologic indications (e.g., leukaemia, lymphoma, sarcoma, head and neck cancer, urinary bladder cancer) in high doses (i.e., up to 12 g/m^2 intravenously and 15 g/m^2 intrathecally). As an immunosuppressant, MTX is used orally in small doses (e.g., in rheumatoid arthritis, 7.5 mg is taken once weekly). MTX is nephrotoxic; therefore, it is necessary to ensure appropriate urinary pH (i.e., minimum 7.5) and sufficient hydration. If urinary pH falls, MTX and its metabolites precipitate in the kidneys damaging the nephron and urothelium, and at worst, cause acute renal failure. MTX is also myelosuppressive, pneumotoxic, hepatotoxic, and causes GI mucositis.

Raltitrexed and **pemetrexed** are derivatives of MTX. They can be used for the therapy of colorectal and lung carcinoma.

Hydroxyurea

Regarding its base mechanism of action, hydroxyurea could also be classified as an antimetabolite. It inhibits nucleotide biosynthesis *de novo* and is most effective during the S phase of the cell cycle. Hydroxyurea blocks DNA repair, as well; thus, it could actually intensify the effects of radiotherapy. It is used orally for the treatment of leukaemia and cervical cancer. Adverse effects, such as myelosuppression, hepatotoxicity, and vomiting, may manifest. The drug may also cause hyperpigmentation and ulcerative processes on the skin, pancreatitis, or pneumotoxicity.

10.3.2.2 Topoisomerase inhibitors

Topoisomerases are key enzymes during DNA replication. They unwind DNA supercoiling, and only after that, are other replication enzymes able to approach and function properly, including helicases, primases, and polymerases, etc. Topoisomerases can induce and later ligate single- or double-strand breaks in DNA to unwind the supercoiling without damaging the DNA. Topoisomerase inhibitors influence the ligation process causing the breaks to persist. Strand breaks are a strong trigger for repair enzymes, and if they are unable to be repaired, apoptosis is initiated.

Topoisomerase I inhibitors – camptothecins

Camptotheca accuminata (Nyssaceae) is a tree native to Southern China. Found in its bark and fruits, the alkaloid, camptothecin, has been identified as having cytostatic effects. Two camptothecin derivatives, **topotecan** and **irinotecan**, are topoisomerase I inhibitors. Topotecan is used orally or intravenously for the treatment of ovarian, cervical, and lung carcinoma. It has myelosuppressive effects and causes GI mucositis. The drug is also mildly hepatotoxic and emetogenic. Irinotecan is administered intravenously to treat colorectal carcinoma (e.g., in the FOLFIRI regimen).

Topoisomerase II inhibitors – podophyllotoxins

The herbaceous plant, *Podophyllum peltatum* (Berberidaceae), is native to northern America. Originally, it was used as laxative because of the purgative effect of peltatins. Later, it was found that other constituents of the plant have cytotoxic effects. Lignan **podophyllotoxin** with a phenylpropanoid structure is used as a base for the semisynthetic derivatives, **etoposide** and **teniposide**. These derivatives inhibit topoisomerase II. Etoposide is used to treat of testicular and lung cancer, while teniposide is reserved for the therapy of haematologic malignancies.

10.3.3 Drugs that alter microtubules

10.3.3.1 Inhibitors of tubulin polymerisation – Vinca alkaloids

Vinca alkaloids are indole alkaloids identified originally in small amounts in lesser periwinkle (*Vinca minor,* Apocynaceae). For medical use, they are currently isolated from *Cataranthus roseus* (Apocynaceae). Vinca alkaloids and their derivatives block the polymerization of tubulin dimers, which is a necessary step during the formation of a functional microtubule and the mitotic spindle, as well. Thus, cell division is attenuated. Vinca alkaloids are administered intravenously.

Vincristine is used for the therapy of lymphoma, leukaemia, multiple myeloma, and various solid tumours (e.g., breast, lung, kidney cancer, sarcoma, neuroblastoma). **Vinblastine** is used for treating lymphoma and testicular and breast cancer. Peripheral neurotoxicity is a characteristic adverse effect of vincristine and vinblastine. Tubulin takes part in axonal transport of substances in the neuron; therefore, this process can be negatively influenced by Vinca alkaloids resulting in symptoms of peripheral neurotoxicity. Other adverse effects, such as GI mucositis and myelosuppressive effects, are common for the whole drug group.

The semisynthetic derivative, **vinorelbine**, can be administered orally and is used for the treatment of lung, breast, and prostate cancer. It has fewer neurotoxic effects because it

primarily influences mitotic tubulin. **Vindesine** is another semisynthetic derivative of Vinca alkaloids.

10.3.3.2 Inhibitors of tubulin depolymerisation – taxanes

This group consists of diterpene alkaloids identified in the bark of Pacific yew (*Taxus brevifolia*, Taxaceae). However, there is only a low concentration of alkaloids in this species; therefore, taxanes are produced semisynthetically from precursors isolated from the European yew (*Taxus baccata*).

Paclitaxel and its derivative, **docetaxel**, affect microtubules by inhibiting depolymerisation. A tubulin filament is not a rigid structure; it is in a constant state of balanced dynamic reorganisation. Taxanes block the spontaneous depolymerisation of tubulin effectively preventing shrinkage of the mitotic spindle during sister-chromatid separation in anaphase.

Taxanes are administered intravenously and have myelosuppressive and neurotoxic effects. They also cause GI mucositis and alopecia. Paclitaxel, conjugated with nanoparticles of albumin, is a modern dosage form of drug with fewer adverse effects and greater efficacy. Albumin enhances the distribution of paclitaxel from blood vessels to tissues. Moreover, it is site-specific because of a cancer-specific albumin binding protein.

Paclitaxel is used for the treatment of breast, ovarian, and lung cancer. Nanoparticle paclitaxel is used for the therapy of advanced breast cancer and pancreatic cancer. Docetaxel is a component of combined chemotherapy regimens used for lung, breast, prostate, and gastric cancer treatment.

10.3.4 Others

Drugs that inhibit protein synthesis – L-asparaginase

This enzyme catalyses the transformation of extracellular asparagine to aspartic acid and ammonia. Asparagine is essential for leukaemia and some other types of cancer cells, which are unable to synthesise this amino acid. When these cells have an asparagine deficiency, their proliferation is attenuated, initiating apoptosis. **L-asparaginase** is administered intravenously, intramuscularly, or intrathecally for the treatment of leukaemia and lymphoma. It can trigger a hypersensitivity reaction (i.e., fever, exanthem, and rash) and rarely anaphylaxis. It is mildly hepatotoxic and may cause vomiting and diarrhoea.

10.4 Immunomodulatory agents used to treat cancer diseases

Interferons have had the widest use in oncology until recently. The most frequently used was **interferon α**, which is available as a native mixture of various subtypes of interferon α isolated from human leukocytes or as recombinant subtypes 2a and 2b. Interferon α stimulates cell-mediated immunity (e.g., NK cells) and has antiproliferative and antiangiogenic effects. It

is administered subcutaneously or intravenously to treat renal carcinoma, malignant melanoma, and haematologic malignances (e.g., multiple myeloma, leukaemia, and lymphoma). Recombinant interleukin 2, **aldesleukin**, can be used for the therapy of renal carcinoma. Both interferons and cytokines cause diarrhoea and flu-like syndrome (i.e., myalgia, fever, anorexia). Interferons also have myelosuppressive effects.

Immunomodulation and antiangiogenic effects are described with **thalidomide** and its derivatives, **lenalidomide** and **pomalidomide**, which are used for the treatment of multiple myeloma and myelodysplastic syndrome. Thalidomide is a hypnosedative as well as a well-known teratogen.

This last decade introduced many novel concepts regarding cancer immunology and immunotherapy; one of which has been that the tumour itself stimulates the expression of substances that inhibit the immune response of the host organism allowing the tumour to evade immune control. Basic research revealed the specific receptors and ligands (i.e., "immune checkpoints") that play important roles in physiological immune system modulation, and moreover, in cancer immunosuppression (e.g., targeting the PD-1 receptor and its ligand PD-L1, or the CTLA4 receptor). Activation of PD-1 and CTLA4 receptors leads to the inhibition of T-cell proliferation and the induction of apoptosis. Recently, a new group of drugs utilising these signalling pathways has been developed and entered clinical practice. Most of the newly authorised immunotherapeutics are monoclonal antibodies (for details see Chapter 10.6 Principles of targeted therapy) administered by intravenous infusion.

Nivolumab and **pembrolizumab** target the PD-1 receptor, while **atezolizumab** and **durvalumab** aim at its ligand, PD-L1. **Ipilimumab** targets CTLA-4 receptor. These drugs are used for the treatment of solid tumours (e.g., urinary bladder cancer, malignant melanoma, lung carcinoma, etc.). A common adverse effect of immune checkpoint inhibitors is the induction of autoimmune diseases (i.e., hypo- or hyperthyroidism, inflammatory bowel diseases, lung inflammation, iridocyclitis, etc.).

Different antibodies are used for the treatment of haematologic malignancies. **Alemtuzumab** binds to CD25, a protein present on the surface of mature lymphocytes. Binding of alemtuzumab leads to the destruction of these cells; thus, the drug is used to treat lymphoma and leukaemia. Recently, it has been proven that alemtuzumab is also an effective treatment for multiple sclerosis. **Ofatumumab** and **rituximab** bind to CD20, which is present on the surface of B cells. Therefore, these drugs are used to treat leukaemia.

More details on different immunomodulatory agents can be found in Chapter 8.7 Immunomodulatory substances.

10.5 Endocrine therapy of cancer diseases

Cancer cells that express receptors for endogenous hormones on their surface (e.g., breast, endometrial, and prostate carcinoma) can be influenced by endocrine therapy. During the treatment of so-called hormone-sensitive cancers, both analogues and antagonists of endogenous hormones or inhibitors of hormone biosynthesis are used. In general, endocrine therapy is tolerated better than chemotherapy. Adverse effects are caused by the absolute or relative insufficiency of a specific hormone; for example, with antioestrogen treatment,

symptoms of climacterium can occur. Likewise, with antiandrogen treatment a decrease in libido occurs. Details about the drugs employed for endocrine therapy of cancer diseases can be found in Chapters 7.4 Pharmacology of hypothalamic and hypophyseal hormones, 7.8 Sex hormones, and 8.5 Glucocorticoids.

Long-term use of **gonadoliberin** (gonadotropin-releasing hormone, GnRH) **analogues** leads to the decrease of gonadotropins (i.e., FSH and LH), and thus, to a decrease of sex hormones (i.e., oestrogens, progestogens, androgens). The concept of this type of therapy is sometimes termed "chemical castration". It is reversible; with withdrawal of GnRH analogues, a return to normal production of hormones is achievable. **Leuprorelin**, **goserelin**, and **triptorelin** are used to treat prostate cancer and are administered by subcutaneous implants or depot injections (i.e., s.c. or i.m.) once monthly or once every three months.

Antiandrogens can be divided between drugs with steroid structure (e.g., **cyproterone**) and non-steroidal drugs (e.g., **flutamide**, **bicalutamide**). Androgen receptor antagonists are used orally for the therapy of prostate cancer. The effect of cyproterone is complex; besides decreasing androgen effects through receptor antagonism, it also decreases androgen synthesis. When compared to non-steroidal antiandrogens, use of cyproterone has lesser risk of gynecomastia.

Antioestrogens are used to treat breast cancer in postmenopausal women. **Tamoxifen** and **toremifene** are selective modulators of oestrogen receptors (SERMs) and are administered orally. SERMs have different effects according to the target tissue. For instance, they increase bone mineral density through a pro-oestrogenic effect, while in mammary glands and the uterus, they exert an antioestrogenic effect. **Fulvestrant** is a full antioestrogen injected intramuscularly. Orally used **aromatase inhibitors**, **anastrozole**, **letrozole**, and **exemestane**, also have antioestrogenic effects. Aromatase is an enzyme responsible for peripheral synthesis of oestrogens, and it is a major producer of oestrogens after menopause, when hormone production in ovaries has terminated.

For the treatment of some cancer diseases, other hormones, such as **progestogens** (**medroxyprogesterone**), **somatostatin analogues** (**octreotide**), and **glucocorticoids** (**dexamethasone**), are used.

10.6 Principles of targeted therapy

With the increasing knowledge of the pathological molecular mechanisms of various diseases, there now exists an urgent need for new therapies targeting these pathological cellular processes. This "targeted therapy" is believed to be more effective and safer, particularly in cases in which common medication has significant adverse effects or limited efficacy. The development of targeted therapeutics has accelerated thanks to the discovery of monoclonal antibody production technologies, for which the Nobel Prize in Physiology or Medicine was awarded in 1984 to N. K. Jerne, G. J. F. Köhler, and C. Milstein. The first monoclonal antibody used in clinical practice was rituximab, granted authorisation for use in the U.S. in 2002. Currently, many of these medical preparations are used in clinical practice. Targeted therapy is irreplaceable for the treatment of, for example, autoimmune or cancer diseases, but it is very costly. Therefore, its use is limited because of limited funds in healthcare systems. Targeted drugs are usually indicated for cases in which conventional therapy fails. In

oncology, the suitable targeted drug for the patient is chosen based on the results of the molecular analysis of specific markers (e.g., receptors, mutations).

The targeted therapy used today has various mechanisms of action. This drug group can be divided into:

- Monoclonal antibodies;
- Tyrosine kinase inhibitors;
- Inhibitors of intracellular (i.e., down-stream) signalling cascades;
- Proteasome inhibitors;
- Differentiation therapy, and
- Others.

Monoclonal antibodies (MAbs)

MAbs are products of one specific clone of B cells (B lymphocytes). Thus, they have a common affinity to one epitope (binding structure) on the antigen. MAbs are produced using hybridoma technology. The process involves human cancer cells and white blood cells of mice that have been exposed to the antigen. Their name has the specific ending, "-mab".

MAbs used therapeutically are divided into categories according to their structure and origin: mouse, chimeric, humanised, and fully human (Table 8). Antibodies acquired from other animal species (e.g., sheep, goat, rat, etc.) are used in diagnostics or research laboratory methods. The closer the structure of the therapeutic antibody to the human type, the less it stimulates production of neutralising antibodies in the treated patient and the less it produces hypersensitivity reactions.

Therapeutic MAbs can be targeted to the structures on cell surface, such as CD antigens (e.g., rituximab), receptors for epidermal growth factor (e.g., cetuximab), receptors for interleukin IL-6 (e.g., tocilizumab), or circulating cytokines like TNF-α (e.g., infliximab, adalimumab).

Fusion proteins represent a specific group of targeted drugs derived from MAbs. These are produced utilising genetic engineering and are composed of a protein having a specific affinity and signalling function and from a fragment of human antibody. For instance, etanercept is composed from the binding domain of a TNF-α receptor and a specific part of the human IgG antibody. This "soluble receptor" (ending in "-cept") binds to circulating TNF-α and competes with the cell surface receptors. The similar drug, abatacept, consists of the extracellular domain of the CTLA4 protein and a fragment of human IgG antibody. Abatacept inhibits the activation of T cells and is used as immunosuppressive agent for the treatment of autoimmune diseases.

Table 8: Nomenclature of therapeutic monoclonal antibodies

Antibody type	Ending	Example	Indication
Mouse	-omab	Not used therapeutically	
Chimeric	-ximab	rituximab	Autoimmune diseases, leukaemia, lymphoma
Humanised	-zumab	trastuzumab	Breast cancer

| Human | -mumab | panitumumab | Colorectal carcinoma |
| Soluble receptor | -cept | etanercept | Rheumatic diseases |

MAbs are administered via intravenous infusion or subcutaneously. MAbs used for subcutaneous administration can be administered by the patient while in in-home care. An adverse reaction common to all the MAbs is the possibility of an allergic reaction and rarely anaphylaxis. The most common adverse reaction presents at the site of injection and includes local erythema, oedema, pain, etc. Some MAbs may induce flu-like syndrome caused by the acute release of cytokines accompanied with fever, chills, myalgia, and headache.

Other adverse effects are caused by the actual mechanism of action of a specific MAb. For instance, drugs that decrease the number of lymphocytes or block their activation can increase the risk of infections or even certain types of cancer. Some MAbs also have specific organ toxicity, such as trastuzumab, which is cardiotoxic and may cause heart failure.

Tyrosine kinase inhibitors

The function of some receptors is bound to their intracellular domain, which has tyrosine kinase activity. Kinases phosphorylate proteins and are involved in the process of sending the signal from the cell surface to the nucleus. The most well-characterised tyrosine kinase receptor is the insulin receptor. However, there are many other tyrosine kinase receptors for ligands, which play important roles in cell proliferation, angiogenesis, etc. Drugs acting as antagonists of these receptors are called tyrosine kinase inhibitors (TKIs). Some substances inhibit various receptors with tyrosine kinase activity at the same time; thus, they are called "multikinase inhibitors". The common ending of this drug group is "-nib", for example sunitinib, gefitinib, imatinib, etc.

TKIs are used mostly for the treatment of kidney, skin, lung, and colon cancer. In comparison with MAbs, TKIs are smaller molecules, sometimes called "small drugs". They are administered orally. A common adverse effect of TKIs targeted against EGFR (epidermal growth factor receptor) is skin toxicity manifesting as exanthema, rash, itching, and dryness of the skin. Inhibitors of VEGFR (vascular endothelial growth factor receptor) may provoke gastrointestinal bleeding. Other TKIs can be hepatotoxic or cardiotoxic.

Inhibitors of intracellular (i.e., down-stream) signalling cascades

After the activation of a receptor, a cascade of processes is induced leading the signal to the cell nucleus and intensifying it. These cascades are maintained by various kinases and phosphatases. Inhibitors of these enzymes used therapeutically have the common ending "-mus". One of the most important kinases in terms of pathological pathways is mTOR (mammalian target of rapamycin), which is a part of the PI3K/AKT signalling cascade regulating proliferation, the cell cycle, and neovascularization. mTOR inhibitors are administered orally. Their adverse effects include changes in blood count (e.g., thrombocytopenia), dyslipidaemia, gastrointestinal intolerance, and hypertension.

Rapamycin is a macrolide structure discovered originally as an antimycotic agent. Its name is derived from Easter Island (i.e., Rapa Nui) in Polynesia because it was isolated from the soil

there. The drug also has immunosuppressive and cytostatic effects, and it is used in transplantology under the alternative name, sirolimus. It also has an application in cardiology – stents containing sirolimus are placed in the narrowed coronary arteries and block their closure in coronary heart disease. Temsirolimus is a prodrug of sirolimus and is used for the treatment of renal carcinoma. Everolimus is used to treat kidney, breast, and pancreatic cancer.

Inhibitors of the proteasome

The proteasome is an intracellular enzymatic complex with proteolytic activity. It degrades specifically marked proteins, which are defectively folded or whose role in the cell is no longer needed. The mark assigned for degradation comprises a sequence of polypeptides (i.e., ubiquitins) on the end of the protein's structure. Proteolysis takes place in the proteasome, and the amino acids released can be used for new proteosynthesis. In hematopoietic cells, a specific type of proteasome can be found, which can be inhibited by bortezomib. Inhibitors of this proteasome have the ending "-zomib". The inhibition of the proteasome leads to the accumulation of defective proteins in the cell, collapse of signalling pathways, and finally apoptosis.

Bortezomib is administered intravenously and subcutaneously for the treatment of multiple myeloma, which is a cancer of the hematopoietic cells. The most important adverse effect of bortezomib is the induction of peripheral neuropathy in up to 60% of patients. Other complications of this therapy include changes in blood count and secondary resistance to bortezomib. Bortezomib can be used in combination with glucocorticoids and alkylating agents.

Differentiation therapy

Many cancer cells in solid tumours lose the characteristics of typical cells within the environment of their respective tissue of origin, and they undergo the process of dedifferentiation. In haematological cancers, abnormal proliferation is characterised by non-differentiated (i.e., non-mature) bone marrow cells. The concept of differentiation therapy has a therapeutic role in oncology. It is based on the effort to transform the cells to the more differentiated and more specialised state, which is associated with decreased proliferation activity. This concept is used in the treatment of leukaemia, melanoma, neuroblastoma, etc.

Retinoids are synthetic substances derived from vitamin A with important differentiation effects. Their mechanisms of action works through binding to specific cytoplasmic (i.e., nuclear) receptors (e.g., RARα). This receptor-ligand complex migrates to the nucleus, where it induces and influences gene expression. Retinoids are known teratogens; thus, it is necessary to ensure effective contraception while using them. Common adverse effects of the drug group are cutaneous – dryness, exfoliative dermatitis, rash, etc.

Tretinoin (all-trans-retinoic acid) is an endogenous metabolite of vitamin A, and it is used therapeutically in promyelocytic leukaemia. ATRA syndrome (i.e., differentiation syndrome, or retinoic acid syndrome) represents a severe adverse reaction to tretinoin manifesting as fever, shortness of breath, oedema, and lung and pericardial effusions.

Bexarotene has a slightly different mechanism of action as it binds to a different group of nuclear receptors (i.e., RXR). Nevertheless, it is similar to tretinoin and the whole drug group

in that a receptor-ligand complex modulates gene expression in the nucleus. Bexarotene is used for the treatment of cutaneous lymphoma.

Other drugs of targeted therapy

Antisense therapy is based on administration of specific complementary oligonucleotides designed to target the sequence of mRNA from the protein of interest that needs to be downregulated. After the binding of the antisense sequence, mRNA cannot be translated into the sequence of amino acids. Drugs and substances in clinical trials usually have the common ending "-rsen".

Fomivirsen binds to mRNA specific to the cytomegalovirus, and thus, it was used for the therapy of CMV retinitis. The drug was authorised for use in the EU in 1999, but three years later, it was withdrawn from the market for non-profitability. It is not used anymore.

Miravirsen binds to hepatic RNA that is utilised by the hepatitis C virus for its replication. This substance is undergoing clinical trials and has favourable pharmacokinetics and efficacy so far.

Mipomersen binds to the mRNA of apolipoprotein B and was intended to treat familial hypercholesterolemia. The effectivity of this drug was sufficient, but adverse events (e.g., liver steatosis, flu-like syndrome, cardiovascular events) led to the refusal of authorisation for use in the EU in 2012. A few other antisense therapeutics are being tested in clinical trials.

Other targeted drugs can combine different mechanisms of action, such as a monoclonal antibody bound to a radionuclide or contrast agent, which is used for nuclear medicine and imaging. Many other molecules targeted to a variety of mechanisms are in development, preclinical phase, or early clinical trials. In oncology, examples of targets are the energetic metabolism of the cancer cell or the induction of apoptosis. Theranostics, another contemporary part of targeted therapy, are substances with both a diagnostic and therapeutic function.

Chapters, wherein different targeted drugs can be found, are as follows: 4.1. Antiasthmatics, 5.8.2. Erythropoiesis defects which are not linked to deficiency of nutrients, 8.7. Immunomodulatory substances, 9.6.4. Drugs used to treat chronic viral hepatitis and other antiviral drugs, 12.8. Rheumatoid diseases and gout tratment, and 17 Ophthalmologic drugs.

11 Drugs used in gynaecology, pharmacotherapy in pregnancy

11.1 Uterotonics

Uterotonics are drugs used to increase the tonus of the smooth muscles of the uterus (myometrium) and induce contractions of the uterus. Clinical use of uterotonics is commenced to induce or enhance weak uterine contractions. Abortion is another indication for use of some uterotonics. The sensitivity of the uterus to contraction stimuli depends on the phase of menstruation cycle as well as on the phase of pregnancy. Uterotonic drugs can be classified into two groups with regard to the characteristics of the induced uterine contractions. The first group, represented by the endogenous substances, **oxytocin** and **prostaglandins**, evokes periodic rhythmic contractions. Whereas administration of ergot alkaloids, namely methylergometrine, leads to strong, persisting tonic contractions. The different pharmacological characteristics determine the clinical use of single drugs.

Drugs inducing rhythmical uterine contractions

Oxytocin

Oxytocin is an octapeptide released from the posterior pituitary gland. It binds to specific receptors found mainly in the myometrium and mammal gland. The number of oxytocin receptors significantly increases during the last trimester of pregnancy. In therapeutic doses, it induces periodical uterine contractions, for which the strength and duration depend on the administered dose. Permanent contractions with uterine perfusion impairment are caused by high doses of oxytocin. This can lead to foetal injury and in the most severe case, abortion.

Oxytocin is indicated for labour induction, the stimulation of weak uterine contractions, breech birth, in uterine hypotony, and atony after delivery or abortion. It is administered as an intravenous injection or infusion, or it can be administered directly into the myometrium in case of Caesarean section. Hypersensitivity, cephalopelvic disproportion, hypertonic contractions, risk of uterus rupture, or foetal malpresentations are all contraindications for oxytocin use. The most common unwanted effect of oxytocin use is increased postpartum bleeding because of the weak vasodilating activity of the drug.

The effect of oxytocin on the mammalian milk gland can be utilised therapeutically, too. Oxytocin contracts the myoepithelial cells of the gland and promotes milk ejections. It is administered five minutes prior to breastfeeding in the form of a nasal spray. The same route of administration is used to treat premenstrual tension coupled with oedema and weight gain. Oxytocin is administered between the twentieth day and first day of the menstrual cycle.

Prostaglandins

Prostaglandins (PG) are endogenous products of the arachidonic acid metabolism. They are produced by the enzyme, cyclooxygenase. $PGF_{2\alpha}$ and PGE_2 are important in gynaecology. The physiological role of $PGF_{2\alpha}$ is its ischemic effect on the myometrium, which leads to its detachment during menstruation. The sensitivity of the myometrium to PG changes during pregnancy as it does in the case of oxytocin. The difference between the effect of PG versus oxytocin is that it induces cervical ripening along with uterine contractions.

Synthetically prepared endogenous PG, **dinoprostone** (PGE_2) and **dinoprost** ($PGF_{2\alpha}$), are used to induce labour, or their analogues, **carboprost** ($PGF_{2\alpha}$) and **misoprostol** (PGE_1), can be used, but primarily to induce abortion.

- **Dinoprostone** is indicated for cervical ripening and uterine contraction induction and to induce labour in women on their expected date of birth.

- **Dinoprost** induces uterine contractions after the fifteenth week of gestation. It is indicated for therapeutic abortion in the case of a pathological pregnancy or to induce delivery. It is administered either systemically (i.e., i.v.) or locally (extra- or intra-amniotic).

- **Carboprost** is administered intramuscularly or intra-amniotically in such indications as abortion, silent miscarriage, and postpartum bleeding caused by uterine atony.

- **Misoprostol** is used in combination with the progestin antagonist, mifepristone, (administered 36-48 hours prior to misoprostol) to induce abortion. It should not be used later than 49th day of amenorrhea. The uterotonic effect of misoprostol leads to cervical opening and expulsion of uterine content.

Because PG are involved in many other physiological processes aside from myometrial contraction, there are a variety of unwanted effects. Gastrointestinal disturbances due to the increased tone of smooth muscle in the GIT and increased peristaltic movements are the most frequent occurrences. Other common complications of PG use are nausea, diarrhoea, vomiting, and GIT spasms.

$PGF_{2\alpha}$ along with PGE_2 are algesic substances, and their increased levels cause dysmenorrhea. NSAIDs can be used as prophylaxis for dysmenorrhea because of the COX blockade (Chapter 8.4.1 Nonsteroidal anti-inflammatory drugs (NSAIDs)). Prostaglandins used as uterotonics promote pain as effectively as do endogenous substances. Therefore, adequate analgesic/anaesthetic therapy should be given along with PG both during the birth and after delivery.

Other less frequent adverse effects of prostaglandin treatment are represented by a temporary increase in body temperature and blood pressure due to the vasoconstrictive effects. The effect on bronchial smooth muscles can evoke bronchial spasms and asthmatic patients are at an increased risk. The unwanted effects are more frequent and intense after systemic use.

Drugs inducing tonic contractions

Methylergometrine is a derivative of the natural ergot alkaloid, ergometrine, with α_1 sympathomimetic and serotonergic effects. It induces contractions of the myometrium and

smooth muscles of the blood vessels after intravenous or intramuscular administration. It decreases the amount of milk produced in lactating women in correlation with the administered dose due to its dopaminergic effects.

Methylergometrine is indicated for post-partum bleeding and uterine subinvolution during puerperium for non-lactating mothers. It is contraindicated for labour induction or to enhance contractions during delivery. It cannot be administered before delivery of the placenta because of the risk of harm to the unborn child. The most common unwanted side effects of methylergometrine are nausea, vomiting, hypertension, and palpitations.

11.2 Tocolytics

Tocolytics have the opposite effect on the myometrium than do uterotonics in that they decrease its tonus and prevent contractions. Namely, they are used for uterine surgery during pregnancy (e.g., Caesarean section), to block excessive uterine contractions that risk harm to the foetus (asphyxia), or to delay the birth itself (in case of preterm delivery). The mode of action of the most common tocolytics is stimulation of adrenergic β_2 receptors.

These substances act as β_2 sympathomimetics, while others antagonise the natural mediator of contractions oxytocin; an example of one such tocolytic is atosiban. Other drugs with tocolytic activity aside from those previously mentioned exist; however, their efficacy is disputable or their use is related to the occurrence of serious adverse reactions. Therefore, such drugs are not used in clinical practice in the Czech Republic. Among these are prostaglandin synthesis inhibitors (e.g., NSAIDs and drugs decreasing the level of calcium in the myometrium), magnesium sulfate, and calcium channel blockers.

Glucocorticoids can be administered to enhance the production of respiratory airway surfactant and to prevent acute respiratory distress syndrome in already ongoing preterm delivery. It can be used in women between the twenty-sixth and thirty-fourth week of gestation, for foetuses with proved pulmonary immaturity, even later. **Betamethasone** (e.g., in two doses at a 24-hour interval) or **dexamethasone** (e.g., four doses at a 12-hour interval) can be used in such cases.

β_2 sympathomimetics

Hexoprenaline and **ritodrine** can be, aside from their more frequent use as a therapy for asthma, (see 4.1.2 β2-sympathomimetics) used for tocolysis. Stimulation of β_2 receptors leads to a decrease or block of spontaneous as well as oxytocin-induced uterine contractions. Drugs are administered intravenously by bolus injection followed by an infusion in the case of acute tocolysis. If there are no more contractions within a period of 48 hours, the woman can be treated chronically with peroral hexoprenaline tablets. Maternal cardiac stimulation is one of the most frequently occurring adverse reactions resulting from betamimetic tocolytic administration. It manifests as an increased heart rate and less frequently as extrasystoles or angina attacks.

Oxytocin receptor antagonists

Atosiban is a synthetic peptide and antagonises the effect of oxytocin at its receptor sites. It is administered intravenously usually as a bolus dose followed by infusion of the drug. The onset of its effect is fast; contractions are significantly inhibited after drug administration within approximately ten minutes. Atosiban is used to prevent preterm labour in women between the twenty-fourth and thirty-third week of gestation. Nausea, cephalgia, and tachycardia are the most common unwanted effects of atosiban. Its effect on the cardiovascular system is not as strong as in the case of betamimetics. Therefore, it can be used in women with diabetes, heart dysrhythmias, and other diseases of the heart.

Others

Magnesium salts

Magnesium sulfate and **magnesium lactate** both decrease calcium levels and block ATPase in smooth muscles; thus, they cause a decrease in contractility. Sulfate is administered as an intravenous injection in acute cases, while lactate is used more as a prophylaxis for oral use in women with changes to their cervix but no contractions present yet. Adverse reactions are more likely to occur after intravenous use and include nausea, vomiting, constipation, hypermagnesemia, hypocalcaemia, and hypothermia. The efficacy of magnesium salts for acute tocolysis is disputable.

Calcium channel blockers

Nifedipine and **verapamil** inhibit the entry of calcium ions into myometrium cells and cause a decrease in contractility. The main indications for use of these drugs are diseases of the cardiovascular system (Chapter 5.1.2 Calcium channel blockers and 5.3 Antiarrhythmics). This is the reason many side effects are also present in the cardiovascular system. The most common side effects reported are vasodilation with a decrease in blood pressure, reflexive tachycardia, and vertigo.

Nonsteroidal anti-inflammatory drugs

Indomethacin is a cyclooxygenase inhibitor and decreases the amount of produced uterotonic prostaglandins. Similar to other NSAIDs, indomethacin is contraindicated during the third trimester of pregnancy as is advised within the SmPC. Besides tocolytic effects, it causes preterm closure of the ductus arteriosus and renal dysfunction in newborns, and there is an increased risk of prolonged postpartum bleeding in mothers because of its antiaggregant activity.

Progestogen (Gestagens)

Progestogens or gestagens can prevent preterm delivery by decreasing the number of oestrogenic receptors as well as decreasing overall myometrium activity. The most common gestagen used to prevent uterine contractions is **progesterone**, which is administered either orally or vaginally. Gestagens are not used for acute tocolysis.
Another drug with a tocolytic effect is ethanol, which is never suitable for clinical use in pregnant women.

11.3 Therapy of vulvovaginal infections

One of the most frequent diagnoses of sexually active women in gynaecology is vulvovaginitis. The imbalance of vaginal microflora is usually involved. The microbiome of the vaginal flora is highly variable with striking interindividual differences. That's why it is almost impossible to describe the "physiological" microbial flora of the vagina. Some diseases with an outbreak of known pathogens are well-defined and lead to clinical signs of vulvovaginitis, whereas in many women, the symptoms are present without a simple definition of the microbial pathogen involved.

The symptoms of vulvovaginal infections are generally described as **vulvovaginal discomfort**. Frequent symptoms are, aside from the subjective feeling of discomfort, discharge, pruritus, and dyspareunia (i.e., painful sexual intercourse).

Vulvovaginitis is a local, non-serious illness from the clinical point of view. On the other hand, it is a disease with intensely unpleasant symptoms, and expedient therapeutic intervention is required. The frequent recurrence and unclear aetiology complicates the therapy of this disease. The differences in general treatment and during pregnancy should be pointed out.

The origin of the vaginitis can be classified with respect to its aetiology into bacterial, viral, mycotic (e.g., Candida), and parasitic. Aside from becoming infected, the disease can be evoked by mechanic irritation or inadequate immune response (e.g., an allergy). In many cases the specific etiological agent is unknown. The most common causes of dysbiosis with clear aetiology and their therapy are described further. Detailed information on single drugs can be found in Chapter 7.8 Sex hormones and Chapter 9 Anti-infective drugs.

11.3.1 Trichomoniasis

This infection is caused by the protozoa, *Trichomonas vaginalis*, which acts as a pathogen in the environment of the vaginal microflora. This parasite is sexually transmitted. It is found exclusively in the epithelium of urethra, vagina, and prostate. The colonisation of urethra and prostate is mostly asymptomatic in men. In women, the infection presents with profuse, frothy yellow discharge in the acute phase, whereas the chronic phase of the infection can be asymptomatic. Women, along with all sexual partners, should be treated simultaneously. Local treatment is usually ineffective because the parasite persists in the urethra. Nitroimidazole antibiotics, like **metronidazole**, can be used via oral administration. The local therapy is recommended for pregnant women during the first trimester.

11.3.2 Bacterial vaginosis

It is a non-inflammatory disease caused by an imbalance of the natural vaginal microflora. Mostly, it is accompanied by a decrease in the number of Lactobacilli species and an increase in anaerobes like *Gardnerella vaginalis, Mobiluncus curtisii*, or *Atopobium vaginae*. Bacterial vaginosis is the most common diagnosis linked to vaginal discomfort and is present in 40-50% of women with discharge. The therapy consists of either orally or locally administered **metronidazole** for seven days. Alternatively, clindamycin can be used, namely

in women in the second and third trimesters. In the case of uncertain diagnosis, therapy with composite preparations containing **miconazole** and **metronidazole** or **nystatin** and **nifuratel** for local or systemic use is possible. Irrigations with **benzydamine** and eventually insertion of **vaginal Lactobacilli** can be used as a prophylaxis against recurrence. The administration of ascorbic acid should be considered, but its therapeutic outcome is still questionable.

11.3.3 Mycotic vaginitis

An outbreak of yeasts (e.g., *Candida albicans, C. glabrata, C. tropicalis* or *C. krusei*), which are otherwise a common part of natural vaginal microflora, causes local mycotic infection. Factors that increase the risk of candidiasis include pregnancy, hormonal imbalances including diabetes, and being immunocompromised. The characteristic symptoms are itching (burning) of external female genitals and white "cottage cheese" discharge. There is also often a combination of candidiasis and bacterial dysbiosis. Azole antimycotics are used in therapy:

- **Locally**, **clotrimazole**, **econazole**, **fenticonazole**, **oxiconazole**, **ketoconazole**, and **miconazole** can be used. These drugs can only be used in the first trimester with increased caution.

- **Systemically**, **itraconazole** or **fluconazole** can be used:
    - In case of serious candidiasis,
    - In immunocompromised patients, and
    - In recurrent candidiasis, wherein systemic antimycotics are administered once a month prior to expected menstruation for six months.

Locally administered **natamycin** or **nystatin** can be used during pregnancy without any restrictions because neither are absorbed from the site of administration. The combinations of **nifuratel-nystatin** and **nystatin-neomycin-bacitracin** are available for the therapy of mixed infections. Vaginal globules with **sodium tetraborate** can be used to prevent recurrence and during pregnancy.

11.3.4 Lactobacillosis

This disease is very similar to candidiasis with regard to its symptoms and can be mistaken easily without microscopic examination. It is caused by an overgrowth of the fibrous forms of lactobacillus. Antimycotic therapy is ineffective. Wide spectrum antibiotics should be used. The drugs of choice are aminopenicillins (e.g., **amoxicillin**, **ampicillin**) and **doxycycline** or **clindamycin** in case of penicillin hypersensitivity.

11.3.5 Aerobic vaginitis

The inflammation caused by an outbreak of aerobic bacteria (e.g., *E. coli*, streptococci group B, enterococci) is characteristic with a yellowish to cream-coloured discharge with an offensive odour. Aerobic vaginitis is one of the causes of preterm drain of amniotic fluid. Pregnant women are examined for the presence of group B streptococcus (35th-37th week), and even asymptomatic women are cured in case of a positive result.

- In the case of symptoms of aerobic vaginosis, **clindamycin** is administered orally or locally antepartum (prior to delivery).

- Asymptomatic women are treated intrapartum (the best time being two hours before the second phase of delivery) by intravenous **clindamycin** or **penicillin**.

Combinations of nifuratel and **nystatin** or **neomycin-bacitracin-nystatin** can be used in case of a suspected mixed-type infection.

11.3.6 Herpes genitalis (genital herpes)

This disease is caused by DNA viruses from the group of *Herpes simplex* viruses (e.g., HSV1, HSV2). Symptomatology differs in primary and recurrent infections, which are common due to the persistence of the virus in the neural ganglia.

- There is a presence of small, painful blisters in primary infections with a healing period of 2-3 weeks.

- Recurrent infections have similar symptomatology, but the healing period is shorter, usually around seven days, and the symptoms are milder.

As is the case with other herpetic infections, antiviral agents can be used (e.g., **acyclovir**, **valacyclovir**). Oral administration is preferred. The efficacy of the therapy depends upon the timely administration of the drug; if possible, it should be administered during the prodromal phase of the disease. After the full development of the disease with its clinical manifestation, both systemic and, in particular, local antiviral therapy have minimal efficacy. The prophylactic use of acyclovir is administered in patients with frequent recurrence of the disease.

Herpetic infections during pregnancy are problematic due to the possible transmission of the disease to the child. In the case of herpetic blisters, a caesarean section is indicated to terminate the delivery. Acyclovir is non-teratogenic and can also be given to pregnant women. Local anaesthetics, or antiseptic rinses, are an appropriate support to alleviate the pain of herpetic shedding.

11.3.7 Atrophic vaginitis

One of the important factors for vaginal microbial equilibrium is the condition of the mucosa. There is a decrease in the level of oestrogens that leads to changes in the vaginal mucosa for those in their prepubescent and postmenopausal period as well as in nursing mothers. The mucous membranes are "brittle"; injuries and bleeding are easier, the vaginal pH increases, and there is an increased risk of infection.

Oestrogens are usually substituted in the form of vaginal preparations containing **estradiol**, **estriol**, or a combination of estriol and lactobacilli. To prevent mucosal injury and to reduce the risk of infection, preparations containing **hyaluronic acid** can also be used prophylactically.

11.3.8 Other causes of vulvovaginal discomfort

There are many other diseases causing vulvovaginal discomfort with an unclear aetiology. These include, for example, allergic or psychosomatic vulvovaginitis, vestibulitis, or cutaneous vulvar diseases. Cervical cancer can also be a cause of discharge. The self-healing of patients believing there is another cause of the discharge may be the reason of a visit to the gynaecologist or a regular cytological examination is postponed. Such a procedure can lead to the progression of the disease.

11.4 Pharmacotherapy in pregnancy and lactation

There are many changes in the body of a pregnant woman including hormonal changes and the alteration of pharmacokinetic parameters (e.g., increased volume of distribution) for some drugs. The risk of a negative effect of medicine on the foetus should be minimised by the use of drugs only in situations with no other therapeutic possibility. Time-proven medicines with well-known safety profiles are usually drugs of choice.

The possible risk of pharmacotherapy during breastfeeding is determined by four factors:
1. The amount of drug in the milk drunk by the infant,
2. Pharmacokinetics of the drug,
3. Safety profile of the drug, and
4. The child's condition.

The administration of the drug should be timed to avoid breastfeeding when the concentration of drug in the milk is the highest. That usually means no breastfeeding for 1-3 hours after oral drug administration. Nevertheless, there are many exceptions (e.g., amoxicillin reaches its highest concentration in breast milk 4-6 hours after oral intake). The drug's pharmacokinetics indicates the rate of its permeation into the milk, the possibility of absorption from the infant's GIT, and its accumulation. Weak alkalis (e.g., nicotine) can reach higher levels in the milk because breast milk has a higher pH than plasma.

The overview of selected drugs used during pregnancy and lactation is discussed in this chapter. Characteristics of single drugs can be found in the following chapters in detail: 3.1 Psychotropic substances, 5.1 Antihypertensive drugs, diuretics 6.4 Antiemetics, 7.1 Treatment of diabetes mellitus, 7.2 Therapy of dyslipidaemias.

11.4.1 Anxiolytics and hypnosedatives

Pregnancy itself can be a significant source of anxiety for women (i.e., fear of labour and labour-associated pain), and most pregnant women suffer from the sleep disturbances. Regime modifications should be a main part of the therapy, if possible. If these changes are not possible or effective, it is possible to use **zolpidem** for insomnia or **SSRI antidepressants** for the management of anxiety.

The administration of benzodiazepines (e.g., for both anxiety and the hypnosedative effect) should be exceptional and should never be used during the third trimester because of the risk of developing addiction. Benzodiazepines also increase the risk of birth defects. In case of necessity, short-acting benzodiazepines (e.g., alprazolam, oxazepam, lorazepam, clonazepam) are used for the short-time therapy. Benzodiazepines are relatively safe during breastfeeding because of lower milk to plasma concentration ratio of the drugs. Nevertheless, the risk of sedation and related impairment of feeding ability even after low doses should be considered in case of infants with decreased benzodiazepine metabolism.

Melissa can be recommended as a suitable phytotherapeutic food supplement. Plant-derived supplements are usually seen by the general public as a completely safe natural alternative, but other herbs used for these same indications, like St. John's wort, hops or valerian root, should not be used during pregnancy as their safety profile is unknown. Alternatively, homeopathic preparations can be used; however, data on their safety and efficacy is unavailable.

11.4.2 Antiemetics

Nausea and emesis is present in 60-80% of pregnant women, mostly during the first trimester. Commonly, the frequency of these gravidity symptoms is 1-2 times per day. Therapeutic measures are recommended for frequent and persistent vomiting (hyperemesis gravidarum).

From available OTC medicines, **vitamin B6** or **ginger** can be used safely, as well.

From prescription-only medicines, antagonists of dopaminergic D2 receptors can be used after evaluation of the risk-benefit ratio. Most common is the use of **thiethylperazine**, less frequently haloperidol and metoclopramide are used. Metoclopramide is not suitable for chronic use and extrapyramidal signs can be seen in newborns when the drug is used in the third trimester.

Optionally, aprepitant, the antagonist of neurokinin receptors, can be used. The therapy with aprepitant is expensive, and because it is a new drug, data on its safety during pregnancy are not sufficient. None of the drugs above are indicated for the therapy of hyperemesis gravidarum and their use is off-label.

11.4.3 Pharmacotherapy of hypertension and dyslipidaemia

Hypertension

Pharmacotherapy is indicated for pregnant women with diastolic blood pressure over 100 mmHg. The therapy of hypertension diagnosed prior to pregnancy should continue over pregnancy. The exception to this rule is the administration of drugs targeting the renin-angiotensin-aldosterone system (RAAS), for instance angiotensin converting enzyme inhibitors (e.g., enalapril, captopril, lisinopril, and ramipril), angiotensin II receptor antagonists (e.g., AT_1-blockers, sartans), and kirens (i.e., renin inhibitors). These drugs are contraindicated because of their teratogenic effect.

In case of mild hypertension, **methyldopa** (α_2 selective agonist) or **labetalol** (mixed α/β blocker) are drugs of choice for pregnant women. Neither drug has teratogenic properties, and both are tolerated well. In case the hypertension persists after labour, these drugs should be discontinued due to the start of breastfeeding. Second line antihypertensives for pregnant women are selective β_1 receptor antagonist (beta-blocker), **metoprolol** (namely for the late stages of pregnancy), and calcium channel blockers (e.g., **nifedipine**). The latter should not be combined with magnesium sulphate due to negative synergism and possible severe hypotension.

All antihypertensives used by the mother are excreted into breast milk, but generally in trace amounts. The exceptions are beta blockers and the calcium channel blocker, nifedipine, with similar milk concentration to plasma levels. In the case of beta blockers, it is recommended to monitor the heart rate of both the mother and newborn and eventually to decrease the dose or substitute the drug.

Dyslipidaemia

Dyslipidaemias represent a group of metabolic disorders, all characterised by a pathological change in the lipidaemic spectrum. They represent one of the most significant risk factors for cardiovascular disease development. The only hypolipidemics used during pregnancy and lactation are **resins** (bile acid sequestrants). Resins are not absorbed from the GIT; therefore, they have minimal adverse systemic effects. Resins block enterohepatic recirculation of bile acids and increase their consumption. This leads to the increased synthesis of new bile acids from cholesterol, which is then eliminated from plasma.

11.4.4 Pharmacology of diabetes mellitus

Women with diagnosed diabetes should plan their gravidity after the hyperglycaemia is fully managed and under control. Mild diabetes can be usually controlled through dietary modifications. Fasting glycaemia during pregnancy should not exceed 5.6 mmol/L; one hour postprandially, it should be less than 7.7 mmol/L, and two hours postprandially, it should not be higher than 6.6 mmol/L. Insufficient compensation for diabetes can lead to placental damage, production of ketones, and finally, a teratogenic effect. The pregnancy of women with diabetes is always a risk for both the mother and foetus.

Human insulins and their analogues (namely short-acting) can be used to treat type 1 diabetes. The common route of their administration is subcutaneously with insulin pumps. During the second half of pregnancy, the demands on insulin increase and persist until the delivery. Oral antidiabetics are contraindicated in pregnancy; therefore, a revision of the drugs administered should be considered in the case of type 2 diabetes, and patients should convert to a combination of short- and long-acting insulins.

Hormonal changes in oestrogens, gestagens, and glucocorticoids increase glycaemia during pregnancy. Moreover, placental lactogen secreted into the blood antagonises the effects of insulin. In some women, these changes lead to hyperglycaemia and to **gestational diabetes**. The incidence of this complication during pregnancy is approximately 4%. Initially, the therapy is based on the modification of the diet with saccharide restriction. This is effective in

70-80% of women. If this therapeutic approach is not sufficient, women are treated with insulins and its analogues.

12 Drugs affecting functions of musculoskeletal system

12.1. Muscle relaxants (neuromuscular blocking drugs)

Muscle relaxants are drugs which decrease the skeletal muscle tone. They are either used to treat pathologically increased muscle tone – in spasms linked to some diseases like lumbago (e.g., lower back pain) – or to decrease physiological tone of skeletal muscles, mainly in anaesthesiology. Muscle relaxants are divided into two groups according to their mechanism of action. **Peripherally** acting muscle relaxants either interfere with neurotransmission in the neuromuscular junction or affect the calcium concentration in myocytes. **Centrally** acting drugs influence the central nervous system.

Centrally acting muscle relaxants

Centrally acting muscle relaxants inhibit mono- and polysynaptic reflexes in the brain and spinal cord. They mainly influence GABAergic transmission. The result is a suppression of the action potential being generated in the nerves. They are mainly used for vertebrogenic syndromes and neurogenic spasms (e.g., following encephalitis, meningitis, tumour, a vascular event, or linked to sclerosis multiplex).

Orphenadrine is a commonly used drug, which is combined with diclofenac (see Chapter 8.4.1 Nonsteroidal anti-inflammatory drugs – NSAIDs) in an infusion given to patients with vertebrogenic syndromes. It only influences pathologically increased muscle tone and has no effect on physiological tone.

Tolperisone is structurally similar to lidocaine (see Chapter 8.1 Local anaesthetics), which is why it has the ability to decrease the electrical activity of motor neurons (the same as lidocaine). It is used to treat spasms after cerebrovascular events.

Baclofen, a GABA derivative, also has an antinociceptive effect and affects the pain caused by spasms. Its common side effects are sedation and somnolence.

Other centrally-acting muscle relaxants are **mephenoxalone**, **tizanidine**, **thiocolchicoside**, and the benzodiazepine derivative, **tetrazepam**. The latter may cause serious skin reactions, which is the reason its use is limited.

Peripherally acting muscle relaxants

Peripherally acting muscle relaxants interfere with the transmission of excitation by motor neurons at the neuromuscular junction. According to the mechanism by which this happens, differentiation between depolarising and non-depolarising drugs is possible.

Depolarising muscle relaxants

Depolarising agents, such as **suxamethonium** (also known as **succinylcholine**), are analogues of acetylcholine. As does acetylcholine, so do these substances bind to nicotinic receptors at

the neuromuscular junction and cause depolarisation of the membrane, which then leads to muscle contraction. Therefore, after the administration, the patients display muscle spasms. These drugs dissociate from the receptor slower than endogenous acetylcholine and are not destroyed by acetylcholinesterase. They stay bound to the nicotinic receptor for a long time (i.e., longer than is physiologically natural) and prevent the neuromuscular junction from restoring its previous state. After early muscle contraction, there is a phase of relaxation due to decreased levels of intracellular calcium ions.

Suxamethonium is used to relax muscles as a part of general anaesthesia or to allow easier endotracheal intubation. It has a rapid onset (i.e., within one minute) and brief duration of action (i.e., 3-6 minutes). A rare, but serious side effect called **malignant hyperthermia**, may occur because of the massive release of calcium from the sarcoplasmic reticulum. This rather unexpected reaction is genetically determined and involves symptoms of muscle rigidity, fever, and metabolic acidosis. It most commonly appears due to a combination of suxamethonium and inhalation anaesthetics, and its onset is within minutes.

Non-depolarising muscle relaxants

Non-depolarising neuromuscular blocking drugs are basically competitive antagonists at the nicotinic receptors of the motor endplate and do not cause depolarisation. Although they are used for similar indications, there are some differences. Non-depolarising muscle relaxants have a slower onset of action (i.e., within five minutes) and longer duration of action (i.e., 15-90 minutes). They are used for longer surgeries or for muscle relaxation in patients on a ventilator.

Their typical side effect is excessive muscle relaxation caused by either overdosing or an interaction with drugs potentiating their effect. This can even lead to muscle paralysis or to a longer neuromuscular block than needed. Other common side effects of non-depolarising muscle relaxants are pain at the injection site and a hypersensitivity reaction due to their association with histamine release.

Vecuronium, **rocuronium**, **pipecuronium**, **atracurium**, **mivacurium**, and **cisatracurium** are found in this drug class.

The blockade caused by non-depolarising agents can be reversed through the administration of **cholinesterase inhibitors** (see Chapter 2.2.1 Cholinomimetics); the advantage of which is to shorten the effect of these muscle relaxants. The effect of rocuronium and vecuronium can be stopped by **sugammadex**, a cyclodextrin derivative, which binds to these substances creating non-active complexes.

Dantrolene

Dantrolene has a unique role as a muscle relaxant. It does not influence neuromuscular transmission, but it prevents calcium ion release from sarcoplasmic reticulum resulting in inhibition of muscle contraction. Dantrolene is only used for **malignant hyperthermia**.

Botulinum toxin

Botulinum toxin can be used for some specific indications (e.g., dystonia, blepharospasm, and hemifacial spasm), yet it is better known for its use as a facial wrinkle reducer. After being

injected, the toxin blocks the release of acetylcholine from the presynaptic end of neurons. The results are evident in 2-3 days and last for up to 5-6 weeks.

12.2 Treatment of Parkinson's disease

Parkinson's disease is a degenerative disease of the brain associated with the loss of dopaminergic neurons in the substantia nigra leading to a lack of dopamine. Symptoms begin to show after a loss of about 50% of neurons and are quite ambiguous at first (e.g., attention deficit, tiredness, depression, etc.). During the progression, more typical symptoms start to appear, such as resting tremor of the limbs, increased tone and rigidity, postural instability, and dyskinesia. Patients have limited range of motion, their movement is slower, and difficulties initiating movement also appear.

Parkinsonian patients walk with a characteristic gait (i.e., small shuffling steps). Aside from the way they walk, their graphomotor functions (i.e., smaller writing) and facial expressions change, too (i.e., almost none). Impaired balance and sudden muscle rigidity (akinesia) may cause a fall. In the early stages, patients react well to treatment, but as the disease progresses, long-term administration of anti-Parkinson's medications may lead to late dyskinesia (i.e., an "on-off" phenomenon involving motor fluctuations, nocturnal akinesia, morning rigidity, and finger cramps) and psychiatric symptoms (e.g., cognitive impairment, drug-induced psychotic symptoms, etc.).

When treating Parkinson's disease, four basic approaches are used:

- To **substitute** inadequate dopamine levels,
- To use **agonists** of dopamine receptors,
- To **inhibit** dopamine **degradation** in the CNS by using MAO-B inhibitors, and
- Ty **restoring the balance** between dopamine and acetylcholine with anticholinergics.

12.2.1 Substitution of lacking dopamine

The first choice for most patients is **levodopa** (L-DOPA). It is a prodrug taken orally on an empty stomach several times a day (e.g., 3-6 times daily). It comes either in the form of gastro-resistant tablets or as prolonged-release tablets (e.g., night-time dose). For patients suffering from a swallowing disorder, levodopa can be given through a percutaneous duodenal feeding tube.

Levodopa readily helps alleviate the symptoms of dyskinesia. In the body, it is transformed by DOPA-decarboxylase to dopamine. This conversion is only needed in the CNS because dopamine cannot cross the blood-brain barrier. Outside the brain, dopamine causes unwanted peripheral side effects, such as gastrointestinal (e.g., vomiting, diarrhoea, and peptic ulcer exacerbation) and cardiovascular issues (e.g., palpitations, hypertension, and orthostatic hypotension). Levodopa is metabolised by COMT (catechol-O-methyltransferase) and to a smaller extent by MAOB (monoamine oxidase B). To reach sufficient levels of dopamine in the central nervous system, levodopa is given in high doses or is combined with another medication.

Carbidopa and **benserazide** are inhibitors of the peripherally acting DOPA-decarboxylase, and **entacapone** and **tolcapone** are inhibitors of COMT. These drugs increase the level of levodopa in the CNS and prevent peripheral side effects. They also allow for use of lower doses of levodopa. Optimum dosage is determined by careful individual titration.

Besides the side effects mentioned above, psychiatric issues can also appear (e.g., hallucinations and delusions, restlessness, anxiety, aggression, addictive and compulsive behaviour, hypersexuality, etc.). Nevertheless, levodopa still is safer to use than dopamine agonists (in the context of psychiatric side effects). During long-term levodopa therapy, effects may wear off. It is a complication wherein symptoms start to return or worsen before the next dose is due. The next step is an increase of the dosage, an adjustment of the dosing interval, or the addition of a COMT inhibitor.

12.2.2 Agonists of dopamine receptors

Parkinson's disease can also be treated with dopamine agonists. During long-term therapy with these drugs, late movement issues are less likely to arise than is the case with long-term levodopa use. However, there is a higher risk of psychiatric complications and the possibility of sudden irresistible sleep attacks. Ergoline dopamine agonists are derived from ergot alkaloids (see Chapter 2.1.2.2 Sympatholytics – α).

Bromocriptine and **dihydroergocryptine** are D_2 agonists and D_1 antagonists. Administration of high doses is necessary. Dihydroergocryptine has a long half-life, hence a risk of accumulation. **Pergolide**, a D_1, D_2, and D_3 agonist, is the most frequently used ergot-derived anti-Parkinson drug.

Serious side effects of the treatment with ergoline dopamine agonists is fibrosis of the cardiac valves, lungs, and other organs. Therefore, non-ergoline dopamine agonists are preferred. Often used, **ropinirole** is an agonist of D_2 and D_3 receptors and has a low risk of psychiatric side effects. It is administered once daily in a prolonged-release dosage form. Pramipexole, a D_1 and D_3 agonist, is also available. **Rotigotine**, a D_2 and D_3 agonist, is formulated as a transdermal patch (transdermal therapeutic system, TTS).

12.2.3 Inhibition of dopamine degradation

In the early stages of Parkinson's disease, **selegiline**, an inhibitor of MAOB, can be given orally. Monoamine oxidase B is present mostly in the CNS, but to some extent in the periphery, as well. It degrades dopamine into ineffective metabolites. Selegiline is only mildly effective in comparison with the drug classes mentioned above as it comes with a higher risk of psychiatric side effects. It also interferes with Parkinson-associated depression due to its interactions with antidepressants. The benefit of selegiline is the fact that when it is taken in the early stages of Parkinson's, the use of levodopa is delayed. Later, the combination of levodopa and selegiline is possible and lower doses of levodopa are needed. The side effects of selegiline are nausea, postural hypotension, sleeplessness, bradycardia, dry mouth, and urinary retention. **Rasagiline** is a derivative with a lower risk of side effects.

12.2.4 Restoring the balance between dopamine and acetylcholine

The lack of dopamine in the striatum causes an imbalance between dopamine and acetylcholine (in favour of ACh). The relative excess of acetylcholine also contributes to Parkinson´s symptoms. Symptoms can be reduced with anticholinergics (acetylcholine antagonists); however, these are not suitable for older patients or those undergoing long-term therapy. Peripheral side effects typical of anticholinergics may appear, such as dryness of mouth, dryness of mucosa, constipation, and urine retention as well as central side effects including confusion and cognitive impairment. Acetylcholine antagonists are used as adjuvant therapy in younger patients who do not suffer from cognitive impairment.

Anticholinergics used in Parkinson's disease are **biperiden**, **procyclidine**, and **amantadine**. Amantadine was introduced as an antiviral agent, but it has anticholinergic and antiglutamatergic effects, as well. Repeated intravenous infusions of amantadine are given to patients in the late stages of Parkinson's to help with dyskinesia.

When pharmacotherapy is no longer effective for patients with no cognitive impairment, there are some other approaches, namely deep brain stimulation, which reduces motor symptoms of the disease.

12.3 Drug-induced extrapyramidal symptoms and iatrogenic parkinsonism

An unusual reaction of the dopaminergic system may be a sign of a neurological disorder (e.g., Parkinson's disease, dyskinesia associated with other neurological conditions, etc.), but it can also be a side effect of certain medications. This is more likely to happen in children and the elderly or during a long-term therapy. Below, drugs capable of causing these side effects are listed:

- Typical antipsychotics (i.e., neuroleptics) – chlorpromazine, levomepromazine, prochlorperazine, perphenazine, haloperidol, etc.;
- H_1-antihistamines (first-generation) – thiethylperazine, promethazine;
- Prokinetics – metoclopramide;
- Older antihypertensives – reserpine, α-methyldopa;
- Antivertigo agents – cinnarizine, flunarizine;
- Antiepileptics – phenytoin, carbamazepine;
- Antidepressants – tricyclic antidepressants, trazodone; and
- The centrally acting muscle relaxant, baclofen.

These drugs usually block dopamine receptors in some parts of the central nervous system. Signs of drug-induced extrapyramidal symptoms can be classified into four groups: acute dystonia, acute akathisia, tardive dyskinesia, and drug-induced parkinsonism.

Acute dystonia and **acute akathisia** have similar root causes; the primary reason they develop is due to an imbalance of dopamine and acetylcholine in various areas of the CNS. Younger patients are affected more often. Dystonia is found in up to 40% of patients on typical antipsychotics and affects the head and neck area (e.g., trismus, retrocollis (RC),

reduced eye and tongue movement, etc.). Limbs are usually unaffected. Akathisia is less common. Patients describe symptoms of compulsive behaviour, motor and psychological restlessness, and repetitive movement. To deal with acute dyskinesia and akathisia, the medication must be changed to **safer antipsychotics** (i.e., atypical ones). Moreover, **anticholinergics** are indicated. The initial dose is given intravenously, followed by treatment with oral forms. Benzodiazepines are also an option.

Tardive dyskinesia is unlike the previously mentioned conditions. It is caused by an upregulation of D_2 receptors, which are chronically blocked by the drugs listed above as well as by hyperactivity of noradrenergic and GABAergic transmission in the basal ganglia. The elderly are more prone to this type of dyskinesia. Approximately 15-20% of patients taking antipsychotics suffer from orobuccolingual dyskinesia with symptoms of the stereotypical involuntary movements of tongue and lips, chewing, and facial grimacing. The condition is more severe if the patient takes anticholinergics, as well. In that case, the anticholinergics need to be gradually discontinued. The next step is to change the medication to a safer one. If the movements are unmanageable and complicate the patients' life, **botulinum toxin A** can be given in the form of an **intramuscular injection**. Benzodiazepines, **β-blockers**, or **calcium channel blockers** can be used, as well.

Drug-induced parkinsonism is the result of defective dopaminergic transmission in the substantia nigra. It is most commonly caused by long-term treatment with antipsychotics, but it can also occur as a result of methanol or carbon monoxide poisoning. The correct course of treatment would be a change of medication (if patient is taking any) to safer one and administering anti-Parkinson medication (see Chapter 12.2 Treatment of Parkinson's disease).

12.4 The treatment of chorea

Chorea is one form of dyskinesia characterised by involuntary and irregular movements; these can have several causes. Aside from the previously mentioned origins (i.e., drug-induced syndromes/iatrogenic parkinsonism, Parkinson's disease), also recognised are Huntington's chorea (hereditary disease), vascular chorea (associated with ischemia of basal ganglia), and chorea minor (Sydenham chorea), which is the result of an autoimmune response that occurs following a streptococcal infection.

The treatment of the unwanted involuntary movement associated with this dyskinesia is carried out according to the symptoms displayed. Antipsychotics can be used to reduce the choreatic movements, whereas typical antipsychotics (e.g., **fluphenazine**, **haloperidol**) are more effective than atypical ones (e.g., **risperidone**, **tiapride**, and **clozapine**) at reducing undesirable movements. Unfortunately, typical antipsychotics are linked to a higher risk of drug-induced parkinsonism and extrapyramidal syndromes.

Some drugs causing a depletion of dopamine in the CNS, such as **reserpine** or **tetrabenazine**, can be used, as well. Although there is a risk of depression on top of the risk of parkinsonism.

Another option is treatment with benzodiazepines (e.g., **clonazepam**), which enhance GABAergic transmission. Although not as effective, treatment with drugs that inhibit glutamatergic transmission (e.g., **amantadine**) can be used.

12.5 The treatment of spasticity and cerebral palsy

Diseases, wherein the function of the skeletal muscles is impaired, are most frequently associated with damage to the neurons of the musculoskeletal system. When **lower motor neurons** are affected, patients exhibit decreased muscle tone and an extinction of muscle and superficial reflexes. This leads to muscular weakness, which progresses over time. Later, it results in atrophy of skeletal muscles, long bones, and even the skin in affected areas. Defects of peripheral motor neurons are typical for illnesses such as poliomyelitis, Charcot-Marie-Tooth syndrome, and first and foremost, myasthenia gravis (see Chapter 12.6).

If **upper motor neurons** are affected, muscle tone increases, muscle reflexes intensify, and superficial reflexes weaken. These symptoms can be signs of myelodysplasia associated with spina bifida or Friedrich disease, but more than likely they are caused by cerebral palsy (CP, also called infantile cerebral palsy). From a clinical perspective, CP is classified as being spastic, athetoid (also called dyskinetic), ataxic, mixed, etc. Below, spastic cerebral palsy and its treatment are discussed.

Spastic cerebral palsy

Cerebral palsy is caused by brain damage occurring in either the prenatal or perinatal period. Generally, symptoms are mild and psychiatric (e.g., minimal brain dysfunction in children associated with attention deficit), but some physical ones may appear, as well (e.g., severe spasticity associated with rigidity). If the patient is not treated properly, the condition develops into a state with severe muscle spasms. Former hypertrophy transforms into atrophy; moreover, the movement of joints is limited, and dislocations and deformities of the long bones occur.

The main pillar of the treatment is **physiotherapy** and **fitted rehabilitation** (e.g., Vojta method (i.e., reflex locomotion), Bobath concept), which is supplemented with the use of orthopaedic medical devices (e.g., corsets, orthosis, etc.) and orthopaedic or neurological surgeries. Medication is not the most important part of the therapy, but it improves the outcome of the physiotherapy or even makes it possible. Most of the drugs mentioned below are also used for spasticity associated with other diseases, such as multiple sclerosis.

Local therapy of spastic conditions

Either local or systemic therapy can be used. For the former, mainly **botulinum toxin A** is used. It is a substance isolated from a culture of *Clostridium botulinum* and is applied intramuscularly into the affected muscles; it relaxes those and removes the pain associated with the spasms and contractions. It also allows the muscles to grow further, which is especially convenient for children. Botulinum toxin irreversibly inhibits cholinergic transmission at the neuromuscular junction, thereby preventing the release of acetylcholine from the presynaptic neuron. Slowly, the innervation of the muscle is restored (i.e., a new neuromuscular junction is created). The effect can last for up to 12 months after just one injection. Usually though, there is a need to repeat the procedure sooner than that. Administration of botulinum toxin improves the effects of physiotherapy and rehabilitation.

Systemic therapy of spastic conditions

Systemically administered medication is recommended when large areas of the body are affected. In such a case, centrally acting muscle relaxants are administered. This class of drugs affects neurotransmitters and neuromodulators of the central nervous system (i.e., they reduce excitation and stimulate inhibitory mechanisms within the CNS).

The most frequently used centrally acting muscle relaxant in these conditions is **baclofen**, which is structurally similar to GABA. It inhibits the release of glutamate and aspartate, both of which are excitatory amino acids. Baclofen is given orally and can even be used in infants. It also has anxiolytic effects and helps control urination, both of which are seen as advantages. Side effects of baclofen are diurnal somnolence and sleepiness, headaches, vertigo, dry mouth, confusion, hypertension, and visual impairment. When the dose is too high, it can cause extensive muscle weakness. As time goes, patients develop tolerance for that given dose. When baclofen is suddenly discontinued after a long-term treatment, rebound phenomenon may occur (e.g., tremor and dyskinesia, rise of body temperature, psychiatric complications and hallucinations, tachycardia, and epileptic seizures). Baclofen is administered either intrathecally via a subcutaneous implanted pump or via a catheter placed into the subarachnoid space. These approaches may decrease the necessary dose and prevent some side effects.

Another class of drugs used to treat spasticity is α_2 agonists, particularly **tizanidine** and **clonidine**. Adrenergic α_2 receptors are situated at presynaptic neuronal membranes, and their activation inhibits the release of neurotransmitters into the neuromuscular junction by way of a negative feedback mechanism. Agonists of those receptors have a similar effect. They are administered orally and are not suitable for children. Tizanidine selectively affects receptors in the spinal cord and supraspinal structures, in which it blocks the release of aspartate and glutamate. Sedation, sleepiness, tiredness, dry mouth, and slight reversible elevation of liver enzymes are side effects common with tizanidine. Both tizanidine and clonidine also affect the cardiovascular system (i.e., causing bradycardia and hypotension); when stopped abruptly after a long-term therapy, rebound phenomenon may occur (e.g., hypertension, tachycardia, and rarely ictus).

To help with a spastic condition, benzodiazepines can be given, as well (e.g., orally or as injections). Of this drug class, **diazepam** and **clonazepam** are relatively effective at lowering muscle tone. Benzodiazepines are agonists of GABA receptors and potentiate the effects of GABA. They act as muscle relaxants, anticonvulsants, anxiolytics, sedatives, and some of them have amnestic effects, as well. When given long-term, a tolerance to benzodiazepines develops and addiction can potentially follow.

Other drugs that can be used to treat spasticity are dantrolene (inhibits release of Ca^{2+} ions from sarcoplasmic reticule), gabapentin, lamotrigine (both interfere with GABA transmission, used as antiepileptics), and riluzole (inhibitor of glutamate transmission, used in amyotrophic lateral sclerosis).

Some cannabinoids are subjects of clinical trials. A combination of **tetrahydrocannabinol** and **cannabidiol** in the form of an oral spray is registered in some countries for the treatment of spasticity associated with multiple sclerosis. Unfortunately, it is only effective in 30-40% of patients. Cannabinoids interact with CB_1 and CB_2 receptors and probably inhibit the transmission of excitative amino acids in the CNS. They can cause psychiatric side effects

(e.g., mood changes, depressions, cognitive impairment, appetite changes, etc.) and gastrointestinal problems, loss of balance, sleepiness, etc.

12.6 The treatment of myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disease that results from antibodies that block or destroy nicotinic acetylcholine receptors (N_M) at the neuromuscular junction. This causes a defect in the transmission of nerve impulses to muscles. MG is more common in women, who are generally more prone to autoimmune diseases. The disease manifests itself as fluctuating muscle weakness; muscles fatigue quickly, which gets worse in the evening, at night, and after physical activity. The first noticeable symptom is weakness of the eye muscles. The progress of the disease may stop and patients may only suffer from ocular myasthenia, in which they experience involuntary eyelid drooping or cannot close their eyes properly. Although, if the disease progresses, facial muscles are affected (e.g., loss of facial expression) as well as head and neck muscles (e.g., problems with chewing, swallowing, articulation, and difficulty holding the head upright may occur). Likewise, other muscles can also be influenced. When patient´s breathing muscles are impaired, the patient goes into so-called myasthenic crisis, which is a very serious condition.

Symptomatic treatment

Symptoms of myasthenia gravis are treated with cholinomimetics – inhibitors of cholinesterase – which increase the concentration of acetylcholine in the neuromuscular junction. **Pyridostigmine** is the first choice for symptomatic treatment. It is a derivative of physostigmine, an alkaloid found in the Calabar bean (*Physostigma venenosum*, Fabaceae family), which is a shrubby African plant with many vines. Pyridostigmine is administered orally 2-4 times daily. **Neostigmine** is a short-acting drug, which is used as an additional medication before and during exercise. **Distigmine** serves as a drug of last resort; it has a long biological half-life and is associated with a risk of accumulation in the body.

Side effects that may appear while taking "stigmines" relate to the activation of peripheral acetylcholine receptors. These side effects are caused by activation of either muscarinic receptors (e.g., salivating, sweating, eye watering, miosis, nausea, diarrhoea, stomach cramps, and bronchospasm) or nicotinic receptors (e.g., muscle cramps and fasciculation). Most of these side effects can be prevented by atropine or propantheline, both of which are parasympatholytics. However, parasympatholytics only prevent the muscarinic side effects and are ineffective at nicotinic receptors. Also, atropine and propantheline do not interfere with the therapeutic effect of the drug. To treat diarrhoea, the antimotility drug, loperamide, is given.

When pyridostigmine is not effective or tolerated, **ambenonium** is used. It is a substance with a quaternary nitrogen in its structure (i.e., charged), which disables it from crossing the blood-brain barrier; therefore, it does not cause any central side effects (e.g., restlessness, confusion, annoyance, etc.). One serious side effect common to all cholinomimetics is a **cholinergic crisis**, which occurs as a result of the accumulation of the drug in the body and is caused by a depolarising block of autonomic ganglia and neuromuscular junctions. Its symptoms are

generalised muscle weakness and can be mistaken for worsening of myasthenia gravis. Cholinergic crisis is a life-threatening condition. If breathing muscles are affected, intubation and artificial ventilation are needed. Atropine is administered intravenously to treat the crisis.

Causal treatment

For causal treatment of myasthenia gravis, immunosuppressants are used. This class of drugs suppresses the amount of B lymphocytes; these cells are responsible for the production of antibodies against N_M receptors. In most cases, these drugs do not act specifically; instead, they affect other parts of the immune system. Patients using immunosuppressants can suffer from infections, sepsis, and are at higher risk of malignant diseases. Therefore, immunosuppressants are only used for progressive myasthenia.

The most commonly used immunosuppressants are glucocorticoids and azathioprine. Glucocorticoids (e.g., mainly **prednisone**, **prednisolone**, and **methylprednisolone**) are titrated until remission (i.e., 6-8 weeks). Then, the dose is gradually decreased until the lowest effective dose is known, and the continued administration of this dose commences. In the first week of glucocorticoid treatment, the symptoms of myasthenia gravis may actually worsen. Also, the rest of the treatment, which is long-term, is associated with side effects (see Chapter 8.5 Glucocorticoids) even though the dose is as low as possible. When high doses of glucocorticoids are given, there is a risk of steroid myopathy. Symptoms include increasing muscle weakness, muscle atrophy (mainly lower limbs), extinction of reflexes, and abnormal curvature of the spine. At this juncture, the dose must be lowered, and patients must be properly rehabilitated.

Azathioprine is a prodrug which is transformed to 6-mercaptopurine in the body. Its metabolites, which are formed intracellularly, inhibit the synthesis of purine nucleotides leading to a cessation in cell division. The effects of azathioprine should appear within three months. It is possible to combine this drug with glucocorticoids; it even enables the continued use of the low dose of glucocorticoids necessary to sustain remission.

Other immunosuppressants can be used for myasthenia gravis, as well. **Cyclosporine A** is expensive; therefore, it is considered a drug of last resort. It is also a strong inhibitor of CYP3A4, which means there exists a high risk of drug interactions. In some special cases, mycophenolate mofetil, the effects of which appear very expediently (i.e., in two weeks), can be used. When patients are resistant to the treatment with cyclosporine A, cytostatics, **cyclophosphamide** and **methotrexate** (see Chapter 10.3 Overview of cytostatic agents), or the immunosuppressant, **tacrolimus**, can be used. An example of an experimental treatment is the administration of **rituximab**, which is a monoclonal antibody against antigen CD20 and is otherwise used to destroy B cells. Immunosuppressants are discussed more thoroughly in Chapter 8.7.1.

Among existing drugs, there are some which can induce myasthenia gravis (e.g., penicillamine and interferon α) or which affect neuromuscular transmission and may worsen the muscular symptoms of myasthenia gravis (e.g., aminoglycoside antibiotics (e.g., gentamicin, Mg^{2+} ions given intravenously – usually orally given magnesium doesn't cause symptom worsening), quinidine, quinine, and chloroquine). If a muscle relaxant is given to a patient with myasthenia gravis, its effects are prolonged. In case a muscle relaxant must be

given (e.g., some surgeries), short-acting non-depolarising agents are preferred (e.g., mivacurium, vecuronium, etc.).

12.7 Pharmacotherapy of Ménière's disease

Ménière's disease affects the inner ear. Inside the labyrinth, endolymph accumulates increasing pressure inside the cochlear ductus. Acute attack of Ménière's disease is caused by the rupture of the membrane which separates the endolymphatic and perilymphatic space inside the inner ear. An acute attack can be preceded by the so-called "aura" (i.e., warning signs), which includes feelings of increased pressure inside the ear, or fullness of the ear. The symptoms of the acute attack are typically loss of balance, vertigo, nystagmus, tinnitus, and partial loss of hearing. Symptoms are usually reversible; however, hearing loss and tinnitus may persist and even worsen. Besides pharmacotherapy, regimen changes are recommended for the treatment of Ménière's disease (e.g., decreased intake of salt, caffeine abstinence, and stress managing techniques).

As prophylactic pharmacotherapy, **betahistine** (betahistine dihydrochloride), is commonly used. It is a weak agonist at histamine H_1 receptors and an antagonist at H_3 receptors. H_3 receptors are mostly present in the CNS, and their function lies in the regulation of histamine transmission. They are "autoreceptors", which means their activation leads to a decrease in neurotransmitter outflow, in this case histamine, into the synaptic cleft. Therefore, antagonists of H_3 receptors enhance histamine transmission. The mechanism of action of betahistine in Ménière's disease has not yet been precisely elucidated. However, increased microcirculation by vasodilation in the inner ear and the inhibition of neuronal activity in vestibular nuclei were confirmed. Betahistine is usually administered one or two times a day in various doses. It can also be used in high doses three times a day during or shortly after an acute attack.

Cinnarizine in an antagonist of H_1 receptors and a T-type calcium channel blocker. It has anti-vertigo and prophylactic effects. It is also commonly used orally to treat cerebrovascular and peripheral vascular diseases and inner ear disorders. Cinnarizine decreases the tonus of arterioles and enhances microcirculation in the inner ear. When used chronically, it may cause extrapyramidal symptoms, such as tremor or iatrogenic parkinsonism by increasing the number of dopamine D_2 receptors. Cinnarizine may also trigger sleepiness and sedation. It can be combined with antihistamines like dimenhydrinate. **Flunarizine** is a similar drug, but is not currently authorised (registered) for use in the Czech Republic.

Other drugs, which are or could be, used as a prophylaxis in Ménière's disease, are vasodilating agents and rheologics. **Standardised extract from the Ginkgo tree** (*Ginkgo biloba*, Ginkgoaceae) is used orally for the treatment of tinnitus and vertigo of vascular origin and circulation disorders of the brain and extremities. It enhances perfusion and the rheological properties of blood, acts as an antioxidant, and is mildly antithrombotic. At first, extract from Ginkgo may worsen tinnitus and vertigo for a short time. Common adverse events of the therapy are GIT problems (e.g., nausea) and headache. If combined with antiaggregant agents (e.g., acetylsalicylic acid) or anticoagulants (e.g., warfarin), the patient

needs to be carefully monitored because of possible potentiation of the effect on blood coagulation.

Vinpocetine is a derivative of indole alkaloids identified in periwinkle (*Vinca minor,* Apocynaceae). It only influences the CNS area and is used orally and intravenously for the treatment of brain circulation disorders (e.g., associated with memory loss, vertigo, headaches, stroke, etc.), hearing problems, and vertigo. Vinpocetine enhances metabolism in the CNS, inhibits vasoconstriction mechanisms of arterioles and aggregation of thrombocytes, decreases blood viscosity, and increases deformability of erythrocytes. Through these effects, vinpocetine enhances microcirculation in the brain. Its adverse effects are mild and reversible (e.g., GIT problems, insomnia, tachycardia, headaches).

Pentoxifylline is a xanthine derivative, which enhances the rheological properties of blood through its influence on the deformability of erythrocytes. It is used orally and intravenously to treat circulation disorders of the lower extremities, brain, and the inner ear. When administered intravenously, it may cause vasodilation and trigger hypotension. This effect is caused by the inhibition of phosphodiesterases in the smooth muscle cells. Other adverse effects comprise mild GIT disorders, headache, and very rarely changes in the blood count may occur.

Cautious use of **diuretics** or **glucocorticoids** are alternatives to the prophylactic treatment. Both groups of drugs exert anti-oedema effects and may decrease the pressure in the endolymphatic space.

An acute attack of Ménière's disease can be alleviated by H_1 antihistamines of the 1st generation (e.g., **embramine**, **moxastine**, **dimenhydrinate**; see Chapter 8.6.2 H_1-antihistamines), the dopamine D_2 antagonist, **thiethylperazine**, or by a combination of cinnarizine and H_1 antihistamines. These drugs may cause intensive sedation and sleepiness.

12.8 Rheumatoid diseases and gout treatment

12.8.1 Treatment of rheumatoid arthritis

Rheumatoid arthritis is a systemic autoimmune disease mainly affecting the joints as well as other tissues and organs. Most patients suffering from **rheumatoid arthritis** (**RA**) are women (i.e., 4:1 women: men). When left untreated, the chronic joint inflammation leads to joint deformities. RA has a bad prognosis, according to epidemiological studies patients with RA live approximately 10-15 years less as compared to the healthy population. Since the etiopathogenesis of RA is not entirely clear, a specific causal treatment is not available. Thus, the treatment of rheumatoid arthritis seeks to induce remission or at least reduce the symptoms, such as the joint pain and inflammation.

12.8.1.1 Disease-modifying anti-rheumatic drugs (DMARDs)

DMARDs are a cornerstone of the rheumatoid arthritis treatment, and therapy is usually lifelong. While their common feature is suppression of both the immune response and the inflammation in the synovial membrane, their mechanisms of action are different. Treatment

by DMARDs immediately follows the RA diagnosis and is started with high doses that diminish over time (i.e., maintenance doses). DMARDs are fully effective only after several days or weeks.

Methotrexate is a **folic acid analogue**, immunosuppressant, and cytostatic drug that interferes with folic acid metabolism (i.e., antimetabolite – see section). It decreases leukocyte chemotaxis and cytokine production. This drug is highly effective at treating RA and is administered once per a week per os or intramuscularly. The full effect is present after 3-4 weeks. Methotrexate can be administered both as a monotherapy and in a combination with other DMARDs or as a targeted therapy. After treatment cessation, symptoms of RA usually return rapidly.

Sulfasalazine is a drug used to treat several autoimmune diseases. In the intestine, it is converted into 5-aminosalicylic acid (**mesalazine**), most of which is not absorbed (e.g., it is effective at treating Crohn disease), and **sulfapyridine**, which has an anti-inflammatory effect.

Leflunomide is an immunosuppressant that inhibits *de novo* nuclear DNA synthesis. It is used to treat highly active RA.

Hydroxychloroquine is a relatively well-tolerated antimalarial drug. However, its efficacy regarding the RA treatment is quite low, and any therapeutic effect appears no sooner than in 6-9 months.

Gold salts (e.g., **sodium aurothiomalate** or **auranofin**) are effective, but they have many side effects (e.g., dermatitis, kidney, or bone marrow disorders). Therapy must be ceased immediately after occurrence of any of these side effects.

Penicillamine is an immunosuppressant with a slow effect onset. The mechanism underlying its immunosuppressive effect is not entirely understood. However, it is understood that penicillamine has chelating properties and removes the heavy metal atoms in case of intoxication or Wilson's disease. Currently, it is rarely used to treat RA.

Cyclosporine A is an effective drug with frequent side effects, such as hypertension, nausea, and headaches (see immunosuppressant drugs section).

Azathioprine is a purine analogue and antimetabolite used as an immunosuppressant. It has frequent side effects, including bone marrow suppression (i.e., myelotoxicity/myelosuppression).

12.8.1.2 Targeted therapy

Compared to the DMARDS, targeted therapy (i.e., biological therapy) is based on a more specific mode of action. Three main groups of drugs can be distinguished according to their specific mechanism. The first one targets TNF- α, a key cytokine mediating the cellular mechanisms involved in inflammation and joint destruction. Examples are **infliximab**, **adalimumab**, and **etanercept**. The second group targets the interleukin-6 receptor and is represented by **tocilizumab**. The third group directly targets T and B lymphocytes; examples include **abatacept** and **rituximab**.

Targeted therapy is usually administered along with DMARDs and NSAIDs. The effect is mostly rapid and intense. Side effects include GIT function or blood pressure disorders as well as an increased risk of infection. Less often, allergic reactions may occur.

12.8.1.3 Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are used as a symptomatic treatment to decrease pain and joint stiffness. On the other hand, they do not modify the levels of acute phase reactants. Out of the NSAIDs, selective COX-2 inhibitors (**celecoxib**, **etoricoxib**) or preferential COX-2 inhibitors (**meloxicam**) are used due to the less frequent occurrence of adverse effects. Out of the nonselective COX inhibitors, **ibuprofen**, **diclofenac**, **indomethacin**, or **tiaprofenic acid** are used. They can be administered per os, in suppository form, or locally in creams or gels.

12.8.1.4 Glucocorticoids

Glucocorticoids have a more pronounced anti-inflammatory effect compared to NSAIDs and act against all phases of inflammation. Long-term treatment by glucocorticoids is associated with severe adverse effects; therefore, the lowest effective dose is taken during chronic treatment, and once allowed by the clinical state of the patient, their administration should be terminated. Faster and better effects of glucocorticoids are achieved through short-term intravenous application of high doses. Another route of application is intraarticular (i.e., inside the involved joint). After treatment cessation, the symptoms of RA often tend to return.

12.8.2 Treatment of gout

Gout is an inflammatory joint disease of metabolic origin. The causative factor of gout is **hyperuricemia** (i.e., elevated blood level of the uric acid), which is a result of increased intake of purines and/or impaired elimination of their main metabolite, uric acid. Alternatively, an elevated purine concentration can be the result of tumour lysis syndrome (i.e., massive destruction of tumour cells during the cancer treatment). In such cases, the concentration of uric acid reaches that of a saturated solution, and in tissues with a low temperature (e.g., the **joints**), uric acid precipitates in its crystalline form (i.e., sodium urate). In the **kidney**, uric acid or its salt, ammonium urate, can cause kidney stones. Asymptomatic hyperuricemia can be treated with a low-purine diet followed by pharmacotherapy in case dietary changes alone are ineffective. In case of symptomatic gout, both hyperuricemia and acute gout exacerbation must be addressed.

12.8.2.1 Treatment of the acute gout flares

Treatment must be started immediately. The following drugs are administered:

NSAIDs - NSAIDS with a stronger effect, despite not being tolerated as well, are chosen for use, and high doses are applied. **Indomethacin** is the first-choice drug (it also enhances renal excretion of uric acid), followed by **diclofenac**, **ibuprofen**, or **etoricoxib**.

Colchicine is a spindle poison that inhibits the metaphase of mitosis. It also acts against neutrophil motility; this leads to decreased phagocytosis of urate crystals, which protects

leucocyte membrane integrity and lysosomal enzyme excretion. Altogether, this decreases inflammation in the diseased joint.

Glucocorticoids can be applied in gout flare-ups intramuscularly or locally intra-articularly.

12.8.2.2 Treatment of hyperuricemia

Hyperuricemia can be normalised through a low-meat diet, purine synthesis blockers (**uricostatics**), or uric acid excretion enhancers (**uricosurics**).

The uricostatics are represented by **allopurinol** and **febuxostat**. They act by blocking xanthine oxidase, an enzyme crucial to purine conversion to uric acid. The purine metabolites that accumulate after xanthine oxidase inhibition have better solubility and can be more easily eliminated by the kidneys.

Allopurinol is a purine derivative that acts as a competitive xanthine oxidase inhibitor. It also inhibits *de novo* purine synthesis. One unfortunate adverse effect is that it can induce a gout flare-up at the start of the treatment. Other adverse effects are rare (e.g., especially dermatitis and other skin disorders), and allopurinol is usually well-tolerated.

Febuxostat is a newer uricostatic drug used to treat hyperuricemia. During gout treatment, this non-purine derivative has proved to be superior to allopurinol in clinical trials. Similar to allopurinol, febuxostat can initially induce gout flare. Other side effects include the diarrhoea, nausea, or liver disorders.

The second group of drugs used during the period between gout flares is the uricosuric group inclusive of **benzbromarone** and **probenecid**. These drugs compete with uric acid for its reverse transporter in the renal tubules. This results in enhanced uric acid losses. The disadvantage of treatment with these agents is an interference with the excretion of other drugs (i.e., pharmacokinetic interactions).

13 Treatment of urgent conditions

13.1 General principles of intoxication treatment

Toxic features of substances have been known since the beginning of human history. Acute intoxications affect all age groups and represent a serious health and social burden. The consequences of an acute intoxication may lead to a permanent disability resulting in organ failure and eventually death. Intoxication occurs after accidental or intentional ingestion of a poisonous substance. However, intoxication may also be caused by a drug which in safe under a recommended dosing threshold, but toxic upon administration of a larger dose. Interestingly, Paracelsus (1493 to 1541) stated that "the dose makes the poison". The toxicity field is vast; therefore, we first summarise the general principles of first aid and most common causes of poisoning. The following section focuses on the pharmacological approaches of treatment with selected intoxications.

Toxic effects of xenobiotics on biological systems and their mechanisms of action are studied by the multidisciplinary science, toxicology. Clinical toxicology focuses on the clinical symptoms, diagnosis, therapy, and prevention of intoxications. Usually, we divide the causes of intoxication into two groups according to the type of substance causing the intoxication: drug intoxications and other intoxications, which are generally caused by xenobiotics found in our environment or households (e.g., carbon monoxide, industrial toxins, heavy metals, cleaning agents, organic solvents, pesticides, herbal and animal poisons, etc.). A specific topic is toxicology related to drugs of abuse (see Chapter 3.2 Drug dependence). The basic terminology, such as lethal dose, LD50, etc., is described in the text dedicated to general pharmacology.

13.1.1 Common causes of intoxications

The term, "poison", refers to substances that may cause damage to the organism and intoxication symptoms. This includes substances of different chemical and physical properties. The precise dose-response relationship is difficult to assess in toxic substances. Populations at an increased risk are elderly people whose organs have a low capacity for elimination, polymorbid patients, or patients with a history of other drug use.

There are several major factors that determine whether the substance will have harmful effect on the organism:

- Route of administration,
- Time of exposure and dose (or concentration), and
- Speed and extent of elimination processes in the body (mainly liver, kidneys).

Most commonly, toxins are administered orally. Less frequently, inhalation of poisonous gases or vapours, intravenous administration, or absorption through the skin are the route of administration. The causes of acute intoxications can be accidental, related to overdose in the case of substance abuse, or intentional as a suicidal attempt. Due to limited space, chronic

intoxications (e.g., cirrhosis due to alcohol consumption) are excluded from this chapter, and only acute intoxications are discussed.

13.1.2 Diagnosis of intoxications

Acute intoxications may be caused by synthetic substances or natural toxins that originate from microorganisms, fungi, plants, and animals. They have different chemical and physical properties, which are reflected by highly variable symptoms of intoxication. In some cases, the signs appear almost immediately or within minutes (e.g., acid burns); in other cases, the symptoms appear after latency, which may last for hours, days, or even weeks (e.g. death cap – *Amanita phalloides,* mercury, radionuclides, etc.).

Some substances act nonspecifically depending on their chemical and physical properties while others interact with specific targets in the body (e.g., receptors or metabolic processes).

The symptoms of intoxication may be specific to the substance or only non-specific symptoms may appear. To assure correct diagnosis and choice of treatment, vegetative symptoms (e.g., salivation, heart functions, vomiting, diarrhoea, breathing, skin coloration, miosis/mydriasis, etc.), motor functions, pain, unconsciousness, behaviour (e.g., disorientation, aggressiveness, hallucinations, delirium), etc. must be checked.

13.1.3 Treatment of intoxications

13.1.3.1 First aid in intoxications

The most important focus is to prevent intoxication from occurring in the first place. The treatment depends on the symptoms of intoxication and supposed substance responsible for it. The aim is to maintain vital functions, stop absorption of the substance, and eliminate the absorbed proportion. To assure correct diagnosis and identification of the toxin, it is necessary to collect packages or containers, remainders of the substance, natural material, etc. for laboratory analysis. For advice, it is possible to contact Toxicological Information Center, General University Hospital, First School of Medicine, Charles University, Prague (phone: +420 224 919 293 or +420 224 919 402).

Symptomatic therapy consists of administration of pain killers, diazepam (10 mg IV) in case of seizures, and antibiotics if there is a risk of bronchopneumonia after aspiration of vomit or when unconsciousness lasts for more than 24 hours. In serious cases, intubation and ventilation support may be necessary as well as β2 agonist or glucocorticoid administration. Likewise, sometimes parenteral nutrition and circulatory support must be provided (i.e., crystalloids: saline, Ringer's or Hartmann's solution IV) along with cardiostimulation and urinary bladder catheterisation.

Generally, intoxications are characterised by the following symptoms, which require symptomatic treatment:

- Respiratory failure,
- Hypoxic brain damage during hypoventilation or seizures,
- Vomit aspiration, bronchopneumonia,

- Homeostasis failure (i.e., pH, ion balance),
- Acute heart failure,
- Acute liver failure, and
- Acute renal failure.

13.1.3.2 Removal of the toxin before absorption

Vomit is rarely induced, only in conscious patients immediately after administration of the toxic substance. Vomiting can be induced later if a large amount of a slowly absorbed substance has been ingested (e.g., slow release tablets, large pieces of fungi or plants) or in case drugs with a high risk of toxicity (e.g., tricyclic antidepressants) were consumed. Vomiting is contraindicated for chemical burns and gasoline poisoning due to risk of inhalation and development of chemical pneumonia.

Gastric lavage can be performed in an unconscious patient after securing airways with an endotracheal cannula to minimise the risk of aspiration of acidic stomach content. The lavage is performed using a gastric tube filled with tepid liquid, such as saline (250 to 300 mL). This procedure gives the best results if used up to one hour after ingestion of the toxin. The lavage is repeated until the liquid becomes clear. A sample of the first lavage is collected for toxicological analysis. After the lavage, approximately 30 grams of activated charcoal is administered (i.e., 25 g in 100 mL of tepid water).

In serious cases, it is recommended to also administer a **laxative** following the activated charcoal to speed up its passage through gastrointestinal tract. Later administration of laxatives is controversial. Repeated administration of **activated charcoal** is preferred in four-hour intervals, also called gastrointestinal dialysis, especially in the cases of intoxication by drugs subjected to enterohepatic circulation. Drugs which are well-adsorbed by activated charcoal are benzodiazepines, antidepressants, barbiturates, paracetamol, digoxin, and salicylates. Drugs with prolonged release of the active substance (e.g., theophylline, calcium channel blockers) require intestinal irrigation with a non-absorbable osmotically active substance (e.g., polyethylene glycol).

In case of percutaneous intoxication, the first procedure is decontamination of exposed skin using a suitable solution for 30 minutes. Patients exposed via inhalation need to be transported immediately from the contaminated environment and should be provided with an adequate oxygen supply.

13.1.3.3 Specific antidotes

Table 9: Selected antidotes

*Note: oxims need to be administered before the toxin is bound irreversibly.

Antidote	Type of intoxication
N-acetylcysteine, methionine	paracetamol
atropine	carbamates
atropine, *oxims	organophosphates (insecticides)
dimercaprol, penicillamine, succimer	Heavy metals (Au, Pb, As, Hg)
deferoxamine	iron

EDTA-Ca	lead
ethanol, ethylene glycol	methanol
flumazenil	benzodiazepines
physostigmine	anticholinergics
phytomenadione (vitamin K1)	coumarins, warfarin
G-penicillin	*Amanita phalloides*
Digoxin-specific antibody	digoxin
glucagon, beta-mimetic drugs	Beta blockers
glucagon, calcium	calcium channel blockers
calcium	fluorides, oxalates
methylene blue	methemoglobinizing substances
naloxone	opiates, opioids
sodium thiosulfate, hydroxocobalamin, $Co_2(EDTA)(H_2O)_6$	cyanides
protamine	heparin
pyridoxine (vitamin B6)	isoniazid

Antidotes decrease or abolish effects of toxins through different specific or non-specific mechanisms. Examples include chelation (e.g., EDTA in lead poisoning), competitive receptor blocking (e.g., flumazenil in benzodiazepine intoxication), enzymatic saturation (e.g., saturation of aldehyde dehydrogenase in methanol poisoning), enzyme reactivation (e.g., oxims after exposure to acetylcholinesterase inhibitors), and supplementation with SH- groups required for metabolite detoxification (e.g., N-acetylcysteine in paracetamol overdose), etc.

Importantly, administration of specific antidotes is based on exact diagnosis. When the intoxication origin is unclear or in cases where no antidote is available, (e.g., alcohol, barbiturates) we use symptomatic treatment. Table 9 shows antidotes used in selected intoxications.

13.1.3.4 Enhancement of toxin elimination from the body

Elimination of toxins and drugs that are mainly excreted by kidneys can be enhanced by increasing urine production. To this end, a loop diuretic can be administered (e.g., **furosemide**). In patients with no contraindication (e.g., brain or lung oedema), a **forced (osmotic) diuresis** procedure can be initiated by administration of mannitol solution. Furthermore, elimination of weak acids (e.g., salicylates, barbiturates) can be enhanced, for example, by alkalisation of urine using a 5-10% solution of $NaHCO_3$. This method is called **forced alkaline diuresis**.

Intermittent haemodialysis is a technique that allows extracorporeal removal of toxins or their metabolites from the intravascular compartment. The device is also called an artificial kidney, and it is available in specialised hospital departments. This approach is effective at eliminating salicylates, methanol, barbiturates, lithium, etc.

Another extracorporeal removal method is **hemoperfusion** through a capsule containing activated charcoal and other sorbents. It is suitable for use in intoxications with barbiturates, theophylline, or carbamazepine. On the other hand, using this method comes with a risk of the

patient developing thrombocytopenia. Indications for extracorporeal removal techniques are life-threatening intoxications with substances present in the intravascular compartment or patients with decreased clearance due to kidney or liver inadequacy. This approach is generally only suitable for drugs or toxins that are weakly bound to the peripheral tissues or plasma proteins (low distribution volume), which have a low molecular weight and are soluble in water.

Peritoneal dialysis is associated with a risk of infection and is generally only used when forced diuresis or haemodialysis cannot be performed.

Hemofiltration is based on ultrafiltration through a semipermeable membrane (i.e., 10 to 30 l/h) and is only used for patients with the most severe conditions (e.g., in kidney failure). In drugs or substances with a very low distribution volume a blood transfusion or plasma transfusion (**plasmapheresis**) can be used.

Exsanguination transfusion, which is a complete substitution of the patient's blood with donor blood, is an exceptional measure. Intravenous administration of lipid microemulsions, which can adsorb lipid micelles (e.g., soybean oil microemulsion) is a new approach. This method enhances elimination of lipophilic substances (e.g., in bradycardia induced by local anaesthetics, calcium channel blockers, β-blockers, or tricyclic antidepressants).

13.1.3.5 Summary

To assure therapeutic benefit for the treatment of intoxications, this algorithm needs to be followed:

- Assure airway patency, respiratory support;
- Controlling pulse, blood pressure, adequate amount of intravascular liquid;
- Maintaining of acid-base and electrolyte homeostasis;
- Treatment of heart rate disorders;
- Treatment of seizures;
- Maintaining optimal body temperature;
- Toxin identification (i.e., sampling for biochemical and toxicological analyses, consultation with TIS);
- Assessment of the ingested dose;
- Assessment of time since the ingestion of the intoxicating substance(s); and
- Initiation of adequate treatment (i.e., stop further toxin absorption, administration of activated charcoal at an amount 5 to 10 times higher than the supposed toxin dose, gastric lavage, enhancement of toxin elimination, and administration of a specific antidote).

13.2 Therapy of the shock states

Shock reactions, despite their very variable aetiology, are relatively uniform in their symptoms and in the late stages, also have negative consequences for the organism. All types of shock are characterised by circulatory failure resulting in a generalised hypoxia. The damage to the tissues and organs, which occurs in the context of insufficient oxygen

saturation, is reversible if treated in the early stages of shock, but irreversible cell damage occurs in the later stages. Therefore, either late diagnosis or delayed therapy worsens the clinical outcome.

Treatment should be initiated immediately with the concomitant implementation of the following measures:

- 1. Apply an oxygen mask for two to five and a half minutes; an ECG monitor should be connected to detect heart arrhythmias, and an O_2 blood saturation monitor should be set up.
- 2. A catheter should be placed into the central vein and measurements of central venous pressure (CVP) taken.
- 3. Placement of a catheter into the peripheral artery to monitor blood pressure and ease sampling of the arterial blood to analyse blood gas and lactic acid should be completed.
- 4. Blood sampling should be completed including: Blood type, complete blood count, platelet count, differential leucocyte count, coagulation, minerals, biochemical parameters, albumin, blood gases, and lactic acid, and in case of suspected poisoning, toxicological analysis should be carried out.
- 5. In the case of sepsis, sampling of biological material (i.e., blood, urine, stool, sputum, pus, exudate fluids, cerebrospinal fluid, bone marrow, biopsy material) for microbiological analysis should be done.
- 6. A urine catheter should be set up for hourly measurement of diuresis. A nasogastric tube should be placed in the GIT as a preventative measure to stop atonic gastric content aspiration as well as to measure fluid losses (i.e., gastric contents) and in case of unconsciousness or intubation, prior to mechanical ventilation.
- 7. Body temperature should be continuously monitored, preferably by the temperature sensor on a Swan-Ganz catheter.

The priority of therapy in these situations is **to restore mean arterial blood pressure** to 75-80 mmHg. Drugs affecting cardiac output, regulating vascular system volume, or solutions increasing the volume of circulating fluids can be used either alone or in combination to achieve this value. In the case of patients with active bleeding and penetrating trauma, the procedure of so-called **"permissive hypotension"** is sometimes appropriate. This involves maintaining a systolic pressure of 80-90 mmHg, subsequent quenching of the cause of blood loss, and finally replacing the volume of blood lost.

Comprehensive shock therapy includes other drugs, which improve the prognostic or the course of shock, such as analgesics, anxiolytics, or oxygen. Because of the rate of the onset of action as well as the variable absorption of drugs due to poorly perfused parts of the drug, a preferable way of administration is intravascularly into the large veins. At the same time, with the onset of therapy, it is also essential to discover the origin of the shock reactions; the next phases of therapy may vary according to the type of shock.

A **non-pharmacological**, therapeutic approach can be used, which is the intra-aortic balloon pump counterpulsation. It is used primarily in case of cardiogenic shock resulting from

various aetiologies. The mechanical support for circulation results in reduced left ventricular load and better blood flow to the myocardium, which can ultimately result in increased contractility and has a beneficial impact on hemodynamics, in general.

13.2.1 The volume therapy

Volume replacement is a tool to increase preload and cardiac output. This therapy is crucial for the treatment of hypovolemic, anaphylactic, septic, and obstructive shock. In some cases, this type of cautious volumetric expansion may lead to increased cardiac output even in cardiogenic shock. However, for severe heart failure, diuretics and vasodilators should be used. The administration of volume replacement should be rapid as well as a renewal of cardiac output and perfusion pressure.

In general, this therapy is initiated intravenously by the infusion of a physiological or Ringer's solution into a subclavian or jugular vein (e.g., 15-20 mL/min) at a dose of 20-40 mL/kg of body weight. The colloidal solutions can be added later. Continuous bleeding, cardiac tamponade, or tension pneumothorax should be considered if there is no improvement in the clinical state despite the large volume replacement.

The amount of the applied substitutions is mostly slightly underestimated due to the estimated loss, and the replacement amount is mainly managed by the clinical response. After successful volume resuscitation, heart rate should slow down, tissue perfusion should be improved, blood pressure increased, and diuresis increased. In case of significant capillary permeability during septic shock, a combination of volume replacement with inotropic agents and vasopressors is appropriate. Depending on their chemical nature, the solutions for volume substitution can be divided into **crystalloids**, **colloids**, and **blood substitutes.**

Crystalloids

The crystalloids, unlike colloids, freely diffuse through the capillary membrane into the interstitium. It is necessary to give a three- to fourfold higher volume than the actual circulating fluid volume to achieve compensation for volume losses in the bloodstream. After the administration of crystalloids, the fluid in the blood stream is increased; concomitantly, crystalloids expand into the interstitial fluid, and associated complications develop.

Typical complications of crystalloid application are an increase in tissue oedema and body weight. After application of an overestimated dosage amount of isotonic saline (0.9%, F1/1), hyperchloremic metabolic acidosis, impaired renal function, and systemic inflammatory response can occur. Other isotonic solutions can be used, for example Ringer's solution. The administration of hypertonic solutions (e.g., 7.5% NaCl) leads to a redistribution of intracellular fluid and transiently increases intravascular volume. This solution is suitable for the initial phase of volume resuscitation. It is also advantageous to combine it with colloidal solutions. Glucose solutions are not suitable for volume replacement.

Colloids

Colloidal solutions represent a heterogeneous group of drugs with different compositions and effects on the volume of circulating fluid. Their disadvantage compared to crystalloids is an

increased risk of anaphylactic reactions and worsening blood coagulation abilities; therefore, it is often preferred to combine crystalloids with colloids.

According to the effect on the amount of circulating fluid, colloids can be divided into:
• Plasma **substituents** and
• Plasma **expanders** (i.e., increasing plasma volume over the volume of the administered solution).

Colloids can be divided into two groups according to their chemical structure:
• **Natural**, whose representatives are albumin solutions and
• **Synthetic**, including dextrans, gelatin derivatives, and hydroxyethyl starch.

Albumin
Albumin is currently available in an isotonic (i.e., 5%) or hypertonic (i.e., 20%) solution. Compared to the synthetic colloids, it is only used marginally, especially in conditions with manifesting hypoalbuminemia.

Dextrans
Dextrans belong to the glucans – the polysaccharide compounds composed of glucose units. Solutions of dextran molecules weighing 40 and 70 kDa are used. Nowadays, preparations with dextrans are considered obsolete due to numerous allergic reactions and the development of hemocoagulation disorders.

Gelatin derivatives
These are derived from bovine collagen, and the molecules are increased in size and weight to approximately 30 kDa. Their effect is short, and it can be prolonged by succinylation. Due to their isotonic properties, they act as plasma substitutes rather than expanders. Like dextrans, they often cause allergic reactions (i.e., 0.5-10% of the time). Their effect on blood clotting is insignificant, and rapid renal elimination results in a mild diuretic effect.

Hydroxyethyl starch
This is a widely variable group in terms of substance structure, molecule size, and the concentration in solutions used. These properties have a fundamental influence on their pharmacodynamic effects as well as their pharmacokinetic properties. In the body, the molecules are progressively hydrolysed, and their size gradually decreases until they are eliminated by the kidney through glomerular filtration. In the Czech Republic, hypertonic and isotonic solutions with a mean molecular size (i.e., 130 kDa) are used, characterised by a good safety profile and a minimum duration of action of six hours. Anaphylactic reactions are rare; there is a minimal influence of hemostasis, and the influence on renal function is comparable to gelatin derivatives. The application of hydroxyethyl starch leads to an increase in the α amylase concentrations in plasma, which can be misinterpreted as a pancreatic disease.

13.2.2 Blood substitutes

Blood transfusions or blood derivative administration is indicated for shock states with blood loss greater than 30%. The blood may be administered whole or as different blood fractions depending on the desired effect.

Erythrocyte concentrates

Erythrocytes are applied in haemorrhagic shock to achieve adequate haemoglobin levels. The whole conserved blood may be used after a patient's blood type has been previously determined, or a blood type of O Rh negative can be administered. In vital indications, the whole blood can also be given. The erythrocyte mass in standard or leukocyte-poor preparations can be administered in shock as well as anaemic conditions.

Plasma derivatives

Fresh, frozen plasma is indicated for conditions involving deficiency of coagulation factors or plasma proteins and for supplementation of blood volume and is the agent used most often in these scenarios.

13.2.3 Inotropics and vasodilatation

If there is no increase in arterial blood pressure and the restoration of diuresis after the use of volume replacements, application of an inotropic follows. Inotropics may only be given after a previous volume addition. Otherwise, blood pressure in the central arteries increases, but the microcirculation in the peripheral tissues deteriorates. It is also necessary to solve hypoxemia, tachyarrhythmia, and eventual mineral disruption prior to inotropic application. Because of the different mechanisms of action leading to the different final effects on the cardiovascular system, inotropics can be divided into sympathomimetics, phosphodiesterase III (PDE III) inhibitors, and calcium sensitisers.

Sympathomimetics

This therapy is usually started with an infusion of **dopamine** at a dose of 0.5-1 mg/kg/min (up to 4 mg/mL/kg). At this dose, dopamine acts positively inotropic and is used to protect the splanchnic area; due to the stimulation of dopaminergic D1 and D2 receptors, the vasodilation of renal vessels is induced. In moderate doses (i.e., up to 10 mg/mL/kg), dopamine is particularly effective at activating the adrenergic β1 receptors increasing the inotropic effect. Another dose increase leads to vasoconstriction due to activation of the α1 receptors.

If the patient does not respond to dopamine treatment, it can be replaced with **noradrenaline** at a dose of 2-4 mg/kg/min or in case of septic shock, **adrenaline**, at a dose of 0.01-0.02 mg/kg/min can be substituted. Adrenaline at higher doses causes peripheral vasoconstriction, including decreased kidney perfusion.

In cardiogenic shock and in patients with low cardiac output, a synthetic dopamine analogue with a non-selective betasympatomimetic effect, **dobutamine**, given at a dose of 2.5-10 mg/kg/min, is added to the dopamine. It increases myocardial inotropy and induces a mild arterial dilatation without affecting the heart rate via β2 receptors. A similar substance with predominant β2 and D1 mimetic effects is **dopexamine**.

Sympathomimetic therapy should be terminated if it is not accompanied by an increase in diuresis, a decrease in lactic acid concentration in arterial blood, and the improving mental state of the patient.

Inhibitors of PDE III

By blocking phosphodiesterase, the degradation of cAMP is reduced. An elevated level of cAMP results in the activation of calcium channels and the input of calcium into the cell. **Milrinone** is used for patients with cardiogenic shock resistant to catecholamine therapy. It has a positive inotropic and vasodilatory effect with minimal influence on heart rate.

Calcium sensitisers

Like the PDE III inhibitors, **levosimendan** is a drug of choice in case of inadequate patient response to catecholamines. Its mechanism of action is to increase the sensitivity of contractile proteins to calcium, specifically the calcium-dependent binding of levosimendan to troponin C. Besides the positive inotropic effect, levosimendan also acts as a vasodilator.

Vasodilators

Vasodilators are applied similarly to the sympathomimetics after previous circulating fluid supplementation. They are mainly used for cardiogenic shock, wherein the reduction in preload and afterload decreases oxygen consumption in the heart. Another target group is patients whose vasoconstriction persists after correction of blood pressure values. In particular, **nitroglycerin** and **isosorbide dinitrate** are used. For more information on Nitrates, see Chapter 5.5 Direct-acting vasodilators.

13.3 Pharmacotherapy for pre-hospital care in patients with polytrauma

Polytrauma is a simultaneous injury of two or more organ systems, at least one of which directly endangering the patient's life. It is the most common cause of death for those in their 40s, and the most common cause of the trauma is a car accident involving head, chest, and abdominal injuries. After checking vital functions at the accident site, the transport of injured patient to hospital follows. Pre-hospital care for a polytraumatised patient in the emergency phase is performed using standard procedures or so-called "protocols of trauma" (for example, the Advanced Trauma Life Support (ATLS)).

Shock therapy

Shock therapy occurs concurrently with urgent cardiopulmonary resuscitation. Due to the polytraumatic injury, patients are endangered by the consequences of traumatic, haemorrhagic, and related hypovolemic shock. In the patients with circulatory stability, the application of crystalloids at a dose of at least 10 mL/kg/hr is recommended after the exclusion of cavity injury. A 2000 mL mixture of colloids and crystalloids in a ratio of 1:1 for blood loss is recommended. For burns, a ratio of 1:2 colloids to crystalloids, given as a rapid intravenous infusion, is recommended. In case blood pressure responds inadequately to the administration of volume substitutions, vasopressors are administered.

Analgesia

In the case of **critical hypotension**, **ketamine** is a drug of choice (slow intravenous bolus 20-40 mg). It is a dissociated anaesthetic with a strong analgesic effect on somatic, but not visceral, pain. Unlike opioids, it does not depress the respiratory centre and, in comparison

with other anaesthetic drugs, does not adversely affect hemodynamics. The duration of bolus administration of this dose is approximately 30-45 minutes. Ketamine may also be used for the analgosedation of paediatric patients. A major adverse effect is the hallucinogenic effect, which can be prevented through combination with benzodiazepines. Alternatively, ketamine may be administered transcutaneously or intranasally in a double dose rather than via intravenous administration to maintain the duration of the effect.

In other cases, when hypotension of the injured patient is non-critical, fractional opioid analgesics, such as **fentanyl** (e.g., 0.05-0.1 mg i.v.) or **sufentanil** (e.g., 0.01 mg i.v.), are administered.

The onset of action after intravenous administration of fentanyl is three to four minutes and has an effective duration of approximately 30 minutes. In comparison to other opioids, it is less hypnotic. A significant complication of fentanyl administration is accumulation of the drug, potentially causing respiratory centre depression after the repeated administration. Sufentanil is seven to 10 times more potent than ketamine; it has a faster onset of action, but a shorter duration of action. The effects of both substances can be antagonised by administering **naloxone.**

Sedation

Principally, benzodiazepines are used to induce sedation in a polytrauma patient (see Section 3.1 Psychopharmacology). They are applied by titration intravenously or intramuscularly. Their effect is not only sedative/hypnotic, but also, they have anticonvulsant, anxiolytic, and slightly myorelaxant effects.

Diazepam is given at the dose of 2.5 to 20 mg, which can be given rectally to paediatric patients or adults in case venous access is not possible. For short-term sedation, before intubation, or as an introduction to general anaesthesia, **midazolam** (DORMICUM), at 2.5-10 mg can be used. It has alternative routes of administration like ketamine, which are transbuccal and intranasal.

Corticoids

Concentrated single dose or short-term, high-dose glucocorticoid therapy is indicated in shock states not responding to standard therapy, acid aspiration, or for inhalation trauma. Due to their immunosuppressive effects, glucocorticoids are used to prevent the development of anaphylactic and toxic shock. For single use, **methylprednisolone** (SOLU-MEDROL) is administered at a dose of 30 mg/kg as a short intravenous infusion.

Antioxidants

Development of an ischemic state is associated with shock. Further, ischemic-reperfusion injury or systemic inflammatory response are conditions that lead to the production of free radicals and increased consumption of endogenous antioxidants in polytraumatic patients. Therefore, it is appropriate to simultaneously administer drugs that are important for the maintenance of basic vital functions as well as antioxidant substances to the injured patients, which can relieve the damage that develops due to the polytrauma and improve the prognosis of the injured patient. Most frequently, **ascorbic acid** is administered intravenously at a dose of 1500 mg.

14 Radiopharmaceuticals and radiocontrast agents

14.1 Radiopharmaceuticals

Radiopharmaceuticals (or medicinal radiocompounds) are unique medicinal formulations containing radioisotopes used in major clinical areas for diagnosis and/or therapy. The main methodological principle of nuclear medicine is the detection of ionizing radiation originating from radioactive conversion of radionuclides using specialised detection devices.

Radiopharmaceuticals consist of a **radionuclide** (i.e., the source of radiation itself) and a suitable **vehicle** selected for its pharmacokinetic properties. Radionuclides are artificially prepared, most having been synthesised in radionuclide generators, accelerators, or in nuclear reactors.

14.1.1 Classification of radiopharmaceuticals

When radiopharmaceuticals are used for **therapeutic application**, the carrier compound provides transportation to the desired site, and the radionuclide provides **target tissue exposure to radiation**. Generally, the purpose is to destroy cancerous tissue (e.g., application of iodine-131 for the thyroid gland, which is applied orally and absorbed specifically by the thyroid cells) or relieve pain (e.g., Strontium-89 and Samarium-153 in patients with bone metastases).

Diagnostic radiopharmaceuticals (also called **radiotracers**) are used for **non-invasive *in vivo* monitoring** of biological phenomena. Radioactive labelling for drug distribution visualisation, positron emission tomography (PET), or single photon emission computerised tomography (SPECT) are common practices. The radionuclide (as a radiotracer) is bound to a carrier via a chelating agent. Properties of the carrier guarantee transport to the target site where the radiotracer is supposed to act. A lyophilised mixture of a vehicle and additives (often prepared in the form of a kit) is mixed with the radionuclide solution to form the final radiopharmaceutical in the dosage form suitable for application.

The **route of administration** is also important. The **parenteral** route is most commonly used (i.e., intravenous, subcutaneous, or intraluminal). It is possible to administer these preparations **orally** in the form of an aqueous solution or gelatine capsules. If required, **inhalation** of gas or mist is an option, as well. **Locally** applied radiopharmaceuticals are preferred for targeted tumour therapy.

According to the **labelling** and production method, the following radiopharmaceuticals are enumerated:

- Long-term nuclides: Samarium-153 (^{153}Sm), Iodine-131 (^{131}I), Strontioum-89 (^{89}Sr);
- Medium-term nuclides: Rubidium-82 (^{82}Rb), Gallium-68 (^{68}Ga); and
- Short-term nuclides: Flourine-18 (^{18}F), Carbon-11 (^{11}C), Nitrogen-13 (^{13}N), Oxygen-15 (^{15}O).

14.1.2 Diagnostic radionuclides (radiotracers)

Technetium-99m (⁹⁹ᵐTc) is typically used for scintillation assays. The letter, "m", refers to the metastable state of the nucleus, which, at a higher energy level, emits γ photons during de-excitation. The half-life of this nuclide is approximately six hours. This relatively short radiation exposure after application is one of the main benefits for diagnostic practice (and also the very limitation for its application therapeutically). The short half-life also allows administration of a "stronger" dose with higher activity in order to achieve better exam results.

Gallium-67 (⁶⁷Ga), as a citrate, is used for tumour testing and to localise areas of inflammation (i.e., so-called gallium scan). Another advantage is particularly high uptake by hepatocellular carcinoma, lymphomas, malignant melanoma, and soft-tissue sarcomas.

Iodine-131 (¹³¹I), despite being the longest used isotope in practice, is being gradually displaced by technetium (⁹⁹ᵐTc). Radioiodine is a mixed β and γ emitter, which is still widely applied for the treatment of differentiated thyroid carcinoma (due to the high iodine uptake capacity of the thyroid) and thrombus identification. A dosimetrically detectable γ radiation component serves as a tracking signal in the therapy of thyroid disease and metastases location. However, for diagnostic examinations, only **iodine-123 (¹²³I)** and **iodine-125 (¹²⁵I)** isotopes (for a better ratio of β and γ radiation) are preferred. Likewise, these isotopes are preferable for the labelling of monoclonal antibodies (¹²⁵I-MoAb).

Flourine-18 (¹⁸F) is a **positron (β) emitter**. However, as a stand-alone drug, its great disadvantages are a short half-life (i.e., approximately 110 min), high energy annihilation radiation, and high requirements for protection from radiation. Instead, **fludeoxyglucose (¹⁸FDG)** is the primary radiopharmaceutical used in positron emission tomography (PET). ¹⁸FDG is a glucose molecule in which one oxygen atom is replaced with an isotope of fluorine-18 and is transported and phosphorylated as classical glucose. Its advantage is high uptake by metabolically active tissues, especially pathological tissues.

The overview of the most commonly used radiopharmaceuticals is summarised in Table 10.

Table 10: Radiopharmaceuticals

Radiopharmaceuticals in SPECT		
⁹⁹ᵐTc	Technetium	broad utility spectrum
²⁰¹Tl	Thallium	myocardial imaging (i.e., perfusion)
¹³¹I	Iodine	thyroid carcinoma (i.e., radiation destruction of tissue)
⁶⁷Ga	Gallium	inflammation and tumours
¹¹¹In	Indium	leukocytes – infection/inflammation imaging
Radiopharmaceuticals in PET		
¹⁸FDG	18F-fludeoxyglucose	primary PET radiopharmaceutical
¹⁸FLT	18F-fluoro-L-thymidine	proliferation marker visualisation of organs poorly visible otherwise by FDG (brain) tumour severity assessment
¹⁸FCH	18F-fluorocholine	proliferation marker brain, lung, prostatic, and oesophageal tumours

^{18}F FET	18F-fluoroethylthyrosin	brain tumour detection (more sensitive than FDG)
^{11}C MET	11C-methionine	brain tumours
^{11}C Ac	11C-acetate	renal, pancreatic, prostatic tumours
^{18}F NaF	18F-sodium fluoride	localisation of primary bone tumours and metastases
Other radionuclides		
^{57}Co	Cobalt	vitamin B12 resorption screening
^{59}Fe	Iron	haematology
^{51}Cr	Chromium	survivability of erythrocytes human plasma albumin labelling
^{42}K, ^{22}Na, ^{24}Na, ^{82}Br	Potassium, Sodium, Bromine	plasma ions
^{85}Sr	Strontium	palliative care in bone malignancies
^{11}C, ^{13}C	Carbon	V/Q lung scan (i.e., ventilation/perfusion scintigraphic lung scan) urea breath test
^{45}Ca	Calcium	bone metabolism screening
^{32}P	Phosphorus	radiolabelled DNA and RNA probes for Northern and Southern blots

14.2 Radiocontrast agents

Contrast agents (i.e., media), used for X-rays, are substances that increase imaging contrast, thereby improving image quality and resolution. Positive contrast media, due to their high atomic number, increase radiation absorption, so they appear in the image as more radiopaque (i.e., "dark spots"). Negative contrast media, of low density, decreases radiation absorption, so their appearance in the image is more radiolucent (i.e., "bright spots").

There are various possibilities for routes of administration: administration via physiological orifices (e.g., GIT, bile ducts, peritoneal cavity), pathological orifices (e.g., fistula), systemic administration (e.g., intravenous, intra-arterial), or into the spinal canal.

14.2.1 Positive contrast media

The basic positive contrast agents include **barium compounds** (i.e., barium sulfate (**BaSO$_4$**)). The white suspension of barium sulphate is most commonly used to visualise the digestive tract. Due to the very nature of the suspensions, specifically their tendency to sediment, the preparation should be thoroughly stirred and homogenised prior to application (even RMP). However, this insoluble salt can cause many complications, such as constipation, diarrhoea,

abdominal pain, and rarely, appendicitis. The possible occurrence of barium stones may result in complete bowel obstruction.

14.2.1.1 Water-insoluble

Iodine contrast agents in a carrier oil have proven to be useful for lymphography and chemoembolisation. Ethyl-iodised poppy oil is also available as an RMP (e.g., Lipiodol Ultra-Fluide).

14.2.1.2 Water-soluble

Aqueous contrast media can be divided according to the route of excretion. **Hepatotropic** agents are excreted via the liver (i.e., with bile); thus, they are convenient for use in cholangiography and are given intravenously to reduce the risk of side effects. **Nephrotropic** agents are excreted via kidneys. An ideal nephrotropic contrast medium would not affect physiological functions, could be rapidly renally eliminated, and allow for intensive contrast. They are classified as high-osmolar (e.g., ioxitalamic acid) and low-osmolar (e.g., iohexol, iopamidol, iopromide, ioversol, iodixanol, iomeprol, iobitridol). They are mainly used for angiography, urography, and as a CT contrast agent. Of the side effects, nausea, vomiting, and feeling overheated are most common.

14.2.2 Negative contrast media

Negative media that reduce radiation absorption are all **gases** (e.g., **oxygen**, **air**, **carbon dioxide**, **nitrous oxide**). Often, they are applied for colon distention, and their administration does not induce significant complications. **Methylcellulose** and **mannitol** are administered per os and are not absorbed in the digestive tract. To the contrary, they absorb what water remains in the intestine, so transient diarrhoea after administration is enabled.

14.2.3 Contraindications and side effects

Contrast agents are not suitable for children under 15 years of age. There is also a risk of iodine allergy (for iodine contrast agents), asthma, eczema, and drug allergy. In 2% of patients, delayed response (e.g., fever, nausea, joint pain) 1-7 hours after application can occur and then spontaneously subside. For pregnant women, consideration should be given with regard to the risks/benefits of application as contrast agents are able to pass into foetal circulation. Nursing women are advised to avoid breastfeeding until at least 24 hours after administration. Contraindications also include renal and cardiac insufficiency and severe DM (e.g., caution must be taken especially when given perorally in conjunction with the antidiabetic metformin!).

The most serious complication is **contrast medium-induced nephropathy (CMIN)**, which can cause acute renal failure necessitating hospitalisation and haemodialysis. The kidneys may be safely protected by nephroprotective agents, such as acetylcysteine or a sodium bicarbonate infusion.

14.2.4 Application of radiocontrast agents

Prior to administration, thorough education of the patient is necessary. The patient should not eat at least four hours before the procedure, but adequate water intake is required. Informed consent is needed, and allergic anamnesis, urea, and creatinine levels should be closely monitored.

After administration, the patient is observed for 30 minutes with vein access kept in place in case of emergency. Steady, sufficient hydration should be secured for 24 hours (i.e., at least half a litre of water before the procedure and half litre after or eventually an infusion should be administered) following the procedure.

15 Phytopharmacology

15.1 Introduction to phytopharmacology

The use of herbs, animals, their by-products, and minerals is as old as mankind. The first written evidence of healing with natural products can be found in almost all ancient civilisations including Mesopotamia, Egypt, India, Greece, Rome, and China. Well-known Ebers papyrus, dated to approximately 1600 BC, contains hundreds of natural remedies including instructions for their preparation. Ancient natural healing was strongly related to religion; therefore, signs of shamanism (i.e., magical ceremonies and formulas) can be found in the description of remedies.

Natural healing by laymen (i.e., not provided by priests) developed primarily in Greece, and around 400 BC, **Hippocrates** became the most well-known layperson representative. In about 300 BC, the author of first herbariums and famous Greek botanist, **Theophrastus**, lived. **Galen**, a follower of Hippocrates, lived in ancient Rome 200 AD. He was the first to use the pharmacological terms, agonist and antagonist, which are still used today. Moreover, he designed the framework for quality management systems for remedial preparation purposes. In the same era, **Dioscorides** wrote *De materia medica*, a fundamental pharmacopoeial work summarising remedies prepared from herbs, animals, and minerals, which was used for the preparation of remedies until 17th century.

The knowledge of ancient Arabic healers and alchemists enriched European phytopharmacology with new herbs and novel laboratory and preparation techniques. In the middle ages, knowledge and healing services returned to the hands of church. That led to the deceleration of research in the field of pharmacology as the church strictly followed the works of ancient Greek medicine men.

In the Renaissance, pharmacological research is revived. First, transatlantic navigations discover new herbs for European pharmacology, and there is a development of alchemy with an increase in the number of chemical compounds. One significant person of this period is alchemist and medicine man, **Paracelsus**. The work of Dioscorides was reworked by Pietro Andrea Gregorio Mattioli in Italy, and **Mattioli's herbal**, which includes the summary of the medical properties of herbs, has been translated in many European countries.

Efforts to critically evaluate the effects of medicinal herbs and to identify compounds responsible for the biological effects prevailed over the empirical and layman's use of herbs in the 19th century. Medical herbs were gradually replaced by their active constituents and more often, with chemical drugs. This practice still endures today; however, the research of medicinal uses of herbs continues.

Ethnopharmacology is focused on, aside from other aspects of plants, herbs used as different ethnic traditional medicines. Researchers cooperate with local shamans and try to discover

new medicinal herbs and their active principles. The tropical forests of Amazonia or Africa can hide new herbal antibiotics, antidiabetics, analgesics, or chemotherapeutics.

Ayurveda – medicine typical for the Indian subcontinent as well as traditional Chinese medicine – is based on the use of a variety of herbs. Both types of Ayurvedic practices are used today as a complement to "modern" pharmacology and are subject to further research. The world of medicinal herbs and phytopharmacology is not obsolete, and many new active principles are waiting to be discovered and described.

Modern **pharmacognosy** is the science of natural (i.e., herbal, animal, and mineral) drugs used as human and veterinary medicines. General pharmacognosy examines the general principles of biosynthesis and the chemistry of natural compounds. A natural drug is a herb, animal, fungi, microbe, or their parts. All natural drugs are referred by their Latin names, and some can also be found in the Czech pharmacopoeia. Examples of the most common parts of herbs and their Latin equivalents can be found in Table 11.

Table 1: The most common parts of medicinal herbs used in therapy and their Latin equivalents.

English name	Latin name	English name	Latin name
whole plant	*Herba*	leave	*Folium*
flower	*Flos*	fruit	*Fructus*
root	*Radix*	rootstock	*Rhizoma*
bark	*Cortex*	seed	*Semen*
tuber	*Tuber*	cone	*Strobilus*

Medicinal herbs are dried and processed into different drug dosage forms. The most frequent form is different types of tea. Some teas are prepared by **macerating** herbal drugs in cold water, whereas **infusions** are made by pouring hot water overtop plant components, and **decoction** is possible by boiling the herbs in water. Syrups are prepared by the addition of sucrose to herbal water extracts. The spirituous extracts from herbs are called **tinctures**. Different types of **extracts** can be prepared using various solvents, and dry extracts are made when the solvent evaporates. Medicinal herbs or substances isolated therefrom can also be found in the form of tablets, capsules, ointments, drops, and other common drug dosage forms.

15.2 Herbal substances

Herbal drugs consist of various compounds. In addition to pharmacologically active molecules, **products of primary metabolism** (e.g., carbohydrates, simple sugars, fats, etc.) are contained in herbs. These substances can be found in all herbs and have an essential physiological role in plants. **Secondary metabolites** are produced from primary metabolites and are usually species-specific. Their function in the plant is often unknown, but they are not necessary for the survival of the plant. Some secondary metabolites can be used in pharmacology and are the subject of study in human toxicology.

Pharmacologically active herbal substances are named herbal **active principles**. Either a single substance or a mixture of active principles can be related to the effects of herbal drugs. The content of active principles in herbal drugs varies depending on different factors, such as geographical location, growing season, process of drying, grade of disintegration, storage conditions, etc.

Herbal substances can be classified according to their biological origin into the following classes:

- Carbohydrates,
- Polyketides,
- Alkaloids,
- Shikimates, and
- Mevalonates (terpenoids).

15.2.1 Carbohydrates

Different carbohydrates are produced in primary versus secondary pathway metabolism in plants. The most common monosaccharides, such as glucose, fructose, mannose, and galactose, are primary metabolites and can represent the sugar moiety of secondary metabolite glycosides. Examples of **specific monosaccharides** synthesised in plants are digitalose, digitoxose, and oleandrose. These saccharides contain an acetyl, methyl, or amino group in their molecule and are part of glycosides.
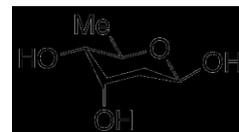
digitoxose

Plants can produce various polysaccharides (e.g., inulin, pectins, gums, and mucilages) beyond the most common cellulose and starches. **Pectins** are formed by α-D-galacturonic acid monomers. Pectins are used in the food industry (e.g., as emulsifiers, thickeners, etc.) and can be used therapeutically for constipation and diarrhoea. They create a hydrated layer on intestinal mucosa through a nonspecific mode of action, which prevents contact of the mucosa with intestinal content. This mechanism lubricates and protects the intestinal mucosa.

Mucilages are polysaccharides similar in their osmotic properties to pectins. They can also form protective hydrated layers over mucosal surfaces. Drugs with mucilaginous content are plantain leaves (*Plantago lanceolata*), flax seed (linen seed, *Linum usitatissimum*), and hollyhock root (*Althaea officinalis*). These can be used as expectorants, antitussives, laxatives, and to protect the inflamed mucosa of the oral cavity and nasopharynx.

15.2.2 Polyketides

Polyketides are compounds whose biosynthesis is based on acetyl coenzyme A. Fatty acids present in seeds (e.g., plant oils) and on the surface of fruits (e.g., waxes) are some of them. Other examples of polyketides are anthraquinones, dianthrones, and anthracyclines, from which many molecules are used therapeutically as laxatives or chemotherapeutics.

Macrolides and tetracyclines are frequently used antibiotics, which have a polyketide structure produced by moulds.

Cannabinoids, some of the active substances in cannabis (*Cannabis sativa* L.), are polyketides, too. Tetrahydrocannabinol (THC) is a psychoactive cannabinoid with muscle-relaxing properties and cannabidiol (CBD) acts as an anticonvulsant.

Other examples of polyketides are **lichen acids** (e.g., cetraric acid, protocetraric acid, ursolic acid, etc.). They possess antibacterial activity, and the extract from Iceland moss (*Cetraria islandica*) is a part of preparations against oral cavity infections.
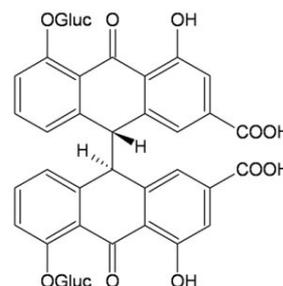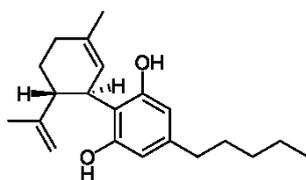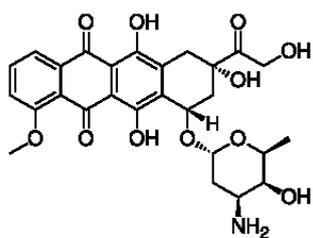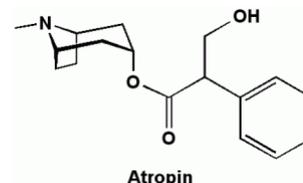

doxorubicin
(anthracycline chemotherapeutic) �archosid (dianthrone, active compound of the laxative, senna)

15.2.3 Alkaloids

The name, alkaloids, describes the character of these compounds – all are natural compounds of alkaline nature. Most also possess a bitter taste. **True alkaloids** are natural compounds derived from amino acids, which contain a basic nitrogen in the form of heterocyclic ring. Other molecules with a basic nitrogen in the molecule, but which are not derived from amino acids, are called **pseudoalkaloids**. Conversely, those with the nitrogen from an amino acid, but not in the typical heterocyclic ring formation, are termed **protoalkaloids**. Alkaloids can be further subclassified with respect to their chemical structure into molecules with tropane, isoquinoline, indole, pyridine, purine, steroid, or terpenic structures. More than 15,000 alkaloids have been identified to date. Therefore, the following review gives only some examples of alkaloids with significant toxicological or pharmacological importance.

Tropane alkaloids

These molecules are derived from ornithine and are present mainly in herbs of the Solanaceae (nightshades) and Erythroxylaceae (coca) families. Parasympatholytic agents, **atropine**, **hyoscyamine**, and **scopolamine**, are alkaloids from deadly nightshade (*Atropa belladonna*), black henbane (*Hyoscyamus niger*), and jimsonweed (*Datura stramonium*). **Cocaine**, found in leaves of the coca plant (*Erythroxylum coca*), was used as a local anaesthetic agent, for example, in ophthalmology. Today, it is no longer used therapeutically, and it is a subject of abuse.

Isoquinoline alkaloids

These alkaloids are derived from phenylalanine and tyrosine. Well-known isoquinoline alkaloids are opioids from opium, such as **morphine** and **codeine**. Morphine is a strong analgesic, whereas codeine has weaker analgesic effects and antitussive activity. Both substances cause constipation and are drugs that are abused. Papaverine, with musculotropic and antispasmodic effects, is a constituent of opium, too.

Another isoquinoline alkaloid is **tubocurarine**, a dimer compound isolated from Amazonian Indian arrow poison. The poison is prepared from the climbing shrub, *Strychnos toxifera*, and used for hunting. Tubocurarine has strong muscle relaxant properties.


morphine
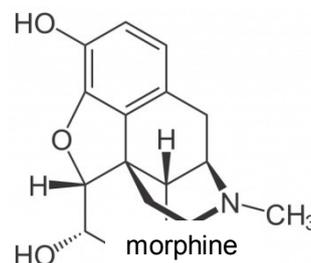
Emetine from the root of ipecacuanha (*Cephaelis ipecacuanha*) is a strong irritant of the vagus nerve and induces emesis. Formerly, it was used as an expectorant and appetite stimulator in low doses.

Indole alkaloids

Alkaloids derived from tryptophan are called indole alkaloids. **Physostigmine**, with a parasympathomimetic effect, is used for the therapy of glaucoma, and its analogues (e.g., pyridostigmine, distigmine, and others) are used to treat myasthenia gravis. It is isolated from the climbing herb, the Calabar bean (*Physostigma venenosum*).
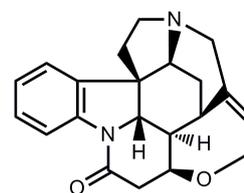

strychnine

Strychnine, a well-known poison from the books of Agatha Christie, is isolated from the strychnine tree (*Strychnos nux-vomica*). It evokes strong muscle contractions and victims die from suffocation.

Important pharmacological activity is known to occur with the use of *Vinca* **alkaloids**, which are isolated from lesser periwinkle (*Vinca minor*). Vincristine and vinblastine are effective chemotherapeutics used for the chemotherapy of solid and haematologic tumours. Vinpocetine is alkaloid with vasodilating activity mostly in the CNS. It is used to increase cerebral perfusion and metabolism after head injuries, stroke, or in neurovascular diseases.

Ergot alkaloids are a special group among other indole alkaloids. They are isolated from ergot fungus (*Claviceps purpurea*), parasitic fungi which grow on different cereals. Intoxications with symptoms of gangrene due to vasoconstriction or hallucinations with convulsions have been described from past use. In the Middle Ages, intoxication was known as "Saint Anthony's fire". It was thought that some of the affected persons might have been bewitched. It is postulated that due to this popular notion, epidemics of ergotism may have been the reason for witch trials in the past. The research of ergot alkaloids led to the development of many drugs including: **methylergometrine**, used as an uterotonic agent in gynaecology, **ergotamine**, **dihydroergotoxine**, used for the therapy of migraines, and other dihydroergotamine derivatives with vasodilating properties.
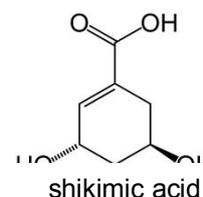
Diethylamide of lysergic acid (LSD) and other derivatives of lysergic acid are hallucinogens that are misused.
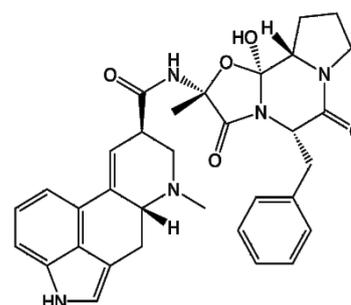
ergometrine

15.2.4 Shikimates

Shikimic acid is a biosynthetic precursor for most herbal molecules with an aromatic ring in their structure. Coumarins, flavonoids, and tannins are the most important shikimates.

shikimic acid

15.2.4.1 Coumarins

Coumarins, lactones of cinnamic acid, can be found, for example, in yellow sweet clover (*Melilotus officinalis*) or sweet-scented bedstraw (*Galium odoratum*). Sweet clover is responsible for cattle intoxication. Flowering herb and fermented hay containing sweet clover contain high amounts of **coumarin**, which can be transformed to **dicoumarol** by microbes. In both animals and humans, dicoumarol inhibits the synthesis of prothrombin and other factors in the coagulation cascade. The symptoms of intoxication are bleeding, haematomas, etc. Its mode of action is competitive antagonism of vitamin K.
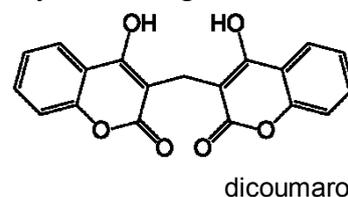
dicoumarol

Today, the safer drug, **warfarin**, has replaced dicoumarol. Coumarin is a fragrant substance also used in cosmetics. **Furanocoumarins**, **derivatives of coumarin**, are found in rue (*Ruta graveolens*) and hogweed (*Heracleum spp.*). They can cause skin irritation and contact dermatitis if skin is exposed to direct sunlight.

15.2.4.2 Flavonoids

Polyphenolic substances with various biological activities are members of the flavonoids. The activity of flavonoids is determined by their structure, mainly according to the position and number of hydroxyl groups and sugars. Many flavonoids possess antioxidant activity and are used to improve the condition of vascular endothelium. They decrease the permeability and fragility of capillaries, thus preventing oedema and bleeding. Natural flavonoids and their semi-synthetic derivatives are used to treat venous insufficiency, varices, haemorrhoids, and lymphedema.

Rutoside (**rutin**) is isolated from the Japanese pagoda tree (*Sophora japonica*) for pharmaceutical use. It is also present in food like buckwheat, asparagus, and different fruits (e.g., apple, peach, plum, tomatoes, etc.). It is used orally in combination with ascorbic acid for diseases causing increased fragility of capillaries, haemorrhoids, vitamin C deficiency, after injuries, and for oedema.

rutoside
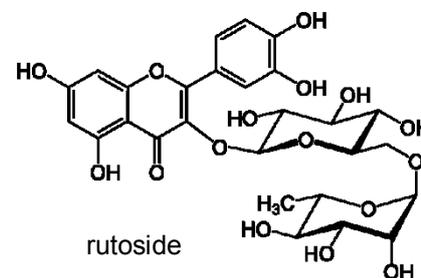
Similar indications require use of its semi-synthetic analogue, **troxerutin**. Products with both rutin and troxerutin are available OTC.

Another preparation containing a micronised mixture of **hesperidin**, **diosmin**, and **other flavonoids** is a prescription-only medicine (POM) and is used for the therapy of venous

insufficiency and lymphedema. There are many herbs rich in flavonoid content (e.g., quercetin, quercetin, naringenin, and luteolin) including birch leaves (*Betula pendula*), haw (*Crataegus spp.*), the flowers and fruits of elder (*Sambucus nigra*), and flowers of the lime tree (*Tilia cordata*). Citrus fruit, grapes, tea, and other foods can contain significant amounts of flavonoids, too.

15.2.4.3 Tannins

Tannins are polyphenolic compounds comprised of gallic acid subunits, which are derived from flavones (i.e., subgroup of flavonoids). They all possess astringent activity, which means that they coagulate proteins. They are mostly contained in the roots, bark, and leaves and are an herbal barrier against infections.

gallic acid
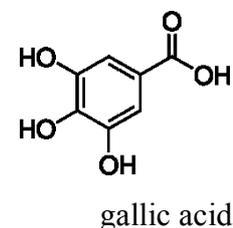
Tannins are used therapeutically as **local astringents** and **hemostyptics** to treat haemorrhoids, skin injuries, and lesions of the oral mucosa (e.g., aphthous stomatitis). Some substances can be administered orally for anti-diarrhoeal purposes. The mode of their anti-diarrhoeal effect is through coagulation of the protein layer on the surface of intestinal mucosa to block contact between chyme and the intestinal wall.

Tinctures prepared from **oak apples** (galla), herb of **agrimony** (*Agrimonia eupatoria*), or **cinquefoils** (*Potentilla spp.*), and **oak bark** (*Quercus spp.*) are used topically for their astringent effect. These preparations contain mostly catechins.

Leaves of **blackberry** (*Rubus fruticosus*), **raspberry** (*Rubus idaeus*), and **strawberry** (*Fragaria vesca*) are for oral use, and the leaves and dried fruits of **blueberry** (*Vaccinium myrtillus*), which contain hydrolysable tannins, have weaker effect. **Black tea**, which is rich in tannins, has an anti-diarrhoeal effect, too.

15.2.5 Mevalonates

Derivatives of the mevalonic acid are called mevalonates or terpenes. Five-carbon chains comprise the basic subunits that create the foundation for the structure of these molecules. An overview of terpenes regarding the number of C5 units they contain is shown in Table 2.

Table 2: Classification of terpenoids

Name	Number of C5	Example
Hemiterpenes	1	Ergot alkaloids, humulone, and lupulone
Monoterpenes	2	Essential oils (e.g., menthol, camphor, geraniol, etc.)
Sesquiterpenes	3	Essential oils (e.g., azulenes, bisabolene, etc.) and bittering agents
Diterpenes	4	Essential oils, resins, vitamin A, E, aconitine, and chlorophyll
Triterpenes	6	Phytosterols, cardioactive glycosides, and saponins
Tetraterpenes	8	Carotenoids
Polyterpenes	n	Natural rubber

The smaller terpenes are quite volatile; thus, they are prepared by distillation. These terpenes are typical components of essential oils and fragrances often used as herbal medicines. They can also have antiseptic, spasmolytic, antiphlogistic, and other effects. Essential oils are present in many herbs; for example, the essential oil of **chamomile** (*Matricaria chamomilla*) is used as a drug with an antiphlogistic and carminative effects. **Mint** (*Mentha × piperita*) is another herb with carminative activity and is used as a cholagogue, too.

Caraway seeds (*Carum carvi*) and **fennel** (*Foeniculum vulgare*) can be used as carminatives and spasmolytics in paediatric care.
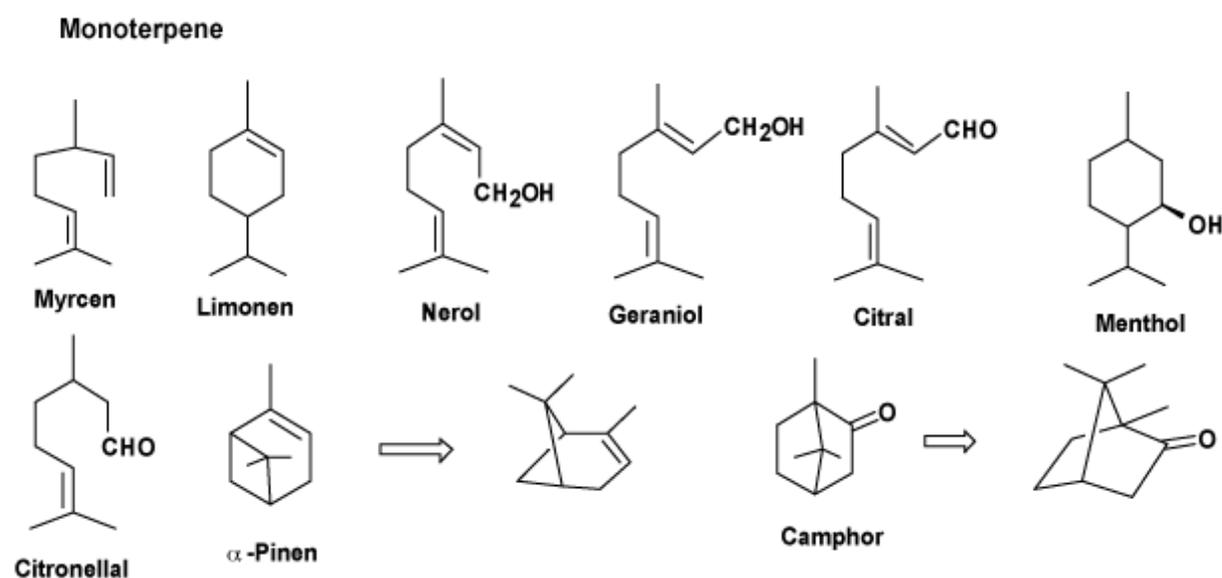

Figure 1: Examples of monoterpenes.

Other examples of drugs rich in essential oils, specifically ones which are used for the therapy of rhinitis, are oils from **pine** (*Pinus spp.*), **eucalyptus** (*Eucalyptus globulus* – blue gum tree), and **wild thyme** (*Thymus serpyllum*). They have secretomotor and antiseptic properties and are present in some nasal drop formulations.

From the triterpenes, the most therapeutically relevant are **saponins**. These substances are natural surfactants and produce soap-like foaming when shaken (*sapo* – Latin for soap). Naturally, they are present in plants in the form of glycosides. They are used as **expectorants** and **diuretics**; their mode of action works through weak irritation of the GIT, upper respiratory tract (i.e., makes mucus less viscous), and kidneys (i.e., increases diuresis).

The root of **liquorice** (*Glycyrrhiza glabra*), **cowslip** primrose (*Primula veris*), and **common ivy** (*Hedera helix*) are used to treat productive cough and inflammation of nasopharynx and/or paranasal cavities. The flower of **mullein** (*Verbascum phlomoides*) has weaker effects. Extracts from cowslip and ivy are components of ready-made

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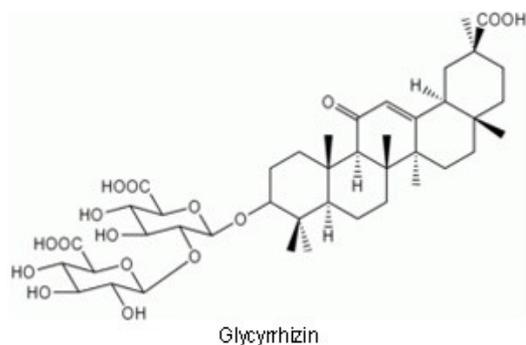
medical preparations (e.g., tablets, syrups, and oral drops).

Other important triterpenes are **cardioactive glycosides**. Their structure includes a cyclopentanoperhydrophenanthrene (sterane) nucleus with a lactone ring with monosaccharide substitutions. Those compounds possess **cardiotonic activity** by blocking Na^+/K^+-ATPase activity in myocardial cells. Dysregulation of intracellular sodium levels leads to an increase in intracellular calcium, and the power of contraction increases, too.

Today, most of the herbs containing cardioactive glycosides are only of toxicological significance. **Lily of the valley** (*Convallaria majalis*), **pheasant's eye** (*Adonis vernalis*), **oleander** (*Nerium oleander*), and **foxglove** (*Digitalis purpurea*) are examples of such herbs. **Woolly foxglove** (*Digitalis lanata*) is the only herb used as a source of lanatoside C, a substrate used for the synthesis of **digoxin**.

lanatoside C
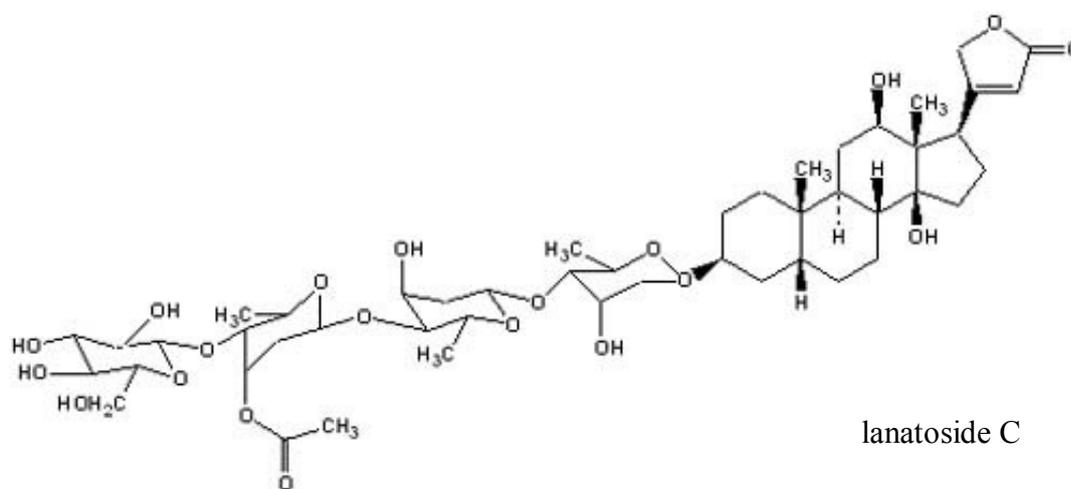
15.3 Self-treatment of selected diseases with phytotherapy

Many of common illnesses can be treated by patients themselves through **self-treatment**. The use of phytotherapy for self-treatment has been increasing recently. Information about the use of herbs for the therapy is tied to many myths and fables, and there are many confusing and sometimes false informational resources regarding herbal therapeutic use found on freely available databases and sources. The most significant trend in laic patients is the rejection of "synthetic" drugs. Medicinal plants contain many substances considered "synthetic" drug xenobiotics with regard to the human body, as has been described previously. At this juncture, it is not possible to determine whether phytotherapy is superior to the use of "classical", "synthetic" drugs. Likewise, it cannot be concluded that use of herbal drugs is related to a decreased risk of adverse reactions. Furthermore, the risk of interactions with co-administered drugs should be carefully evaluated.

Therefore, **herbal medicines are neither harmless nor omnipotent**, and their use should follow the same rules as apply to any other type of self-therapy:

- The herbal medicine should be selected with respect to the knowledge of active constituents or upon recommendation from a specialist,

- the patient informational leaflet should be read carefully and instructions followed for use of the preparation, and

- the patient's physician or pharmacist should be contacted in case of any problems occurring.

A review of medicinal herbs used for self-treatment and their active constituents are given in Table *3*.

Table 3: Summary of medicinal herbs for self-therapy and their main active constituents

Symptoms	Drug	Medicinal herb	Components	Note
Mild psychiatric distress (nervousness, short-term insomnia)	*Melissae herba* Melissa	*Melissa officinalis* Lemon balm	Essential oils: citronellal, neral, geraniol, linalool, caryophyllene, etc.	
	Passiflorae herba Passion flower	*Passiflora incarnata* L. Purple passionflower	Alkaloids: harmane, harmine; flavonoids	
	Humuli strobilus Hop cone	*Humulus lupulus* Common hop	Essential oils: myrcene, farnesene; bitter acids: humulone, lupulone	
	Hyperici herba St. John's wort	*Hypericum perforatum* St John's wort	Naftodianthrone hypericin; hyperforin, flavonoids	CYP3A4 induction
	Valerianae radix Valerian root	*Valeriana officinalis* Garden valerian	Essential oils "valepotriates": valtrate, isovaltrate; GABA, flavonoids	Smell attracts cats
Dry cough, xerostomy	*Althaeae radix* Marshmallow root	*Althaea officinalis* Common marshmallow	Mucilages, pectin	Leaf can be collected
	Farfarae folium Coltsfoot leaf	*Tussilago farfara* Coltsfoot	Mucilages, flavonoids, triterpenic substances	Flower can be collected
	Plantaginis folium Ribwort plantain	*Plantago lanceolata* English plantain	Mucilages, aucubin	Has antiphlogistic activity
	Malvae flos	*Malva spp.*	Mucilages,	

	Mallow flower	g. *Mallow*	anthocyanins	
Productive cough, cold, sinusitis	*Liquiritiae radix* Liquorice root	*Glycyrrhiza glabra* L. Liquorice	Saponins, flavonoids	Also, used as a sweetener
	Primulae radix Primula root	*Primula veris* Common cowslip	Saponins	
	Verbasci flos Mullein flower	*Verbascum phlomoides* L. Woolly mullein	Saponins, mucilages, flavonoids, aucubin	
	Hederae herba Ivy leaf	*Hedera helix* Common ivy	Saponins	
	Thymi herba Thyme	*Thymus vulgaris* Common thyme	Essential oils: thymol, carvacrol, cineol, etc.	
	Serpylli herba Wild thyme	*Thymus serpyllum* Wild thyme	Essential oils: thymol, carvacrol, citral, linalool, etc.	
	Eucalypti aetheroleum Eucalyptus oil	*Eucalyptus globulus* Tasmanian bluegum	Essential oils: eucalyptol, pinenes, phellandrene, cymene, etc.	Has antiseptic activity
	Pini aetheroleum Pine silvetris oil	*Pinus spp.* g. Pine	Essential oils: bornyl acetate, pinenes, phellandrene, etc.	Has antiseptic activity
Urinary tract infections, dysuria	*Urticae herba* Nettle leaf	*Urtica dioica* Common nettle	Minerals, flavonoids, organic acids, acetylcholine, tannins, silicic acid	Diuretic effect
	Betulae folium Birch leaf	*Betula pendula* Silver birch	Saponins, flavonoids	Diuretic effect
	Ononidis radix Restharrow root	*Ononis spinosa* Spiny restharrow	Saponins, flavonoids, essential oils	Diuretic and antiseptic effects
	Equiseti herba Equisetum stem	*Equisetum arvense* Field horsetail	Saponins, flavonoids, silicic acid	Diuretic effect
	Uvae ursi folium Bearberry leaf	*Arctostaphylos uva-ursi* Kinnikinnick/Bear berry	Arbutin, triterpenic acids	Antiseptic effect
	Vaccinium vitis-	*Vaccinium vitis-*	Proanthocyanidins	Blocks bacterial

	idaea fructus Cranberry	*idaea* Lingonberry	, organic acids	adhesion to the urinary tract walls
	Solidaginis herba Goldenrod	*Solidago virgaurea* *European goldenrod*	Saponins, flavonoids, essential oils	Diuretic and antiseptic effects
Flatulence, meteorism	*Menthae herba* Peppermint leaf	*Mentha × piperita* Peppermint	Essential oils: menthol, piperitone, pinenes, etc.	Spasmolytic, cholagogue
	Matricariae flos Matricaria flower	*Matricaria chamomilla* Chamomile	Essential oils: azulenes, bisabolol; flavonoids	Spasmolytic, antiphlogistic
	Foeniculi fructus Fennel, bitter	*Foeniculum vulgare* Fennel	Essential oils: fenchone, limonene, 4-anisaldehyde, trans-anethole, etc.	Also, used in paediatry
Digestive problems (insufficient gastric activity)	*Zingiberis rhizoma* Ginger	*Zingiber officinale* Ginger	Essential oils: zingiberene, gingerol, bisabolene; zingerone, etc.	Stomachic agent, antiemetic, choleretic
	Gentianae radix Gentian root	*Gentiana lutea* Great yellow gentian	Bittering agents, tannins, pectin	Amarum
	Absinthii herba Wormwood	*Artemisia absinthium* Absinthe	Bittering agents, essential oils: thujone, thujol	Amarum; thujone is a neurotoxin and teratogen
	Cinnamomi cortex Cinnamon	*Cinnamomum zeylanicum* Ceylon cinnamon	Essential oils: cinnamon aldehyde, eugenol, pinenes, phellandrene	Stomachic agent, taste and smell enhancer
Digestive problems (insufficient activity of gall bladder)	*Menthae herba* Peppermint leaf	*Mentha × piperita* Peppermint	Essential oils: menthol, piperitone, pinenes, etc.	Spasmolytic, cholagogue
	Curcumae rhizoma Turmeric, javanese	*Curcuma xanthorrhiza* Temulawak	Curcumin, essential oils	Cholagogue, antiseptic
	Cynarae folium Artichoke leaf	*Cynara scolymus* Artichoke	Cynarine, organic acids	
Liver	*Cardui mariae*	*Silybum marianum*	"Sylimarin" –	Cholagogue,

disease	*fructus* Milk thistle seed	Milk thistle	mixture of flavonolignans and flavonoids	hepatoprotective agent
Diarrhoea	*Rubi fruticosi folium* Blackberry leaf	*Rubus fruticosus* European blackberry	Hydrolysable gallotannins	
	Rubi idaei folium Raspberry leaf	*Rubus idaeus* European raspberry	Hydrolysable gallotannins	
	Fragariae folium Strawberry leaf	*Fragaria vesca* Wild strawberry	Hydrolysable gallotannins	
	Myrtilli folium et fructus siccus Blueberry leaf and fruit	*Vaccinium myrtillus* European blueberry	Tannins	
	Theae folium Tea, general	*Camellia sinensis* Chamomile tea	Catechin tannins	
	Tormentillae rhizoma Tormentil	*Potentilla erecta* Common tormentil	Catechin tannins	
Obstipation	*Psyllii semen* Psyllium seed	*Plantago ovata/psyllium* Blond plantain/ psyllium	Indigestible swelling polysaccharides, mucilages, aucubin	Volume laxative
	Lini semen Linseed	*Linum usitatissimum* Common flax	Mucilages, oils, fresh fruit contains cyanogenic glucoside, linamarin	
	Sennae fructus, folium Senna pods and leaf	*Cassia angustifolia* Alexandrian senna	Dianthrones sennosides, flavonoids, mucilages	Irritating laxative, fruits have weaker effect
	Aloe Aloe	*Aloe spp.* g. Aloe	Aloin and aloinosides (A and B)	Irritating laxative
	Rhei radix Rhubarb	*Rheum palmatum* Chinese rhubarb	Rhoeo anther glycosides, pectin, oxalic acid	Low doses antidiarrheal effect, higher doses irritating laxative

15.4 Interactions of phytotherapeutics with co-administered drugs

Active components of herbal drugs are subject to the same biological processes as other xenobiotics. They are absorbed, distributed, biotransformed, and excreted. Pharmacokinetic interactions with co-administered drugs are possible during all these steps. Simultaneously, herbal drugs possess their own biological activity; pharmacodynamic interactions of their active components with co-administered drugs are known, too. The most problematic herbs, in the terms of drug-drug interactions, are St. John's wort, ginkgo, and garlic.

St. John's wort (*Hyperici herba*, see Table 3) is used for its mild hypnosedative, anxiolytic, and antidepressant effects. One mode of action of St. John's wort is increasing serotonin levels. Therefore, many of its **pharmacodynamic interactions** are based on the **potentiation of the serotonergic drugs** as well as increasing levels or effects of serotonin at synapses. Its combination with SSRIs, MAOIs, and other antidepressants can evoke serotonin syndrome (e.g., headache, agitation, confusion, hallucinations, tremor, sweating, hypertension, tachycardia, and vomiting); this adverse reaction is classified as serious and can be lethal. Active components of St. John's wort, hypericin and hyperforin, are **inducers** of the liver enzyme, **CYP3A4**. Therefore, those substances can decrease plasma levels of co-administered drugs, which are substrates of this enzyme.

Ginkgo leaves (*Ginkgo folium*) are used for their vasodilating effect induced by a complex of active constituents, namely **flavonoids** and **ginkgolides**. Likewise, they are used for cerebral and extremity perfusion disorders, in vestibular disorders and tinnitus, and frequently, in geriatrics. Ginkgolides are strong **inhibitors of PAF** (platelet activating factor) and can potentiate the effect of anticoagulants and antiplatelet drugs. Cases of serious bleeding were documented when combined with warfarin.

Garlic (powder prepared from cloves, *Allii sativi bulbus pulveratum*) is used for its immunostimulant, antimicrobial, and anthelmintic effects in the GIT. It is recommended to treat hypertension and atherosclerosis in traditional medicine. It was proven that garlic mildly decreases LDL cholesterol, blood pressure, and activates NO synthase. Its active constituents are essential oils, **allicin** and **ajoene**, which influence thrombocyte aggregation, the binding of fibrinogen on activated thrombocytes, and the production of the prothrombotic, thromboxane A_2. Use of garlic carries a risk of potentiating anticoagulant and antiplatelet drug effects.

Ginseng (*Panax ginseng*) is another example of an herb interacting with co-administered drugs. Its roots are a component of preparations used in geriatrics. The active components are triterpene **ginsenosides**, which act as mild immunostimulants and improve cognition. Cases of a serious decrease in the plasma levels of **warfarin** and **oral antidiabetics** were documented when combined with ginseng. The mechanisms of these interactions have been the subject of recent research.

Eastern purple coneflower (*Echinacea purpurea*) is an herb used as an **immunostimulator**. It contains a combination of sesquiterpenic alcohols, tannins, and essential oils, which are responsible for its effects. From a pharmacodynamic point of view, it should not be combined

with **immunosuppressives** due to possible antagonism. High doses are **hepatotoxic** and should not be used chronically or in combination with other hepatotoxic drugs. Coneflower extract **inhibits CYP3A4**; therefore, it can increase the plasma levels of its substrates.

Herbal drugs with mucilage content, which are used as antitussives and expectorants (e.g., marshmallow root, mallow flower), produce a hydrated layer over the mucosa of the GIT, which can decrease absorption of co-administered drugs. These medicines should neither be used at high doses nor chronically.

16 Drugs used in dentistry

16.1 Drugs used in prevention and treatment of diseases in dental hard tissues

16.1.1 Enhancement of enamel and dental resistance

Tooth decay is an infectious process that damages hard tooth tissue, which can lead to pulpitis or periodontitis. Its pathogenesis involves several factors: the condition of hard dental tissues, the presence of cariogenic bacteria, the consumption of carbohydrates and acidic foods, the level of oral hygiene, etc. In the Czech Republic, this dental condition is particularly serious in children; under five years of age, at least one tooth decay has occurred in more than 60% of children, but the adult dental condition is not otherwise satisfactory.

The consumption of acidic foods and the activity of the oral microflora reduce the pH in the mouth, and the gradual demineralisation of the enamel occurs when the critical pH value is exceeded. Proper diet and dental cleaning techniques can reduce the rate of demineralisation. Hypomineralisation of enamel is generally accompanied by a lack of **Ca**, **P**, **Mg**, and **vitamins D**, **C**, and **A**, which can be expected under the following circumstances: inadequate diet, GIT disease, some endocrine diseases, some medications, etc.

The most effective means of enamel remineralisation is **fluoride** intake/application (F-):

• From diet and water,
• Systemically using drugs, and
• Locally using dental hygiene and special dentistry techniques.

Fluorides have an affinity for the hydroxyapatite of hard tooth tissues forming fluorohydroxyapatite, which is more resistant in low pH conditions. Historically, the fluoridation of water or milk has made a significant impact regarding healthy teeth in populations that have been closely studied. For example, in the 1950s, drinking water fluoridation was introduced in the town of Tábor, and the incidence of tooth decay was reduced by 80% as compared to the control city. Only fluoridated salt is available in the Czech Republic, fluoride water and milk are not widely used.

Sodium fluoride tablets containing 0.25 mg of F- are used for systemic supplementation. These products are currently available OTC. The tablets dissolve in the mouth (in this case, the local effect is also significant), or they are ingested with plenty of water. Fluorides are absorbed in the duodenum and distributed to, among other places, the saliva, which then has the local effect of promoting enamel remineralisation. Fluorides are excreted via the kidneys.

Systemic tablet supplementation is only indicated individually due to the consideration of fluoride intake via other routes (e.g., drinking water, toothpaste swallowing in children, etc.). The optimal preventative dose of F- is 0.04-0.07 mg/kg/day. High intake for a long time can lead to **fluorosis of the enamel**, which is the appearance of differently stained areas on the surface of teeth, but this is merely a cosmetic effect. These stains are highly resistant to tooth decay. Typically, higher fluoride intake can cause **bone fluorosis**; this involves the remodelling of bone structure, a worsening of the mineralisation of bone mass, and an increased the risk of fractures, for instance, at the femoral neck. Although fluorine supplementation initially activates osteoblasts and reduces the ability of osteoclasts to decompose bone mass, the pathological conversion and manifestations of osteomalacia gradually occur. Therefore, the dose of fluoride administration should always be considered.

Fluoridated toothpastes appeared for the first time in the 1970s, and their use has rapidly expanded. They contain **sodium fluoride**, **stannous fluoride**, **sodium monofluorophosphate**, or **amine fluoride**. The concentration in toothpaste for children (i.e., from two years old and up) and adults is different. Fluoridated toothpaste is not recommended for use on first-cut teeth in infancy or for toddlers. For pre-school and elementary school-aged children, the necessity of adult supervision of dental care is always required to prevent toothpaste swallowing and to demonstrate correct cleaning techniques.
Stannous fluoride reduces short-term proliferation of oral microflora, making it suitable for use in periodontal disease. Some mouthwashes are also fluoridated. Applications for highly concentrated fluoride products exist primarily for use in special dentistry treatments or dental hygiene procedures (e.g., remineralising gels, lacquers, etc.).

16.1.2 Dental desensitisation

By grinding the enamel and revealing the dentin layer, intraoral stimuli such as changes in temperature, pH, etc. may cause significant pain in patients. The status of dentin hypersensitivity is generally poorly therapeutically viable. Sometimes it helps to remineralise the enamel by local application of **fluorides**.
If a cement layer in the teeth is removed and such an action induces significant pain, **adhesives** or **fillers** suitable for the dental cervix (neck) can be applied. The protein content of dentin tubules can be coagulated through topical application of solutions of **zinc chloride** or **tannin**.

There is also a product containing **arginine** and **calcium carbonate**, which, by means of the binding of arginine to dentin, helps to transport calcium carbonate into dentin tubules to form a stuffing. The efficacy of commonly available potassium-containing toothpastes (generally referred to as toothpaste for sensitive teeth) remains controversial.

Laser dentine treatment is a modern method that requires some time for testing and optimisation. The laser dries the dentine layer and produces a non-porous layer. However, it is known that unwanted microsprays can be generated in the dentin layer through the action of a laser with an improperly high energy or pulse duration.

16.1.3 Treatment of dental pulp and root canals

Extensive carious lesions endanger the pulp of the affected tooth. If the lesions do not penetrate the tooth, the drilled tooth is treated with **calcium hydroxide**, which has antiseptic effects as well as dentinoplastic effects; meaning, it promotes formation of the tertiary dentin layer and remineralisation of the site. After that, the filler is made. In case of major affection and pulp inflammation, the procedure is performed with local anaesthesia, during which the pulp is amputated and extirpated.

An alternative procedure (e.g., for paediatric dentistry, acute emergency treatment) is the chemical devitalisation of the pulp by local application of **formaldehyde**, local anaesthetics, and Cayenne silica (contains antiseptically and locally aesthetically active eugenol). After 14 days, a new treatment with devitalised pulp extirpation is recommended.

Long-term pulp inflammation may result in its devitalisation. Generally, the cause of the infection originates as a carious lesion that continues penetration inward into the tooth. Infections can spread through the coronary and root parts and affect the surrounding bone. Often, an inflammatory vesicle is formed around the affected tooth, which can also be a source of systemic infection. The aim of the so-called endodontic treatment is to maintain the devitalised tooth, to remove infectious matter and necrotic tissue, and to close the root with filler material.

Powerful **antiseptics** are used to reliably kill microorganisms present in dental channels (e.g., **chloramine**, **sodium hypochlorite**, **peracetic acid**, **hydrogen peroxide**, and **calcium hydroxide**). For more details, see Chapter 9.1 Disinfectants and antiseptics. Local ozone applications can also be used. The advantage of these treatments is the necrotic tissue (proteins) coagulates, which allows for it to be suctioned off.

Mechanical fillings (e.g., gutta-percha pins with sealers aka sealants, epoxy resins, and glass ionomer cements), combined with **antiseptics** (e.g., zinc oxide, eugenol, and calcium hydroxide) or **anti-inflammatory substances** (e.g., salicylates), are used to fill the cleaned channels.

16.2 Drugs used to treat oral mucosal and periodontal disease

Depending on the type of disease, anti-inflammatory drugs, astringents, local anaesthetics, antibiotics, antiviral drugs, antifungals, or immunomodulators are used to treat lesions of the oral cavity and periodontium. The use of **herbal medicine** (see below) is also popular and effective. Formulations suitable for oral cavity treatment include mouthwash solutions, oral sprays, ointments, adhesive pastes, and gels.

An alternative to, for example, antifungal drugs, is the use of a **vaginal tablet** that adheres to the mucous membrane of the mouth (i.e., this use is off-label and outside the approved indication).

Adhesive dosage forms are very often **gels** - colloidal systems formed by gel-forming agents, such as cellulose derivatives (e.g., carboxymethylcellulose) or polyacrylate.

Protein-depleted **blood plasma extract** with low-molecular peptides, amino acids, and nucleic acids also have adhesive properties; they form a long-lasting coating on the mucous membrane of the mouth.

Table 14 presents an overview of the pharmacotherapy of selected diseases of the oral cavity and periodontium.

Table 14: Pharmacotherapy of selected diseases of the oral cavity and periodontium

Disease	Drug Class	Drugs	Drug Dosage Forms	Note
Chronic gingivitis	Antiseptics	Chlorhexidine, benzydamine and others	Sprays, solutions for rinsing and spreading, lozenges (pastilles)	
	Astringents	Aluminium acetate-tartrate, tannin	Aqueous or glycerol solutions for rinsing and spreading	
Periodontitis	Antiseptics	Chlorhexidine and others	Sprays, solutions for rinsing and spreading, lozenges	
	Antibiotics and chemotherapeutics	Metronidazole, spiramycin, amoxicillin	Oral tablets, capsules	To manage acute exacerbation
Acute necrotising ulcerative gingivitis	Antiseptics	Hydrogen peroxide, hexetidine, chlorhexidine, iodophors	Sprays, solutions for rinsing and manual spreading, lozenges	
	Antibiotics and chemotherapeutics	Metronidazole, clindamycin, doxycycline, macrolides	Oral tablets, capsules	As a more difficult treatment course to support local therapy
Recurrent aphthous stomatitis (mouth sores)	Antiseptics	Chlorhexidine, benzydamine, hexetidine	Sprays, solutions for rinsing and manual spreading, lozenges	
		Gentian violet	Solution for manual spreading	Used in paediatrics, but

			slightly obsolete
	Anti-inflammatory drugs, analgesics	Choline salicylate	Gel	
	Local anaesthetics	Lidocaine	Gel	
Herpetic gingivo-stomatitis	Antiseptics	Carbetopendecinium bromide	Spray, solution	Application of other antiseptics is painful
	Antivirals	Aciclovir	Oral tablets	As a more difficult course, recurrences
	Adjuvants	B-complex, vitamin C	Oral tablets	
Herpes labialis	Antivirals	Aciclovir, penciclovir, tromantadine, docosanol	Ointment	Frequent application (every two hours)
Oral candidiasis	Antifungal drugs	Clotrimazole, itraconazole	Vaginal tablets, rinse solutions	
	Antiseptics	Chlorhexidine, benzydamine, hexetidine, sodium tetraborate, gentian violet	Sprays, solutions for rinsing and manual spreading, lozenges	
Lichen planus	Anti-inflammatory drugs, immune-suppressants	Dexamethasone	Solution for manual spreading	
	Adjuvants	B vitamin complex and vitamins C, D, A	Oral tablets, capsules	
Angular cheilitis	Antifungal drugs	Nystatin, natamycin, econazole, clotrimazole	Ointment	
	Antibiotics	Mupirocin, neomycin + bacitracin	Ointment	
	Adjuvants	Riboflavin or B-complex vitamins	Oral tablets	
Post-extraction alveolitis	To clean dental alveoli	Sterile saline solution		
	Antiseptics	Hydrogen peroxide	Solution for rinsing and manual spreading	

16.3 Drugs used in salivary disorders

Saliva within the oral cavity serves an indispensable function; it aids in digesting and grinding food, buffering the oral cavity, remineralising the enamel, repairing soft tissues in the mouth, maintaining the balance of oral microflora, and fulfilling an immune function (e.g., it contains lysozyme, cytokines, defensins, etc.).

Increased saliva secretion

Hypersalivation (ptyalism) is present during mechanical irritation of the oral cavity during dental examination and treatment. In addition, it can accompany oral cavity injury, some CNS diseases, and occurs concurrently with heavy metal poisoning. Problems with swallowing saliva are seen in patients with mobility disorders, such as myasthenia gravis or Parkinson's disease. Increased secretion may also be caused by certain drugs, such as parasympathomimetic pilocarpine, acetylcholinesterase inhibitors, iodides, etc.

Ptyalism can be treated by oral administration of the parasympatholytic, **atropine**, which suppresses gland secretion.

Decreased saliva secretion

Hyposalivation is the cause of xerostomia. Dry mucosa and tongue are susceptible to infections, injuries, increased risk of caries, and food intake is also more difficult.

Xerostomia often occurs in seniors due to dehydration, metabolic diseases (e.g., diabetes, hypothyroidism), and certain vitamin deficiencies; it is also typical in Sjörgen's autoimmune syndrome.
Iatrogenic hyposalivation develops after therapeutic head and neck irradiation in oncology or from drug use (e.g., tricyclic antidepressants, parasympatholytics, sympathomimetics, first generation H1 antihistamines, diuretics, sedatives, antipsychotics, opioid analgesics, etc.).

Therapeutic solutions include the use of toothpastes, mouthwashes, sprays, gels, and chewing gums containing **salivary enzymes** (e.g., lysozyme, lactoperoxidase), **immunoglobulins**, and **peptides**, and mucosal moisturising aids.

Saliva substitutes, like **artificial saliva**, are formed through the combination of a salt solution (e.g., KCl, NaCl, $MgCl_2$, $CaCl_2$, Na_2HPO_4, NaF) with carboxymethylcellulose (i.e., a gel-forming agent) and are used several times a day to rinse the mouth. The possibility of systemic administration of parasympathomimetics, such as **pilocarpine** or **cevimeline**, should also be considered. Cevimeline is registered abroad for use in patients with Sjörgen's syndrome. The undesirable effects of parasympathomimetics are sweating and acceleration of GIT peristalsis with diarrhoea and nausea.

16.4 Herbal therapy in dentistry

In dentistry, medicinal plants are mainly used for their anti-inflammatory, antimicrobial, analgesic, astringent, and locally anaesthetic effects. They can be used to rinse the oral cavity, for mucosal lesions, and to treat root canals.

Drug dosage forms

Vegetable-based drugs may be used in dentistry either unprocessed (less common) or formulated into drug dosage forms. The most common herbs used are tea blends, which are fragmented drugs designed to prepare macerations, decoctions, and creams - see Chapter 15.1 Introduction to phytopharmacology. In addition, alcoholic tinctures and extracts are often used; these can be formulated into aerosols (i.e., sprays for the oral mucosa), gels used to massage into gums, or ointments.[2]

Plant extracts are often added to toothpastes and mouthwashes to inhibit the formation of dental plaque, reduce gingivitis, prevent gum bleeding, and reduce tartar production.

The effective substances

The most important components of herbal drugs used in dentistry are flavonoids, essential oils, tannins, coumarins, iridoid glycosides, triterpenes, carotenoids, vitamins, and minerals. For more details on these groups, see Chapter 15.2. Herbal substances.

Some **flavonoids** may act as antibiotics (i.e., by blocking bacterial cell division), anti-inflammatory agents, or anti-oedematous compounds.

Essential oils are effective mucosal and skin antiseptics; they act against viruses, bacteria, yeasts, fungi, and protozoa. Their significant feature is that, unlike synthetic antibiotics, microorganisms cannot create resistance. **Eugenol**, **carvacrol**, and **thymol** have the most powerful effects in this regard. Eugenol and thymol, for their strong antibacterial and slightly anaesthetic action, are used to treat dental cancers during the treatment of dental necrosis.

Tannins can form insoluble compounds with proteins, and they have an astringent effect; hence, they are able to accelerate wound healing as well as act in a haemostyptic manner (i.e., stop minor bleeding). This can be used, for example, to accelerate healing of mouth sores or lesions on the gums. For more detailed information on herbal pharmaceuticals in dentistry, see Table 15.

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[2] In some Third World countries (e.g., Kenya, Tanzania), the local inhabitants chew extracts called Miswaki. This natural "toothbrush" is the only form of dental hygiene in many regions. It has been shown that some of the ingredients in these Chewing sticks (Miswak in English) have the ability to prevent gingivitis and tooth decay.

Table 15: Medicinal plants and their use in dentistry

Medicinal plant and its part used	Active substances	Effects of plant	Use in dentistry
Chamomile flower (*Matricaria chamomilla*)	Essential oils, flavonoids	Anti-inflammatory	Oral cavity rinse for wound healing, inflammation treatment, chemically irritated or burned areas
Arnica montana (flower)	Essential oils, flavonoids, sesquiterpenic lactones	Anti-inflammatory, analgesic, increases blood supply to tissues, antiseptic	Oral cavity rinse, relieves inflammation, improves wound healing (not to be used internally!)
Salvia officinalis (leaf)	Essential oils, antibacterial flavonoid, carnosol, tannins	Anti-inflammatory, antiseptic, astringent	Infusion for rinsing of oral cavity and throat, gargle, extracts (Florsalmin®) for manual spreading, or after dilution for rinsing
Galls on *Quercus robur* L.	Tannins	Astringent	Tincture for rinsing and manually spreading on gums (see above)
Krameria root (*K. argentea* + *K. lappacea*)	Tannins	Astringent	Tincture for rinsing and spreading on gums (see above)
Myroxylon (Peruvian balm)	Phenolic acids, terpenes	Antiseptic, granulation	Treatment of complications after tooth extraction (rare)
Calendula officinalis, marigold (flower)	Essential oils, flavonoids, carotenoids, tannins	Anti-inflammatory	Rinsing of the oral cavity, improved healing after surgery, and inflammation
Garlic (onion)	Essential oils (alliin)	Antiseptic	Chewing of raw garlic for five minutes sterilises the oral cavity; garlic tincture can be given for infections of the oral cavity
Gum arabic (*Acacia senegal, syn. Senegalia senegal*, resin)	Salts (e.g., Ca^+, Mg^2+, K^+) of polysaccharides, cyanogenic glycosides, enzymes	Remineralising, antiseptic	Enhancing enamel remineralisation (i.e., due to high Ca^{2+} salt of polysaccharides) and inhibition of dental plaque formation
Melaleuca alternifolia (tea tree oil)	Essential oils (cineol)	Antiseptic	Spreading on infectious lesions in the oral cavity, one of the strongest natural

			antiseptics and disinfectants
Commiphora myrrha (gum myrrh)	Essential oils (eugenol)	Anti-inflammatory, antiseptic, locally anaesthetic	Tincture for manual spreading or rinsing (after dilution)
Syzygium aromaticum - cloves (flower bud)	Essential oils (eugenol)	Anti-inflammatory, antiseptic, locally anaesthetic	Tincture for rinsing and spreading manually on gums

17 Ophthalmologic drugs[3]

17.1 Antimicrobial substances

Infectious and non-infectious inflammations may attack different parts of the eye, hence their classification to conjunctivitis (conjunctiva inflammation), iridocyclitis (inflammation of the iris and the ciliated column), blepharitis (inflammation of eyelids), keratitis (cornea inflammation), otitis (iris inflammation), vitritis (vitreous body inflammation), chorioretinitis (inflammation of the chorioid and the retina), neuroretinitis (ocular nerve inflammation) etc.

Substances used in eye infection therapy can be divided to antibiotic and chemotherapeutic categories, virostatics, antimycotics and non-specific antiseptics. In vast majority of cases local administration in the form of eye drops, ointments, gels, eye inserts or sub-conjunctiva injections is preferred to systemic administration, especially for the sake of achievement of high local concentration of the drug with minimised adverse effects.

A particular medicament selection depends on the infection originator; the originator is often typical of the infection localisation – for example keratitis is mostly caused by *Staphylococcus aureus et epidermidis, Streptococcus pneumonieae, Pseudomonas aeruginosa* and *Proteus*, or adenoviruses and *Herpes simplex virus*. In lighter cases the drug is chosen empirically on the basis of clinical image of the infection. In more severe cases a swab is analysed and targeted drug selection is performed.

Antibiotics and chemotherapeutics

Antibiotics used for bacterial infection therapy include aminoglycoside antibiotics and fluorinated 2nd generation quinolones. For severe cases more antibiotics are combined in a preparation for spectrum extension. In the case of inflammations with allergic component antibiotics are sometimes also combined with glucocorticoids.

The most often used aminoglycoside drugs include **tobramycin, gentamycin, kanamycin and neomycin** (the latter in combination with bacitracin), or fluorinated quinolones **ofloxacin, levofloxacin and mofloxacin**. **Sulfacetamide** of sulfonamide group or **chloramphenicol** are used less often. **Dexamethasone** or **betamethasone** are used in combination with glucocorticoids (in combination with aminoglycoside drugs or chloramphenicol).

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[3] Note: This chapter summarises specific of pharmacotherapy in ophthalmology; most of the drugs are also used for other indications, though. Mechanisms of action, adverse effects and other specifics are summarised in the relevant chapters (antibiotics, chemotherapy drugs, glucocorticoids, non-steroid antiphlogistics, local anaesthetics).

Virostatics

Viral infections are most often caused by adenoviruses and herpetic viruses. Virostatics used most frequently for their treatment are administered locally (**aciclovir, ganciclovir**), or for immune reaction and cornea vascularisation attenuation corticoids are sometimes added after antivirotic therapy; however, premature corticoid administration may damage the cornea. A new approach is represented by application of vaccines against HSV 1 and 2, which prevent irreversible changes, although they cannot prevent the infection.

Antimycotics

Mycotic infections of the eye are mostly caused by *Aspergullus* and *Candida*. The administered antimycotics include older **amphotericin B, nystatin, natamycin** and newer azole antimycotics such as **ketoconazole, clotrimazole, fluconazole, itraconazole, or voriconazole)**.

Antiparasitics

Toxoplasama gondii is the most common eye tissue parasite. Therapies include some products not authorised for use in the Czech Republic (ILPL production in pharmacies or individual import) – **propamidine isethionate** or antiseptic **chlorhexidine** in combination with systemic **itraconazole** therapy.

Antiseptics

These substances are intended for eye infection prevention rather than therapy (for example after contact with a foreign object, swimming in dirty water etc.). The reason is that antiseptic preparations show insufficient bactericidal effect and in the case of already progressing (bacterial, viral or parasitic) infection only delay effective therapy. The substances used include **1.7% boric acid, benzododecinium bromide** and **carbethopendecinium bromide.**

17.2 Anti-inflammatory, anti-allergic and immunosuppressive drugs

Anti-inflammatory therapy in ophthalmology is used for addressing non-infectious inflammations (most often uveitis), allergic inflammations (conjunctivities, blepharitis) and in some case of infectious inflammations for suppression of pathologic immune reactions, prevention of synechia, or neovascularisation of eye tissues.

Anti-inflammatory and at the same time immunosuppressive therapy is represented by local administration of corticoids in the form of eye drops and ointments – the drugs used include **dexamethasone, hydrocortisone, cortisone, prednisolone**. Where anti-inflammatory corticoid therapy is not responded to there the next options include systemic glucocorticoids followed by systemic immunosuppressive therapy (**cyclosporin, azathioprin, methotrexate**).

Non-steroid antiphlogistics (**indomethacin, nepafenac, diclofenac**) are used in ophthalmology for attenuation of post-operative pain and prevention of inflammations and inflammatory complications and also for peri-operative suppression of miosis.

Allergic inflammation mostly results in bilateral reddening, burning or itching sensation, sometimes even in the wider eye area. Typical treatment of allergic inflammations includes local antihistaminic drugs - **antazoline**, **ketotifen**, sometimes in combination with sympathomimetics – **tetryzoline.**

Antihistaminic drugs used in ophthalmology include for example **levocabastine, antazoline, epinastine** as a substance with combined effect on H_1 receptors (antagonist) and α1 receptors (agonist).

Mastocyte stabilisers - **cromoglycate** (Cromohexal) or **olopatadine** – substances with antihistamine (H_1) effect at the same time acting as mastocyte stabilisers – may be administered against seasonal – for example pollen – allergies.

17.3 Substances for treatment of ocular vascular disorders

Targeted therapy has penetrated into many areas, including ophthalmology, in the past decade. In ophthalmology targeted therapy is mainly applied against **age-related macular degeneration** (AMD) and recently also against other eye disorders resulting from **neovascularisation**, such as in the case of diabetic retinopathy, diabetic macular oedema, occlusion of the central retina vein and neovascularisation glaucoma. Uncontrolled neovascularisation related to these diseases may irreversibly damage the eye and result in blindness.

Age-related macular degeneration (AMD) is the main cause of vision loss in senior population in developed countries.

- Dry form of AMD os characterised by continuous loss of central acuity with peripheral vision preserved.

- Wet form of AMD represented by mere 10 % of AMD cases is responsible for up to 90 % cases of vision loss. This form is connected with new vessel overgrowing into the space between the pigment epithelium of the retina and the light-sensing uvulas or scotopic cells, followed by sub-retinal bleeding, swell and scarring in the macular area (the acuity area of the retina).

Effective pharmacological treatment of the wet form of AMD did not exist before introduction of biological therapy. Substantial improvement was only brought by medicines attenuating vascular proliferation, i.e. substances acting **against the vascular endothelial growth factor (VEGF),** supporting uncontrolled neovascularisation connected with this disease. This factor takes four main forms, A, B, C and D. The ophthalmology-relevant VEGF-A exists in four isoforms with different numbers of amino acids: VEGF121, VEGF165, VEGF189 and VEGF206.

Pathological growth of new vascular formations is mainly caused by VEGF165. VEGF165 selectively stimulates endothelial cell growth and vascular leak. Intravitreal administration of drugs against VEGF stabilises the quickly progressing disease and even improves acuity. This disease would progress rapidly without this therapy and would lead to vision loss.

Drugs used:

Aflibercept (Eylea) is a fully human receptor fusion protein, composed of parts of VEGF-receptors 1 and 2, and human FcIgG, up-taking VEGF-A and placental growth factor (PlGF).

Ranibizumab (Lucentis) is a fragment of humanised monoclonal antibody against VEGF-A.

Pegaptanib (Macugen) is an oligonucleotide binding to and inactivating VEGF165.

Bevacizumab (Avastin) – a VEGF ligand preventing its binding to its receptors and new vessel generation. Bevacizumab is not currently authorised for AMD indication (only authorised for treatment of colorectal and breast carcinomas) and thus is used in the "off-label" manner for AMD treatment.

Vortepofin (Visudyne), administered by systemic infusion, damages biological structures within the scope of the diffusion area, following laser activation, leading to local vessel occlusion, cell damage and necrosis under certain conditions. In the Czech Republic this photodynamic therapy is not available at the moment.

Wider use of drugs against VEGF is so far prevented by their high price.

17.4 Anti-glaucoma and miotic drugs

Glaucoma is an ocular disease with unclear etiology, more often affecting women (66 %) than men, usually after 40th year of life. The common feature of most glaucoma types is increased intraocular pressure. This symptom is not present in all glaucoma types, though, but represents one of the major risk factors. Intraocular pressure is the cause of eye damage in the case of congenital glaucoma, chronic closed angle glaucoma and other secondary glaucoma types. Normal tension glaucoma (NTG) is the cause of 1/3-1/2 open angle glaucoma cases. Glaucoma is the second most frequent cause of vision loss globally.

Glaucoma therapy is above all aimed at prevention of ocular nerve damage, reduction of intraocular pressure and minimisation of complications and side effects of the therapy. Acute glaucoma attacks require immediate assistance of an ophthalmologist.

Anti-glaucoma drugs, with the only exception of acetazolamide, are only administered **locally** in the form of eye drops, or rarely ointments. According to the principal therapeutic effect they may be categorised as follows:

- Substances **reducing production** of intraocular fluid

- Substances **affecting outflow** of intraocular fluid
- Substances with **osmotic** effect – hyperosmotics

17.4.1. Substances reducing production of intraocular fluid

Carboanhydrase inhibitors

Ophthalmology uses as active agent **acetazolamide** (systemically!) and further locally administered derivates not used elsewhere such as **dorzolamide** and **brinzolamide**.

Beta adrenerg receptor blockers – beta blockers

Substances used in this area include above all **timolol** *(non-selective without ISA),* **betaxolol** *(beta 1 selective, without ISA),* **carteolol** *(non-selective with ISA).* These substances (above all *timolol*) are often combined with active agents of other groups – most often with carboanhydrase inhibitors or prostaglandins.

Non-selective and selective sympathomimetics

Out of this rather broad spectrum of medicaments glaucoma therapy uses **brimonidine**. Therapy of neovascular glaucoma also uses a stabilised form of **adrenalin** in drops prepared rarely as an IPLP compound.

17.4.2 Substances affecting outflow of intraocular fluid

Parasympathomimetics (miotics)

Miotic drugs, substances formerly used for open angle glaucoma treatment, reduce intraocular pressure by narrowing the pupil and thus improving intraocular fluid outflow through the trabecular tissue. They are substances of parasympathomimetic group. Parasympathomimetics reduce intraocular pressure well, but on the other side reduce acuity and worsen vision in darkness (by narrowing the pupil). Patients taking Miotic drugs should not drive. They are not often used for glaucoma treatment and the main reason for their administration is miosis before intraocular surgery. Parasympathomimetics available in the Czech Republic include **carbachol or pilocarpine** as HVLP product, and further IPLP products with pilocarpine, or less often with **physostigmine**. Effect of pilocarpine usually manifests itself in 15 minutes and only lasts for 3 – 4 hours; pilocarpine eye gel is applied at bedtime with the effect lasting for up to 24 hours post application.

Selective sympathomimetice

Clonidine and brimonidine are α2 selective agonists. Their mechanism of action is based on reduction of intraocular fluid formation in combination with increased uveoscleral outflow.

Prostaglandins and their derivates

Prostaglandin derivates, analogues to prostaglandin F2α, are selective agonists of prostanoid receptors reducing intraocular pressure by increased outflow of intraocular fluid form the anterior eye segment. Authorised substances include **latanoprost, bimatoprost, travoprost, tafuprost.** An interesting and anecdotic adverse effect related to their long-term use is eyelash lengthening.

17.4.3 Substances with osmotic effect – hyperosmotics

Hyperosmotic substances increase plasma osmolarity, thus inducing water molecule transfer from the eye to the vessels, which significantly reduces intraocular pressure. Representatives worth mentioning include **mannitol** (for peri-operative i.v. administration) and **glycerol** (administered p.o.). These substances need systemic administration. They burden the cardiovascular system and that is why they are not often used in glaucoma therapy.

17.5 Mydriatics and cyclophlegics

These substances widen the pupil and induce transient cyclophlegia, i.e. paralysis of the ciliary muscle, preventing pupil accommodation. This is used for the purpose of the ocular fundus examination. Mydriatics and cyclophlegics may also be used for treatment of intraocular inflammations. Accommodation suppression is also beneficial in the case of iridocyclitis where accommodation is painful.

On the basis of their application these substances are classified as follows:

- **Diagnostic mydriatics** – with short effect and suitability for diagnostic interventions.

- **Therapeutic mydriatics** – with long-term effect and suitability for treatment of iridocyclitis for long-term pupil extension leading to prevention of iris-lens symphysis (fundus synechia) and for iris inflammation mitigation.

Anticholinerg drugs

Dominant drug class in this indication:

- **Therapeutic mydriatics - atropine** (HVLP) and **scopolamine** (magistraliter preparation) with 7-14 day effect

- **Diagnostic mydriatics** – those with short-term action include **tropicamide** (4-6 hr effect), **cyclopentolate** (1 day, both HVLP) and **homatropine** with up to 3-day effect (magistraliter preparation)

Anticholinerg drugs reduce tear production and may cause dry eye sensation. Other logical adverse effects include increased intraocular pressure and blurred vision. Where mydriasis induction together with cyclophlegia is not the aim sympathomimetics are used instead of anticholinerg drugs.

Sympathomimetics

Sympathomimetics applied in the eye reduce hyperaemia and induce mydriasis, not affecting intraocular pressure too much. They are mainly used for fundus examination, in eye surgery, as vasoconstringent preparations for differential diagnostics of conjunctivitis and iridocyclitis, or for disturbance of synechia in uveitis.

The ones usable include **phenylephrine, ephedrine and ibopamine**.

17.6 Other ophthalmologic drugs

17.6.1 Decongestion drugs

Calming of hyperaemic conjunctiva is done with some sympathomimetics (the same as in the case of nasal drops) – **naphazoline, tetryzoline, oxymetazoline, oxedrine**. Some eye drops containing these substances are over-the-counter drugs, however, their inappropriate application may worsen the primary cause ("red eye"); the cause must always be considered and sympathomimetics applies in justified cases only.

The effects of sympathomimetics are sometimes supported by other drugs depending on the cause of the hyperaemia – for example **esculin** reducing capillary break rate or **antazoline** – antihistaminic with anti-allergic effect.

17.6.2 Local anaesthetics

Local anaesthetics are used in ophthalmology for desensitisation before surgery or various diagnostic interferences. They may be applied locally in the form of drops (topical anaesthesia) - gels, ointments or injections (infiltration anaesthesia – retrobulbar – behind the bulb, peribulbar – with a shorter needle, or intracameral – in the anterior chamber). Retrobulbar anaesthesia is rarely used for the risk of the bulb and the ocular nerve injury. Recent about 2 decades have witnessed return towards topical anaesthesia at the expense of injection anaesthesia.

Local anaesthetics used in ophthalmology include esters **oxybuprocaine, tetracaine**, and amides **bupivacaine, lidocaine**. Other local anaesthetics used abroad include articaine.

17.6.3 Diagnostics

Fluorescein sodium salt – *Fluoresceinum natricum 1–2%* **-** HVLP and IPLP and the unofficial **Bengali red** *(Roseum bengalense natricum 2%)* are used in diagnostic procedures such as for examination of cornea disintegration with epithelium damage. Bengali red is suitable in the case of conjunctiva epithelium damage. Both substances are prescribed n the form of IPLP eye drops.

To prevent microbial contamination of aqueous solutions of the colours there are the **diagnostic filtration strips** – they are pieces of dry filtration paper saturated with diagnostic

colour (fluorescein, Bengali red, lissamine green - unofficial). The strip is then inserted in the conjunctiva and the colour is diluted by tears.

17.6.4 Tear substitution in case of dry eye syndrome

Dry eye syndrome is a complex pathophysiological term demoting one of the most common eye disorders. Dry eye syndrome means hyperosmolar or unstable tear film. Dry eye syndrome can have several causes (age-related, hormonal, immunological, pharmacological, hypo-nutritional, post-traumatic, inflammatory etc.). Accompanying symptoms include burning or tingling sensation, painful twinkling etc.

Therapy is based on non-irritant biologically compatible polymers such as **polyvinylalcohol** (PVA), **polyvinylpyrrolidone** (PVP), **hydroxypropylmethylcellulose** (HPMC), **carbomer, hyaluronic acid, xyloglucane, dexpanthenol** or their combinations.

17.6.5 Other ophthalmologic drugs

Cornea damage of various etiology is addressed by auxiliary medicinal products supporting metabolic and resorption processes in the eye. Intraocular resorption (resorption of exudate, minor bleeding etc.) is accelerated for example by isotonic solutions of inorganic iodine salts (such as the pharmacopoeia eye drops with potassium iodide - Kalii iodidi oculoguttae). Mechanism of action is apparently based on histamine release causing vasodilation. Stronger anabolic effect on cornea cells is manifested by androgens or synthetic anabolic drugs (HVLP).

Note: This chapter summarises specific of pharmacotherapy in ophthalmology; most of the drugs are also used for other indications, though. Mechanisms of action, adverse effects and other specifics are summarised in the relevant chapters (antibiotics, chemotherapy drugs, glucocorticoids, non-steroid antiphlogistics, local anaesthetics).

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