2 Botanical description

2.1 Systematics and Taxonomy

Prof. Dr. Markus Veit

The genus *Cannabis* belongs to the family *Cannabaceae* which according to current knowledge comprises ten genera – including *Humulus lupulus* (hops) as another medicinal plant genus. The taxonomic classification of *Cannabis sativa* has long been the subject of debate and differences of opinion (Clarke and Merlin 2015; McPartland and Guy 2017; Small 2015b; Small and Cronquist 1976). However, there is now a broad consensus among taxonomists to regard *Cannabis sativa* as monospecific – that is, as a species with subspecies (McPartland 2018; Small 2015a).

The great morphological and chemical diversity of *Cannabis sativa* is the result of 6000 years of selection and domestication, with different uses by humans in different geographical regions of the world. Domestication and crossbreeding took place in two directions: first, with the aim of obtaining cannabinoid-rich plants; and second, with the aim of obtaining plants that have low cannabinoid content and are well suited for fiber production or whose seeds produce a high oil yield. As a result, enormous genomic differences have arisen between the resulting plant groups (▸ Chapter 3.4; van Bakel, Stout et al. 2011; Sawler, Stout et al. 2015). In this context, it is difficult today to distinguish between wild, locally native populations and plants or plant groups that have escaped from cultivation (Clarke and Merlin 2013, 2016a, 2016b). Small and Cronquist (1976) established a threshold for distinguishing between industrial hemp (both fiber hemp and oilseed) and marijuana (drug type) of *Cannabis sativa* based on the relative dry weight concentration of Δ^9-THC (or THCA) in the female inflorescences of the plant. Accordingly, plants containing more than 0.3% Δ^9-THC (or THCA) are considered marijuana/drug type, while plants below this threshold are categorized as industrial hemp. In terms of its magnitude, this threshold fits quite well with the limit of 0.3% THC applicable under German narcotics law. Small and Cronquist (1976) have also proposed a model for classifying the subspecies and cultivars of *Cannabis sativa* based on characteristics of the achenes (= fruits, which commonly – botanically incorrectly – are usually referred to as seeds) and the ratio of Δ^9-THC (or THCA) to CBD.

SUBSPECIES OF CANNABIS SATIVA

Cannabis sativa* subsp. *sativa

Plants of limited intoxicant ability, Δ^9-THC comprising less than 0.3% (dry weight) of upper third of flowering plants and usually less than half of cannabinoids of resin. Plants cultivated for fibre or oilseed or growing wild in regions where such cultivation has occurred.

a) *Cannabis sativa* subsp. *sativa* var. *sativa*

Mature fruits relatively large, seldom less than 3.8 millimeters (mm) long, tending to be persistent, without a basal constricted zone, not mottled or marbled, the perianth poorly adherent to the pericarp and frequently more or less sloughed off.

b) *Cannabis sativa* subsp. *sativa* var. *spontanea* Vavilov

Mature fruits relatively small, commonly less than 3.8 mm long, readily disarticulating from the pedicel, with a more or less definite, short, constricted zone toward the base, tending to be mottled or marbled in appearance because of irregular pigmented areas of the largely persistent and adnate perianth.

***Cannabis sativa* subsp. *indica* (Lam.) Small & Cronquist**

Plants of considerable intoxicant ability, Δ^9-THC comprising more than 0.3% (dry weight) of upper third of flowering plants and frequently more than half of cannabinoids of resin. Plants cultivated for intoxicant properties or growing wild in regions where such cultivation has occurred.

a) *Cannabis sativa* subsp. *indica* var. *indica* (Lam.) Wehmer

Mature fruits relatively large, seldom less than 3.8 mm long, tending to be persistent, without a basal constricted zone, not mottled or marbled, the perianth poorly adherent to the pericarp and frequently more or less sloughed off.

b) *Cannabis sativa* subsp. *indica* var. *kafiristanica* (Vavilov) Small & Cronquist

Mature fruits relatively small, usually less than 3.8 mm long, readily disarticulating from the pedicel, with a more or less definite, short, constricted zone towards the base, tending to be mottled or marbled in appearance because of irregular pigmented areas of the largely persistent and adnate perianth

Following this concept, McPartland and Small (2020) have made a stronger subdivision of the taxon *Cannabis sativa* subsp. *indica* that takes into account the geographical origin of the ancestors of this taxon.

At the species or subspecies level, the epithets "sativa" and "indica" have often been and continue to be used inconsistently and arbitrarily – this is especially true for the non-scientific literature. In this regard, cultivars or varieties are often labeled "sativa" or "indica" based on the THC:CBD ratio of the plants, without their taxonomic classification or genetics reflecting this (McPartland and Small 2020). This is also the reason concepts for further subdivision of the taxon into the two species *Cannabis sativa* and *Cannabis indica* with respective subspecies have become less accepted (Clarke and Merlin 2013, 2016a, 2016b). However, the two-species concept takes into account the geographic origin and (human) distribution of the taxa, which is why it corresponds to an ethnobotanical and agronomic rather than a genetically oriented taxonomy.

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2.2 General botanical characteristics

2.2.1 Habitus, sprout and sex distribution

The wild type of *Cannabis sativa* is an herbaceous, mostly dioecious, annual species (o Fig. 2.1). Like hops, it is a sexually polymorphic plant. In such plants, the inheritance of sex is controlled by the presence of sex chromosomes. As a rule, female plants are homogametic of type XX and male plants are heterogametic of type XY.

Cannabis sativa shows considerable variability in its phenotypic characteristics (o Fig. 2.2 and o Fig. 2.5; Small 2018). Depending on the phenotype and its cultivation or growing conditions, plants grow between 60 cm and 4 m high. The stems of the hemp plant are quadrangular at the beginning. In the course of the growing season they become hexagonal; at the base and the shoot tip they are always round.

Fiber bundles develop in the bark portion; this is where the primary fibers are located. These reach a length of up to 20 mm. The secondary fibers develop from the cambium. These reach a maximum length of 2 mm. The leaves of the hemp plant have lanceolate or occasionally ovate or obovate leaflets with serrate (rarely double serrate) margins. The larger leaves (sometimes called "fan leaves") are compound and consist of an odd number (3–13) of leaflets (o Fig. 2.3) that emanate from a single point at the distal end of each

Fig. 2.1 Habitus of a female cannabis plant with stocky growth habit

Fig. 2.3 The foliage leaves (fan leaves) of Cannabis consist of an odd number of leaflets with serrate (rarely double serrate) margins.

Fig. 2.2 Phenotypes of various cannabis cultivars used for medicinal purposes

petiole. Petioles are 2–7 cm long, arranged in pairs on the lower stem and alternate near the tip of the stem. 7–12 pairs of leaves can form during vegetative growth. With the onset of flowering, phyllotaxy (leaf position) changes from opposite to alternate and longitudinal growth largely ceases. Furthermore, the number of newly formed individual leaves decreases. In the leaf axils at the point of attachment of the petioles, the so-called nodes of the main shoot, undifferentiated primordia (flowering plants) are initially visible; these will develop into male or female flowers. Cannabis is considered a quantitative short-day plant: i.e. flower formation is strongly favored when photoperiod falls below a specific threshold, but can also occur independently under certain circumstances. Thus, the beginning of the generative phase – in addition to the photoperiod – depends, among other factors, on the developmental status of the plants and the temperature.

The structure of inflorescences is distinguished as either dioecious or monoecious. Whereas dioecious females produce their flowers in the form of false spikes in the leaf axils of a dense deciduous shoot, the inflorescence of dioecious males resembles a loose panicle (o Fig. 2.4). In contrast, female flowers of occasional or cultivated monoecious plants (referred to as hermaphrodites) are located at the tips of the side shoots (Faux, Berhin et al. 2014; Rana and Choudhary 2010). Male flowers are located sporadically in the leaf axils. These types of cultivars are characterized by higher seed yields and higher homogeneity of the crop compared to the dioecious varieties due to synchronized ripening. Mechanical harvesting is easier. Therefore, they are used for fiber and oilseed production. Different cultivars may also have different shoot architectures in dioecious plants, depending on selection for different utilization needs. For example, dioecious hemp cultivars selected for fiber production are generally tall, with lower branching and less woody stem tissue to maximize bast fiber production, while drug-type cultivars are generally highly branched to increase female flower production.

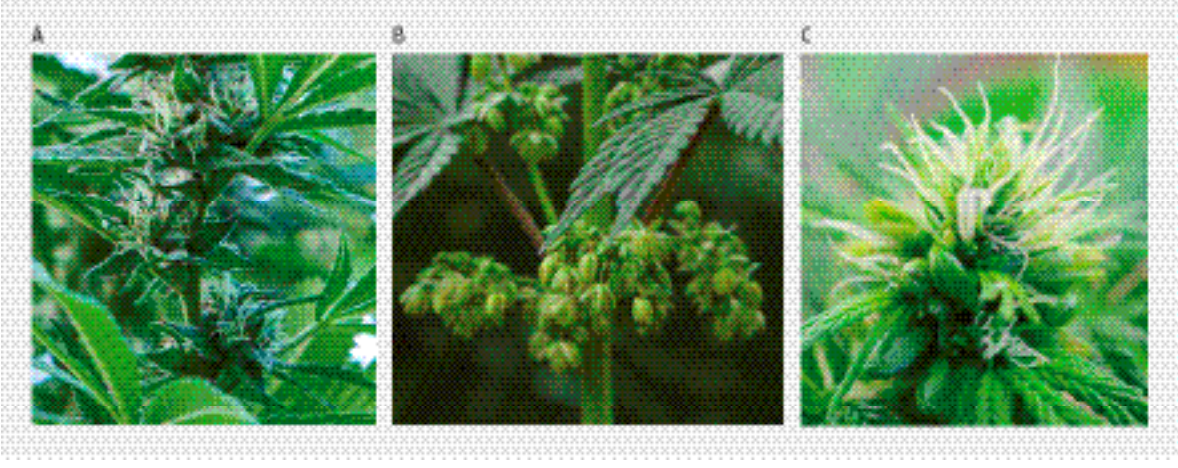
While selected traits in domesticated cultivars are genetically fixed by continued selection, environmental conditions such as temperature and solar radiation (or exposure in indoor cultivars ▸ Chapter 4.1.6), as well as site conditions (soil or substrate composition, water supply) also influence morphology (Small 2018). In addition, environmental conditions also influence foliage coloration. For example, *Cannabis sativa* can exhibit foliage and stems striped by anthocyanins – especially after exposure to frost.

2.2.2 Inflorescences and flowers

Cannabis is a short-day plant: that is, the development of fertile inflorescences is significantly induced by day length (= photoperiod) being below a specific threshold. The first sign of the beginning of the flowering period is the emergence of primordia on the nodes of the main shoot or stem of the plant, in the leaf axils at the point of attachment of the petioles behind the stipules. Prior to the formation of the flowering parts, male and female plants are indistinguishable. Only general trends in the appearance of plants of different sexes can be identified (Clarke 1997).

The female flowers are developed insimple inflorescences that known as racemes and are present in dense clusters (compound racemes). The paired, inconspicuous female flowers appear with two long, white, yellow or pink stigmas protruding from the sheath of a thin-walled, green perigonal bract (o Fig. 2.4). The latter arises under each flower and grows to envelop the fruit. These bracts and later involucral husks have a high density of glandular trichomes (o Fig. 2.5). These are secretory resin glands in which the cannabinoids and terpenes are synthesized and accumulated (Livingston, Quilichini et al. 2020; ▸ Chapter 3.1.2). The number of glandular trichomes varies from cultivar to cultivar. Other young above-ground plant parts may also have a relatively high density of this type of epidermal secretory glands, but this never approaches the same density as seen in the inflorescences.

In female flowers, three types of trichomes are distinguished on the basis of their morphology: bulbous, sessile (= sitting) pre-stalked and stalked trichomes (o Fig. 2.6; Hammond and Mahlberg 1973; Livingston, Quilichini et al. 2020; Tanney, Backer et al. 2021). Bulbous trichomes are the smallest and produce few terpenoid metabolites. The sessile and stalked trichomes are similar only architecturally; both have a spherical head and sit on a multicellular stalk on or above the epidermal surface. The pedunculate trichomes are larger and more abundant (Hammond and Mahlberg 1977). Livingston, Quilichini et al. (2020) studied the mor-



o **Fig. 2.4** Sitting in the leaf axils are **A** female flowers, **B** male flowers and **C** inflorescences of a hermaphrodite with female and male flowers

Fig. 2.5 Female inflorescences of various cannabis cultivars, richly covered with trichomes

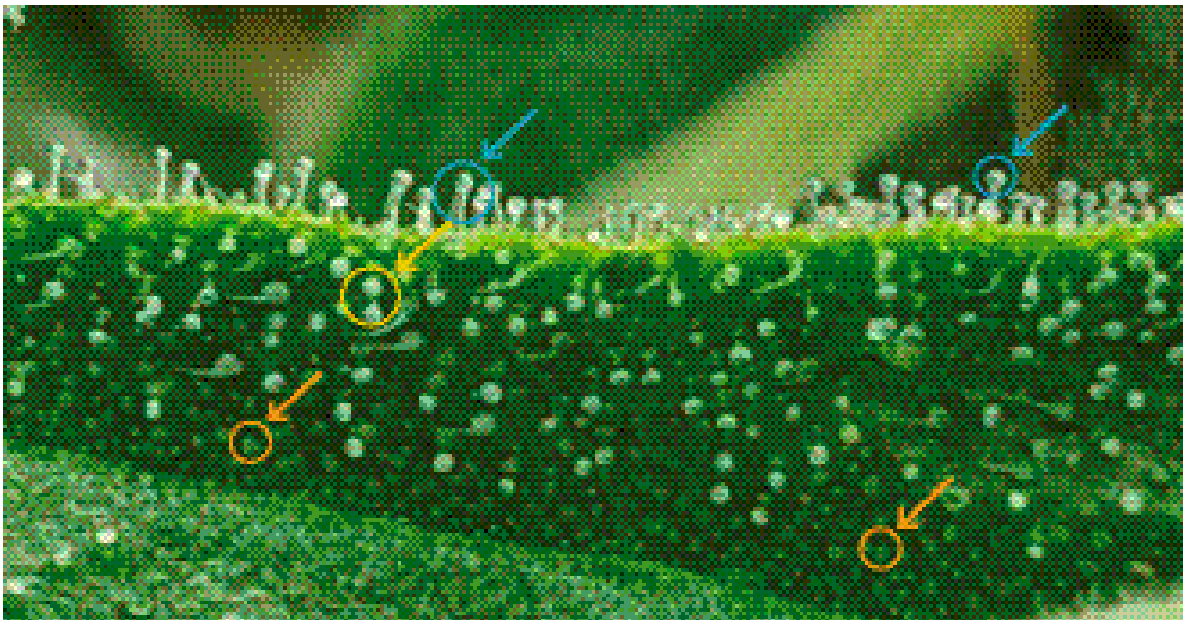


Fig. 2.6 Bulbous, non-secretory cystolith hairs (orange arrows), sessile (yellow arrows), and pedunculate (blue arrows) trichomes on female cannabis inflorescences

phology, compartmentalization and physiology of glandular trichomes in more detail. They showed that stalkedtrichomes arise from transient, sessile progenitors during flower development (Fig. 2.7) and are anatomically and biochemically distinct from sessile trichomes. This is also true for other trichome types on the anthers of male flowers and vegetative leaves, which contain secondary metabolite profile which is characterized more by terpenoids and fewer cannabinoids. The high cannabinoid contents of stalked glandular trichomes are the result of a pronounced expression of key enzymes of terpene and cannabinoid biosynthesis (▸Chapter 3), which increases during flower development. In addition, cannabis plants also possess non-glandular trichomes (e.g. cystoliths), which are hair-like and have a single or multicellular structure (Fig. 2.6).

The individual male flowers are small, short-stalked, drooping, and arranged in larger, loose, inflorescences (Fig. 2.4). They appear in pairs, usually on special flowering branches, but also at the base of some vegetative branches. The male flowers are greenish or whitish, have five petals and conspicuous stamens. They bear bulbous glandular trichomes on the anthers and filaments and produce large quantities of small, light-colored, dry pollen grains. After releasing their pollen, the male plants die several weeks before the female plants of the same population reach seed maturity. The female

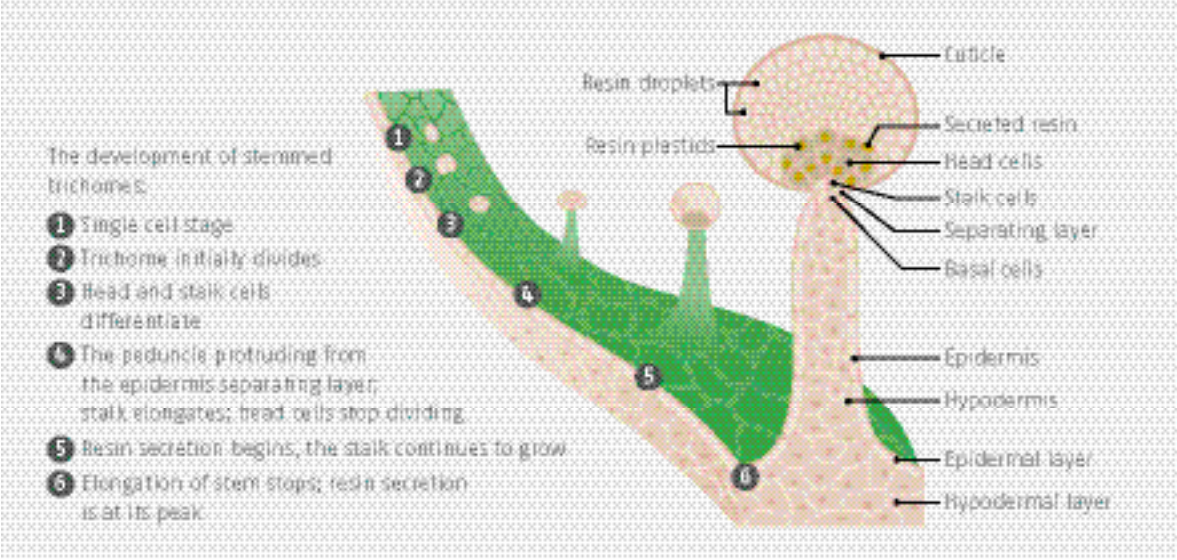


Fig. 2.7 Origin and characteristics of glandular trichomes of cannabis.
Glandular trichomes are formed by a single epidermal cell first bulging outward (1) and then dividing anticlinally (perpendicular to the surface) (2). This is followed by a periclinal division (parallel to the surface) that separates the secretory cells initial from the initial cells of the bearing parts. A second periclinal division separates basal and stalk cells (3). The two basal cells do not divide further, while the stalk cell layer continues to proliferate perpendicular to the first division (4). The secretory disk enlarges radially and divides until 8–13 secretory cells are formed and resin secretion begins; a membrane detaches from the outer skin of the gland head, enclosing the exuding resin and giving the head a spherical appearance (5). Cell division is now complete. The disk of secretory cells continue to extend to twice the original diameter; depending on the trichome type, the stalk cells continue to divide and extend, lifting the gland head up to 500 µm above the epidermal surface (6); (according to Clarke 1997).

Fig. 2.8 Cannabis fruits (achenes) A in cracked fruit wall (= pericarp) B in opened fruit wall C seed embryo ("seed") without fruit wall

plants, however, continue to grow during fruiting. Fruits mature in 3 to 4, but possibly 8 weeks. Since female plants usually bear flowers at different stages of development, this results in uneven maturity of hemp fruits in wild populations. Cultivars that show largely synchronous fruit ripening are used for oilseed production.

2.2.3 Fruits

The fruits of the hemp plant develop from a one-seeded ovary. They are small ovoid achenes, generally 2–5 mm long (= nut fruits in which the seed coat and the pericarp lie close together; ○ Fig. 2.8), and protected by bracts (▸ Chapter 2.2.2). Their coloration can vary from white, yellow, orange, gray, brown to black. The color and patterning of the fruits is also used for taxonomic classification (▸ Chapter 2.1).

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2.3 Cannabis breeding and current cultivars

Cannabis produces large quantities of pollen and fruit. Nevertheless, it is not easy to improve the plant through classical selective breeding. Cannabis populations are almost always dioecious. Male and female flowers are therefore found on separate plants, which are therefore not normally capable of self-fertilization. However, self-fertilization is the most effective sexual reproductive method for fixing desirable charactersbecause the respective genes are more likely to be present in both the male pollen and the female ovule if they originate from the same plant. In dioecious cannabis cultivars, the recessive alleles controlling a selected trait locus (aa) are present in two separate individuals: a male or pollen parent (either Aa, aA, or aa), and a female or seed parent (also either Aa, aA, or aa). As a result, qualitative traits are usually controlled at single loci by dominant allele forms (AA, Aa, and aA), which are much more common (3:1 ratio) than recessive ones (aa) and whose heritability is therefore high. Quantitative charactersare more often controlled by different allele forms at different loci; therefore, their heritability is low, making improvement by breeding difficult (Clarke and Merlin 2013, 2016). Female plants provide the majority of commercially valuable cannabis products, including fiber, seeds or drugs, while male plants merely fertilize female plants and are occasionally harvested for their fiber. This, too, makes it difficult for plant breeders to identify potentially beneficial charactersin a male parent, since those charactersmust ultimately come to expression in the female plants of the following generations. All cannabis plants are wind pollinators, so for breeding purposes, the selected female seed parents must be isolated from the male pollen parents until they are to be pollinated by a selected male parent to avoid accidental fertilization or seed formation. Successful breeding of open-pollinated varieties requires the identification of plants with advantageous charactersand then the creation of F1 breeding lines by repeated selection, hybridization between these lines, stabilization of the lines by means of vegetatively propagated clones of the parents, and field testing of their progeny. Today, genomic markers are also increasingly used in breeding (Barcaccia, Palumbo et al. 2020; Posselt 2010). It is a costly and lengthy process to develop these types of genuine cultivars. The numerous cultivars that have been preserved and are available today therefore do not only originate from commercial breeding projects, but are also the result of diverse activities of individual, not infrequently private initiatives. In addition to the F1 hybrids, today there are a large number of cultivars that are the result of the selection of female plants without cross-pollination. For this purpose, male plants which do not undergo any particular selection process initially are used as pollen donors for crosses with selected female

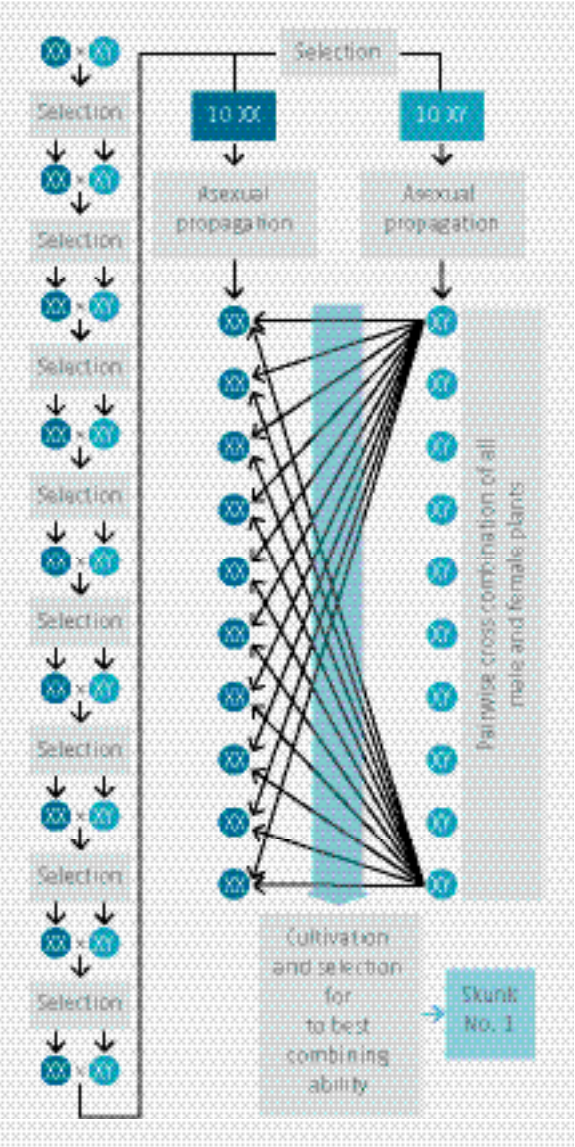

Fig. 2.9 Method for breeding stable, heterozygous cultivars (here Skunk No. 1): To obtain the cultivar, plants of F2 progeny were selected to perform nine consecutive inbreeding cycles to increase their homozygosity. Ten female and ten male plants were then selected and vegetatively propagated to be used as parental lines in all possible pairwise cross combinations to obtain a heterozygous cultivar with a nevertheless stable genome (according to Barcaccia, Palumbo et al. 2020).

clones in order to produce hybrid seeds. (○ Fig. 2.9). The seeds obtained as result, which do not have the genetic constitution of F1 hybrids, are then used to select female plants, which are subsequently propagated by cuttings or meristem culture. In addition, in recent years, seed has also been obtained by means of self-pollination to produce so-called "all female" varieties. This is possible with silver thiosulfate, which inhibits ethylene production and is applied to some branches of the female plants (▸ Chapter 4.1.3). Due to the lack of ethylene, male flowers with viable genetically pure female pollen are formed on the female plants. Self-fertilization then produces seeds which, when germinated, yield a purely female generationfrom female plants.

This combines the advantages of asexual propagation (i.e. fixation of the female genotype) with the advantages of sexual propagation (i.e. propagation via seeds instead of cuttings or meristem culture) (Barcaccia, Palumbo et al. 2020). At the same time, empirical data show that female plants that are not fertilized have higher cannabinoid contents. In the past, it was necessary to remove all male plants from a culture for such "sinsemilla" plants, which is no longer necessary for purely female cultures. It is inevitable that the propagation of female plants via seeds can also lead to unstable populations that are characterized by a certain genetic diversity; this is a risk that does not exist with clonal populations from female cuttings.

The breeding or selection and domestication process, with the aim of obtaining cultivars with high cannabinoid contents, has led to the culturing of chemotypes known as "strains". In order to characterize these strains, their contents of CBD and/or THC or CBDA and/or THCA are usually exclusively specified. In this regard, there has been criticism – quite justifiably – that this type of characterization is not sufficient to distinguish the diversity of different chemotypes from each other (Mudge, Murch et al. 2018). It is now known that domestication has resulted in a loss of CBDA metabolism in some cultivars and a shift between CBDA and THCA pathways in others, through up or down-regulation of specific enzymes within the biosynthetic pathways (▸ Chapter 3.4). The effects of domestication in modern cannabis cultivars are therefore a lack of chemical diversity and a loss of biodiversity. These cultivars, moreover, are much less likely to be distinct strains than groups of very similar chemotypes. The latter were recently differentiated into five cannabinoid chemotypes by Schilling, Dowling et al. (2021); these are discussed in more detail in ▸ Chapter 3.4.

■ **DEFINITION** **Cultivar:** A cultivar is a defined group (variety) of cannabis plants that is clearly distinguishable from other cannabis plants on the basis of morphological, physiological, cytological, chemical or other characters. As a rule, these are not wild plants but individuals obtained by breeding or selection, which are stable in terms of character and uniform among themselves.
Chemovar: Chemovars (or chemotypes) are cannabis cultivars that may not be morphologically distinct, with distinct secondary metabolite patterns. They may have minor genetic or epigenetic differences, which may have little or no effect on the morphology or anatomy of the plant; i.e. they are reflected only in terms of the chemical phenotype. This can affect both cannabinoids and terpene patterns, as well as other secondary metabolites where appropriate. Cultivars are usually also chemovars.

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6 Pharmacological basis of cannabinoid action

6.1 The endocannabinoid system

Prof. Dr. Thomas Herdegen

Understanding the physiological functions of the endocannabinoid system (ECS) is the essential basis for applying treatments with medical cannabinoids (mCB) rationally, and for ensuring constructive discussions on how they are prescribed.

6.1.1 What is the endocannabinoid system?

As we find so often in medicine, the biblical quotation from Goethe's Faust "In the beginning was the word" also applies for the term 'endocannabinoid system'. In 1753, Carl von Linné created the generic term cannabis, derived from the ancient Greek word for hemp, κάνναβις. The effects of ingredients from cannabis soon suggested that endogenous binding sites for them existed. Nevertheless, it took until the 1990 s before the two most important binding sites of plant cannabinoids could be cloned and named cannabinoid receptors (CB receptors) according to their ligands. At the same time, the first endogenous ligands of these CB receptors were isolated: arachidonylethanolamide (AEA; syn. anandamide) along with other ethanolamides, as well as 2-arachidonylglycerol (2-AG). Thus, the ECS was also neurobiologically defined by:

- the CB receptors and other non-CB receptor binding sites for cannabinoids (▸ Chapter 6.1.4);
- the endogenous ligands for CB, called endocannabinoids (EC), but which also interact with other non-CB receptor binding sites (▸ Chapter 6.1.5.1);
- the enzymes (lipases, hydroxylases, and others) responsible for the formation, transport and degradation of endocannabinoids (▸ Chapter 6.1.5.1).

Our body is full of cannabinoid receptors (CB), the binding sites for the "intoxicating" THC from cannabis plants, and it constantly produces larger amounts of molecules or messengers that stimulate these CB receptors, like the exogenous cannabinoid THC. The physiological effects of the ECS (= stimulation of CB receptors) are therefore ubiquitous in our body. In this respect, it would only seem logical that disruption to the ECS would lead to injurious symptoms and would represent a significant contribution to the pathogenesis of numerous neuropsychiatric diseases.

The ECS can be understood by analogy with the endorphin system, whereby the opioid receptors are stimulated both by endogenous endorphins and by exogenous or iatrogenic opioids, which also originally came from a plant source (opium poppy; Papaver somniferum), and are now available in the form of diverse synthetic derivatives. This analogy thereby extends to the important role of the endorphin system in our physiological health and the significance of its dysfunction for disease.

There is another connection between the two systems: the ECS modulates the endorphin system, and consequently, our responsiveness to opioids (▸ Chapters 6.1.2.1 and 6.1.4.4).

In this respect, the endorphin system and its pharmacological ligands, including the drugs acting on it, can serve in many respects as a model for the future development of medical cannabinoids (mCB), such that disorders and dysfunctions of the ECS should in future be treated pharmacologically and medically as a matter of course, with the aid of diverse, standardized mCB drugs, as can already be said to be the case today for opioid drugs, prescribed millions of times over.

6.1.2 Physiology

To better understand the physiological mechanism of action of ECS, a distinction can be made between its function as a modulator of the nervous system, on the one hand, and its function as a modulator of the immune system, on the other. In simple terms, the CB receptors can also be assigned to these two systems: CB1 relating to the nervous system; and CB2 relating to the immune system.

The ECS is a key system for the regulation of diverse brain functions and cerebral processes such as mood, perception, learning and memory formation, but also pain (Kendall and Yudowski 2016). In essence, the endogenous ligands of the CB receptors are rapidly remodeled and inactivated as required (▸Chapter 6.1.5.1).

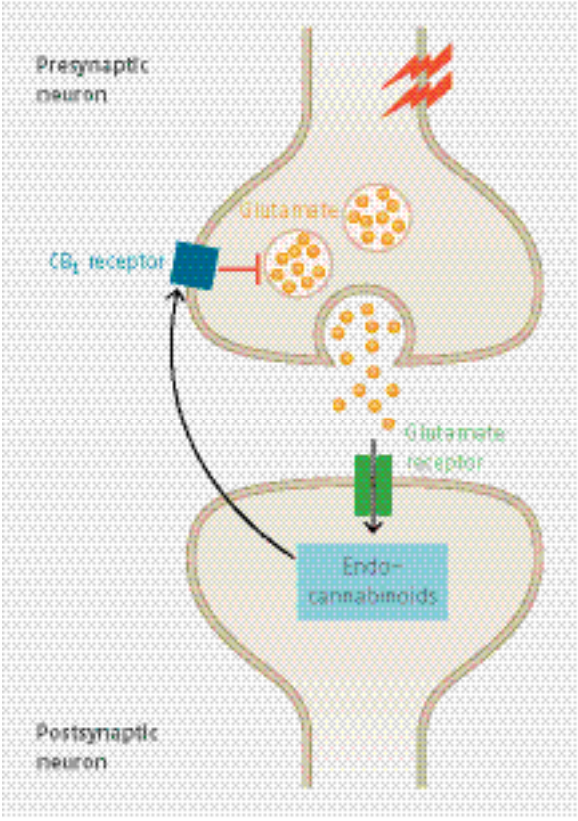
6.1.2.1 CB1 and the nervous system

Put simply, the ECS functions as a neuro-vegetative relaxation or recovery system and serves to maintain our psycho-vegetative homeostasis (Patel, Hill et al. 2017). In the nervous system, although CB1 is the dominant CB receptor, other binding sites are also relevant, such as CB2, TRPV or GRP55.

Retrograde filtering and synaptic plasticity. The central element of psycho-vegetative relaxation is a "neurochemical brake"; in mechanistic terms, this is a reverse inhibition by CB1 in the nervous system (Katona and Freund 2008): during intense neuronal stimulation – not only during excitation, but also during inhibition – endocannabinoids (EC) are synthesized in the postsynaptic neuron and released into the synaptic cleft, where they retrogradely activate the inhibitory CB1 receptors of the presynaptic neuron. As a consequence, there is no presynaptic release of further transmitters and thus no further stimulation of postsynaptic receptors (○ Fig. 6.1; Moreira and Lutz 2008). However, not only excitations of neurons are terminated or blocked via this mechanism, but also inhibitions; thus, disinhibition and therefore excitation of neurons can also occur. Synaptic inhibition and disinhibition via CB1 are important modulators of long-term depression and excitation (LTD, LTP); these synaptic processes also form the basis for learning and memory.

The endocannabinoid system thus modulates neuronal excitation via the CB1 receptor in the sense of a filter function against excessive synaptic activity – excitation as well as inhibition. The inhibition of excitotoxicity can also have a neuroprotective effect. (Chiarlone, Bellocchio et al. 2014).

In accordance with this filtering function of the ECS, cannabinoids are less involved in inhibiting the spontaneous basal discharge of neurons, but rather mainly influence suprabasal excitations evoked by somatopsychic stimuli. Thus, physiological basal neuronal activities remain largely unaffected, whereas pathologically enhanced processes are inhibited or normalized. As with pharmacological use dependence (for example, dependence on antiarrhythmics or antiepileptics), one could speak of a **physiological use dependence** with endogenous cannabinoids: their effect is more pronounced the more the physiological system is derailed or the further it has moved away from homeostasis.



○ **Fig. 6.1** Retrograde signal modulation by endocannabinoids at the CB1 receptor. Following synaptic excitation (discharge flashes, glutamate), postsynaptic endocannabinoids are released, retrogradely stimulating the presynaptic inhibitory CB1 receptor and thus inhibiting presynaptic activity (Herdegen 2020).

Incidentally, this specificity of their effect also contributes significantly to the therapeutic breadth of medical cannabinoids.

Neurophysiological effects. The ECS is a central modulator or regulator of many neural systems and control circuits (□ Tab. 6.1; recent reviews in Zou and Kumar 2018; Chanda, Neumann et al. 2019; Köfalvi 2008), such as:

- psycho-vegetative systems for coping with stress and anxiety;
- cognitive systems for learning and memory formation;
- emotional systems for coping with depressive and anhedonic affect;
- autonomic-vegetative systems, e.g. for regulation of appetite or nausea.

Some clinically relevant functions are representative of the diverse neurobiological effects of the CB1-dominated ECS:

Mood. CB1 stimulation leads to physiologically essential neuroprotective or adaptive changes, such as expres-

Tab. 6.1 Effects of the endocannabinoid system (ECS) mediated predominantly through CB1

Effect on	Site of effect	Effect (* = Therapeutic goal of the use of medical cannabinoids)
Psychic homeostasis	Limbic system, sympathetic nervous system	Reduction of anxiety and pain* Lowering muscle tone and blood pressure* Promotion of relaxation*
Muscular stimulation	Cerebellum, motor system	Inhibition of motor activity* Spasmolysis, muscular relaxation*
Anxiety	Limbic system, basal ganglia	Improvement of fear extinction* Reduction of fear reactions (anxiolysis)*
Appetite	Hypothalamus, autonomic nervous system	Increase of appetite*
Reward	Nucleus accumbens, prefrontal cortex	Stimulation of the reward system, addictive behavior
Pain processing	Pain pathway, posterior horn, peripheral nervous system	Analgesia* Less aversive pain evaluation* Reduction of opioid tolerance*
Sleep	Formatio reticularis	Sleep promotion*
Emesis	Vomiting center, enteric nervous system	Antiemesis* Provocation of emesis
Blood pressure, chronotropy	Sympathetic ganglia, enteric nervous system	Hypotonic reactions, (reflex) tachycardia
Decidualization	Uterus	Inhibition of differentiation of decidua cells from mucosal epithelial cells

sion of the antidepressant and neuroplastic growth factor brain-derived neurotrophic factor BDNF (Navabpour, Rezayof et al. 2021) or to the increased release of norepinephrine and serotonin, which are known to be the pharmacological therapeutic targets of anxiolytics and antidepressants (review: Colino, Herranz-Herrer et al. 2018; Mendiguren, Aostri et al. 2018).

It is these mood-stabilizing effects that are targeted in both medical and recreational use: specifically, the alleviation of stress, fear and anxiety (stress, fear, anxiety; Chanda, Neumann et al. 2019) and – often associated with it – to the alleviation of (neuropathic or psychosomatic) pain or pain perception.

Stress regulation. The ECS is a central modulator of stress homeostasis. It activates the stress axis under physiological conditions, but at the same time limits those changes that make stress pathological (Chanda, Neumann et al. 2019).

Dopamine, attention and reward. One of the most important functions of the ECS is the modulation of the dopaminergic reward system (Oleson, Hamilton et al. 2021). This effect, which is so vital physiologically (in fact, it is species-preserving), is also the "Achilles heel" of cannabinoid use: this is where the generator of cannabinoid addiction is anchored. Conversely, this is the target of CB1 antagonists (e.g. rimonabant) in addiction therapy.

Pain defense. The ECS is present throughout the pain system. Pain inhibition by endocannabinoids (or by cannabinoids used therapeutically) includes inhibition of nociception and transmission to the supraspinal nuclei, suppression of aversive emotional coloration, elimination of fear (fear extinction), inhibition of pain-associated inflammatory processes and intervention in pain-related processes such as stress-induced analgesia (reviewed in Woodhams, Chapman et al. 2017; Kendall and Yudowski 2016; Vučković, Srebro et al. 2018).

Pain defense is a good example of the diversity of cooperative interactions of the ECS. First, CB1 and CB2 signaling cooperate in this process; second, the ECS also influences the endorphin system and patient responsiveness to opioids (Bruehl, Burns et al. 2019), by allowing CB receptors to heterodimerize with opioid receptors and prevent their habituation or the development of tolerance to exogenous opioids

(reviewed in Wendelmuth, Wirz et al. 2019; Gastmeier, Gastmeier et al. 2022). Finally, CB receptors and opioid receptors still cooperate with the potent analgesic TRPV1 receptors (Zádor and Wollemann 2015) and their full agonist AEA, an endocannabinoid (▸ Chapter 6.1.5.1).

Food intake and appetite. Stimulation of CB1 activates food intake and coordinates the dopaminergic mesolimbic reward system including hypothalamic appetite control (Silvestri and Di Marzo 2013). Depending on the sensation of hunger or satiety, the blood concentration of endocannabinoids such as AEA changes, and these changes in turn correlate with the connectivity of brain areas relevant to eating behavior (Martín-Pérez, Contreras-Rodríguez et al. 2021). Overactive CB1 signaling is sometimes found in eating disorders.

Cardiovascular nervous system. Vasodilation and positive inotropy in the heart are representative of CB1 effects in the autonomic nervous system. Interestingly, CB1 also activates AMP kinase (Chanda, Neumann et al. 2019); for example, the antidiabetic drug metformin exerts its therapeutic effect via stimulation of AMP kinase.

6.1.2.2 CB2 and the immune system

All elements of the neuronal ECS are also found in the immune system: the CB receptors, the endocannabinoids and the corresponding enzymes for metabolization (Rahaman and Ganguly 2021). CB2 and to some extent CB1 are present in the vast majority of immune cells. They are involved in both innate and adaptive immunity. The receptor density of CB2 on immune cells is 10 to 100-fold higher than that of CB1. The endogenous ligands (EC) have predominantly anti-inflammatory and immunosuppressive effects. However, antagonistic effects are also repeatedly described, depending on the individual context in which CB receptors and endocannabinoids interact. A pharmacological therapy approach would stand to reason, although to date there are no reliable clinical data.

6.1.2.3 Other binding sites for cannabinoids and endocannabinoids

In addition to CB receptors, there are other receptors which endogenous and exogenous cannabinoids can bind to, and whose signal transduction can in some cases contribute significantly to cannabinoid effects (▸ Chapter 6.1.4.3).

Functional binding (activation as well as inhibition) to $GABA_A$ receptors, TRPV1, PPARγ, adenosine-3 receptors, or GRP55 has been demonstrated for the endocannabinoid 2-AG (▸ Chapter 6.1.5.1) (reviewed in Baggelaar, Maccarrone et al. 2018). This also applies to the endocannabinoid AEA (▸ Chapter 6.1.5.1).

6.1.3 Disorders of the endocannabinoid system

In accordance with its physiological importance for neuro-homeostasis, dysfunctions of the ECS can also be expected as part of neuropsychiatric clinical pictures. Indeed, numerous nervous system disorders lead to dysfunctional changes in the ECS: either cannabinoid receptors are diminished in expression and/or the synthesis of their endogenous ligands is downregulated; alternatively, receptors as well as ligands may be limited in terms of their efficacy.

As for physiology, dysfunction of the ECS as well as its effects are presented separately below for the nervous system with dominant CB1 receptors and the immune system with dominant CB2 receptors, respectively.

6.1.3.1 Dysfunctional CB1 signal transduction in the nervous system

Some common neuro-psychiatric disorders will be used to illustrate how disturbances in CB1-mediated EC action contribute to the pathology of various clinical pictures (for more details, see ▸ Chapter 7.7).

Post-traumatic stress disorder (PTSD). In cases of post-traumatic stress disorder (PTSD) and in subjects with a history of trauma, positron emission tomography (PET) shows a significant increase in free CB1-binding sites and a decrease in blood CB1-ligands (Neumeister, Normandin et al. 2013). This decrease was more pronounced in women, who are known to be more frequently affected by PTSD, than in men. In line with this finding of a gender-specific pathogenesis, it is also hypothesized that ovarian sex hormones influence the ECS in post-traumatic stress disorder (Ney, Matthews et al. 2018; Zer-Aviv and Akirav 2016).

Depression. Dysfunction in the sense of underactivity of the ECS has repeatedly been observed in depression (Bridgeman and Abazia 2017). Numerous animal studies demonstrate both a disordered function of the ECS in affective disorders as well as the antidepressant effect of cannabinoids or activators of the ECS (reviewed in Colino, Herranz-Herrer et al. 2018). The dramatic effect that underfunctioning or even a blockade of CB1 receptors can have was demonstrated by the drug rimonabant (used to treat withdrawal), which as a selective CB1 antagonist provokes depressive symptoms, and even suicidality, in humans (Thomas, Martin et al. 2014) and therefore had to be withdrawn from the market.

The antidepressant effects of endocannabinoids and exocannabinoids include increases in the expression of the neuronal growth factor, brain-derived neurotrophic factor (BDNF), whereby suppression of this factor plays an important role in the pathogenesis of affective disor-

ders (Bennett, Arnold et al. 2017; Rea, McGowan et al. 2019), and leads to increases in the biogenic amines serotonin and norepinephrine, which are key molecules in the pharmacotherapy of depression and anxiety disorders.

Anxiety disorders. Mice in which the CB1 receptor has been genetically knocked out show symptoms of an anxiety disorder in addition to depressive behavior (Rácz, Nent et al. 2015). The ECS is considered an important factor for fear-extinction, which is of great neuro-physiological importance. Impairments to this psychological defense response can also be attributed to disturbances in the ECS (Bennett, Arnold et al. 2017). The ECS is currently thought to be more important for normalizing aversive memory content than reward memory. This has two important therapeutic implications:

1. First, aversive memory content can be inadequately erased in depression, and cannabinoids can counteract this in an affect-stabilizing manner.
2. Second, reward memory is closely coupled with dopamine: the relatively low interaction of CB1 with the reward system or the relatively weak release of dopamine contributes to the low addictive potential of cannabis. This is in marked contrast to other addictive substances associated with a massive "hit-like" dopamine release.

Stress. Glucocorticoids (GC) are known to be central players in both adaptive and dysfunctional processes of the stress axis. Their negative effects include suppression of CB1 receptors (reviewed in Colino, Herranz-Herrer et al. 2018). Disruption of the ECS by glucocorticoids is considered a predictor of maladaptive stress responses in patients with early childhood trauma, among others (Atsak, Morena et al. 2018).

Pain. Dysfunctional alterations in the ECS can be demonstrated in animal studies as well as in patients with chronic pain (reviewed in Colino, Herranz-Herrer et al. 2018; Corcoran, Roche et al. 2015; Woodhams, Chapman et al. 2017 and Starowicz and Finn 2017); for example, decreased expression of CB receptors or dysfunction of the dopamine and fear processing systems have been documented (La Porta, Bura et al. 2015). Frequently, activation of the ECS is found both in nociceptive pain and in tissues of neuropathic injury, which is interpreted as an expression of endogenous pain defense (Vučković, Srebro et al. 2018). Finally, reference should be made to the reduction of neuropathic pain caused in cancer patients as a result of nerve damage caused by cytostatic drugs (vincristine, cisplatin) (Ward, McAllister et al. 2014).

Upon substrate saturation of fatty acid amide hydrolase (FAAH), which is involved in the degradation of certain endocannabinoids, the analgesically active endocannabinoid AEA can be degraded by the inflammatory and pain-increasing cyclooxygenase-2 (COX-2), explaining the effective analgesia achieved by co-medication with FAAH and COX-2 inhibitors (Coxibs) (Woodhams, Chapman et al. 2017).

Other "EC deficiency syndromes". The list of diseases involving possible ECS disorders is long. Diseases such as migraine, fibromyalgia or inflammatory bowel disease (IBD) have also been referred to as EC deficiency syndromes in the literature (Bridgeman and Abazia 2017). Therapeutic success with cannabinoids supports such a view. However, the pathogenetic involvement of a dysfunctional ECS often plays only a minor role.

Influence on the vegetative or enteric nervous system. The ECS is an important modulator of the autonomic nervous system, where there is high expression of CB1 and CB2 receptors. Disturbances of the ECS can therefore lead to dysregulation of vegetative functions – including in psychovegetative diseases where dysregulation may be particularly significant.

6.1.3.2 Dysfunctional CB2 signal transduction in the immune system

In line with the predominant anti-inflammatory and immunosuppressive effects of the immune ECS, stimulation of the ECS is considered an anti-inflammatory therapeutic option. Conversely, a dysfunctional immune endocannabinoid system is thought to promote (auto)immune diseases (Rahaman and Ganguly 2021). Thus, inhibition of the ECS (receptor deletion or inhibition of endocannabinoid synthesis) promotes colitis in animal experiments; conversely, EC stimulates anti-inflammatory immune defenses. Genetic polymorphisms of enzymes that reduce EC are associated with the expression of systemic lupus erythematosus, for example (reviewed in Rahaman and Ganguly 2021). However, concrete therapeutic approaches have not yet emerged from this preclinical empiric evidence.

6.1.3.3 Differentiation from dysfunctional changes as a result of cannabis abuse

It is imperative to distinguish and differentiate disease-related changes or functional-neurochemical dysfunctions of the ECS from those neuropathological changes that are:

a) generally manifest in addictive disorders; or
b) specifically result from non-medically indicated recreational use of cannabis ("smoking pot" etc.).

6.1.4 Cannabinoid (CB) receptors

As stated above, the linguistic and chemical relationship between endocannabinoids (EC) and cannabis plant-derived phytocannabinoids is based on their

common ability to stimulate the endogenous CB receptors CB1 and CB2. Both CB receptors are coupled to inhibitory G-proteins, the pertussis toxin-sensitive Gi/o receptors, and belong to the metabotropic receptor group (similarly to dopamine, adrenaline, histamine, angiotensin or acetylcholine receptors).

6.1.4.1 CB1 receptors

CB1 is the most important receptor of the neuronal ECS; it also mediates the psychotropic effects of endo- and exocannabinoids. In the brain, it is one of the most abundantly expressed G protein-coupled receptors (GPCR).

Functions and expression

The CB1 receptor inhibits neuronal excitability by CB receptor-mediated opening of hyperpolarizing potassium channels or by closing of excitatory calcium channels. The underlying second-messenger cascade is shown in ○ Fig. 6.2. The principle of the retrograde brake or filter function is described in ▸ Chapter 6.1.2.1. Thus, CB1 inhibits or modulates the synthesis and/or release (Cohen, Weizman et al. 2019) of:

- biogenic amines such as serotonin, dopamine and norepinephrine;
- transmitters such as acetylcholine, GABA or glutamate;
- neuropeptides.

However, CB1 is not exclusively expressed presynaptically. Due to its postsynaptic expression, CB1 can bring about its own inhibition (autogenous inhibition). In addition to its membrane localization, CB1 is also found intracellularly and even in mitochondria. Moreover, activation of G-proteins has also been described. Another consequence of CB1 activation is the inhibition of intracellular metabolic processes such as the activity of the ubiquitous second messenger adenylate cyclase, or the MAPK signaling pathway.

CB1 can constitutively activate G protein, even in the absence of agonists. This basal activity is also responsible for the highly polar localization on presynaptic axons (Rozenfeld 2011).

AEA and other ligands. The main endogenous ligand for CB1 is AEA (▸ Chapter 6.1.5.1). At the same time, CB1 is the major binding site for THC and mediates most of the effects of THC. CB1 is among the most abundantly expressed GPCRs in the brain (Kano, Ohno-Shosaku et al. 2009). Regions with many CB1 receptors include the olfactory bulb, hippocampus, basal ganglia, limbic system, cerebellum and core areas of the pain pathway. There is moderate expression in the cortex, amygdala, hypothalamus, brainstem and spinal posterior horn (□ Tab. 6.1). It has only a minor presence in the spinal anterior horn and thalamus. In addition to neurons, CB1 receptors are also found on glial cells such as astrocytes, oligodendrocytes, and microglia.

In peripheral organs, tissues, as well as in the peripheral nervous system (posterior root ganglia, nerve endings of the skin), CB1 receptors are present in the gastrointestinal and genitourinary tracts, the heart, the spleen and the vascular endothelium, among others, and show particularly high expression on the nerve endings of the sympathetic nervous system. Again, CB1 receptors predominantly attenuate neuronal excitation, such as excitation of the sympathetic nervous system, which explains, among other things, a certain level of orthostatic dysregulation (with reflex tachycardia) due to cannabinoids. CB1 plays an important role in the GIT-brain axis, regulating appetite, digestion and intermediary metabolism.

Neurochemical characterization

CB1 is encoded by the gene CNR1 and consists of 472 amino acids (473 in rats and mice with 97–99% sequence homology). In addition to the classical CB1 receptor, there are two isoforms generated via splicing. They differ in their patterns of expression, with the classic full length CB1 predominating in the brain (reviewed in Zou and Kumar 2018). It is possible that these genetic variations are relevant for cannabis dependence (Schacht, Hutchison et al. 2012).

In 1988, a THC binding site was discovered for the first time in the rat (Devane, Dysarz et al. 1988). However, crystallization and further clarification of its structure were only achieved a few years ago (Hua, Vemuri et al. 2016). The crystallized CB1 features seven transmembrane helices typical of rhodopsin-like G protein-coupled receptors.

In addition to stimulating $G\alpha_{i/o}$- and Gβ/γ-proteins, CB1 can associate with β-arrestin independently of G protein and thus influence GPCR desensitization, including the effects of THC (reviewed in Zou and Kumar 2018). Information on the significance of the different transmembrane helices can be found in Schierle and Merk (2017).

6.1.4.2 CB2

The CB2 receptor is an immunomodulator. It is mainly expressed in hematopoietic cells and immune cells, such as microglia, B- and T-lymph cells in the spleen and tonsils, respectively, or leukocytes. Stimulation of CB2, which is also coupled to inhibitory $G_{i/0}$ proteins, has substantial antiphlogistic and (auto-)immunosuppressive effects (Hashiesh, Sharma et al. 2021). Stimulation of CB2 also mediates analgesia, but its mechanisms remain unclear. Contributing factors include anti-in-

flammatory effects and inhibition of excitatory ion channels.

The signal transduction of CB2 is thought to be complex. Thus, it is postulated that intracellularly localized CB2 mediates signal transduction in a different manner than the typical membrane-localized CB2 (Brailoiu, Deliu et al. 2014).

Function and expression

CB2 is weakly expressed under normal conditions, but is upregulated in immune cells, including glial cells of the nervous system, in response to inflammation, pain and nerve injury.

An important role of CB2 is to inhibit the release of chemokines and cytokines, inhibit the spread of neutrophils and macrophages, and generally to suppress inflammatory processes (Abrams and Guzman 2015; Mechoulam and Parker 2013; Niu, Huang et al. 2017). Via CB2, the ligands can also elicit analgesic effects, such as the release of the potent β-endorphin on keratinocytes. On some immune cells, such as mast cells, CB2 receptors cooperate with CB1 receptors. Further details on the function of CB2 in the immune system can be found in ▸ Chapter 6.1.2.2.

CB2 is found strongly expressed in almost all immune cells and, in small amounts, in abdominal organs. Whereas CB2 can be detected only in small amounts in the brain, the neurophysiological effects of CB2 can clearly be depicted, for example, in the prefrontal cortex (Boon, Chameau et al. 2012). It is likely that intraneuronal expression of CB2 regulates calcium currents particularly effectively (reviewed in Zou and Kumar 2018). Recently, other neuronal effects of CB2 have been described, including reduction of dopaminergic discharge from the ventral tegmental area (VTA) and suppression of cocaine-induced self-application (Zhang, Gao et al. 2017). This "anti-addictive" effect often serves as an argument for co-medication of CBD for products which predominantly contain THC.

2-AG. The main endogenous ligand for CB2 is 2-arachidonylglycerol (2-AG; ▸ Chapter 6.1.5.1).

Neurochemical characterization

CB2 is encoded by the CNR2 gene and consists of 360 amino acids in humans. CB2 and CB1 have a sequence homology of 44%. The sequence homology of CB2 between rodents and humans is only about 80% and thus varies significantly more than for CB1. In humans, two CB2 isoforms (formed via splicing) with different localization are known (reviewed in Zou and Kumar 2018), whereas as many as four isoforms have been described in rats.

CB2, like CB1, inhibits adenylate cyclase and stimulates MAPK. The effects on calcium and potassium channels are unclear.

6.1.4.3 Other cannabinoid receptors or binding sites

In addition to CB1 and CB2, there are numerous other binding sites for endo- and exocannabinoids. Information on clinical significance is only known for some of these; most findings are from in vitro experiments, with some coming from animal studies. The best studied are binding sites whose inhibition or stimulation reduces pain (Vučković, Srebro et al. 2018). These analgesic binding sites include:

- G protein-coupled receptor 55 or 18 (GPR55 or GPR18, respectively, syn. N-arachidonoyl-glycine receptor, NAGly);
- PPARγ;
- Transient receptor potential channels (TRP) with their subgroups TRPV, TRPA and TRPM.

6.1.4.4 Interactions and heterodimerization with CB

Endo- and exocannabinoids do not only act via simple interaction with their binding sites. Interaction of these binding sites e.g. via heterodimerization with other widespread receptors, such as the opioid receptors, is also clinically relevant; this activity substantially increases the scope of action of cannabinoids. In addition, further interactions between CB, opioid and TRPV1 receptors have been described (Zádor and Wollemann 2015; Smith, Selley et al. 2007).

6.1.5 Ligands

Agonists for CB receptors and other binding sites of the ECS can be divided into:

- Endogenous eicosanoids or endocannabinoids (EC) such as AEA, 2-AG, virodhamine, and other ethanolamides such as palmitoylethanolamide (PEA) or oleoylethanolamide (OEA) ▸ Chapter 6.1.5.1;
- Classical (natural or plant) agonists such as THC and CBD, including their derivatives ▸ Chapter 6.1.5.2;
- Synthetic agonists and antagonists ▸ Chapter 6.1.5.2.

Overviews of the endocannabinoids can be found in Köfalvi (2008), Baggelaar, Maccarrone et al. (2018), Burstein (2018), Chanda, Neumann et al. (2019), Rahaman and Ganguly (2021) and Zou and Kumar (2018).

6.1.5.1 Endogenous ligands (endocannabinoids)

The body produces a number of molecules that activate CB receptors; these are termed endocannabinoids (EC). The most important and best known are anandamide (AEA) or 2-arachidonoylglycerol (2-AG) as well as derivatives of long-chain unsaturated fatty acids (eico-

Tab. 6.2 Overview of the major endocannabinoids AEA and 2-AG

	AEA	2-AG
Pharmacodynamics		
CB1	High affinity partial agonist Main endogenous ligand	Full agonist, medium affinity
CB2	Agonist, only weakly active	Full agonist, medium affinity Main endogenous ligand
TRPV1	Agonist	Agonist
GRP55	Agonist	Agonist
Pharmacokinetics and metabolism		
Synthesis	From NAPE via NAPE-PLD	From triglycerides containing arachidonic acid via DAGL
Reuptake into the synapse	Via anandamide transporter (ANT)	
Degradation	FAAH (basic pH) NAAA (acidic pH)	MAGL ABHD6, ABHD12
Serum level (nmol/l)	1–5	10–500

sanoids), which are synthesized de novo from membrane-bound fatty acids as needed by the action of phospholipases (Hinz 2017; Palmer, Thakur et al. 2002; for an overview, see ▫ Tab. 6.2). EC are partial or full agonists of CB receptors. As they are generated as part of membrane or transmembrane metabolism, endocannabinoids are also categorized as bioactive lipid mediators.

One of the best known precursor molecules for endocannabinoids is arachidonic acid, which is also a precursor of prostaglandins and leukotrienes, as well as an indirect target of anti-inflammatory glucocorticoids and COX inhibitors (NSAIDs).

The effects of endocannabinoids, however, are not limited to CB-mediated effects. Endocannabinoids, just like exocannabinoids, can interact with additional targets (receptors such as enzymes).

Metabolism of EC. EC are derivatives of arachidonic acid with autocrine and paracrine effects.

In neurons, immune cells or other somatic cells, EC and other ethanolamides are formed from membrane-bound precursor molecules, primarily with the involvement of phospholipase Cβ and D (PLCβ and PLD, respectively) and diacylglycerol lipase (DAGL; ○ Fig. 6.2). They are rapidly hydrolyzed and inactivated by FAAH and monoacylglycerol lipase (MAGL), respectively (▫ Tab. 6.2). FAAH also degrades other fatty acid amides in addition to EC, such as OEA and PEA. This means that co-players of the ECS also interact with other intermediary systems at the level of the degrading enzymes.

EC and eicosanoids including their metabolites are in constant exchange: thus, hydrolyzed AEA can either be converted "back" into arachidonic acid, or via COX-2 into proalgesic prostaglandins. COX inhibitors such as ibuprofen can therefore have analgesic effects via inhibition of COX-2-mediated conversion of AEA. Numerous compound-specific interactions with EC have also been described for paracetamol (Bertolini, Ferrari et al. 2006; Ratner, Kaczmarek et al. 2018).

Following release into the intracellular synaptic space, the uncharged, hydrophobic EC cannot diffuse freely like other neurotransmitters. They are either transported, or degraded by either endocytosis or the action of enzymes.

Arachidonoyl ethanolamide (AEA)

The name anandamide (synonymous with arachidonoyl ethanolamide, AEA) is derived from Sanskrit "ananda", meaning bliss. This endocannabinoid is the major endogenous ligand for CB1, while other acylethanolamides do not interact with CB and therefore are not endocannabinoids. In addition, AEA acts as a full agonist of TRPV1 and activates GRP55; it inhibits the 5-HT3A receptor (antiemesis), potentiates glycine receptor action (including inhibition of glutamate transmission and excitotoxicity), activates PPARγ (neuroprotection) and inhibits T-type calcium channels (▫ Tab. 6.3).

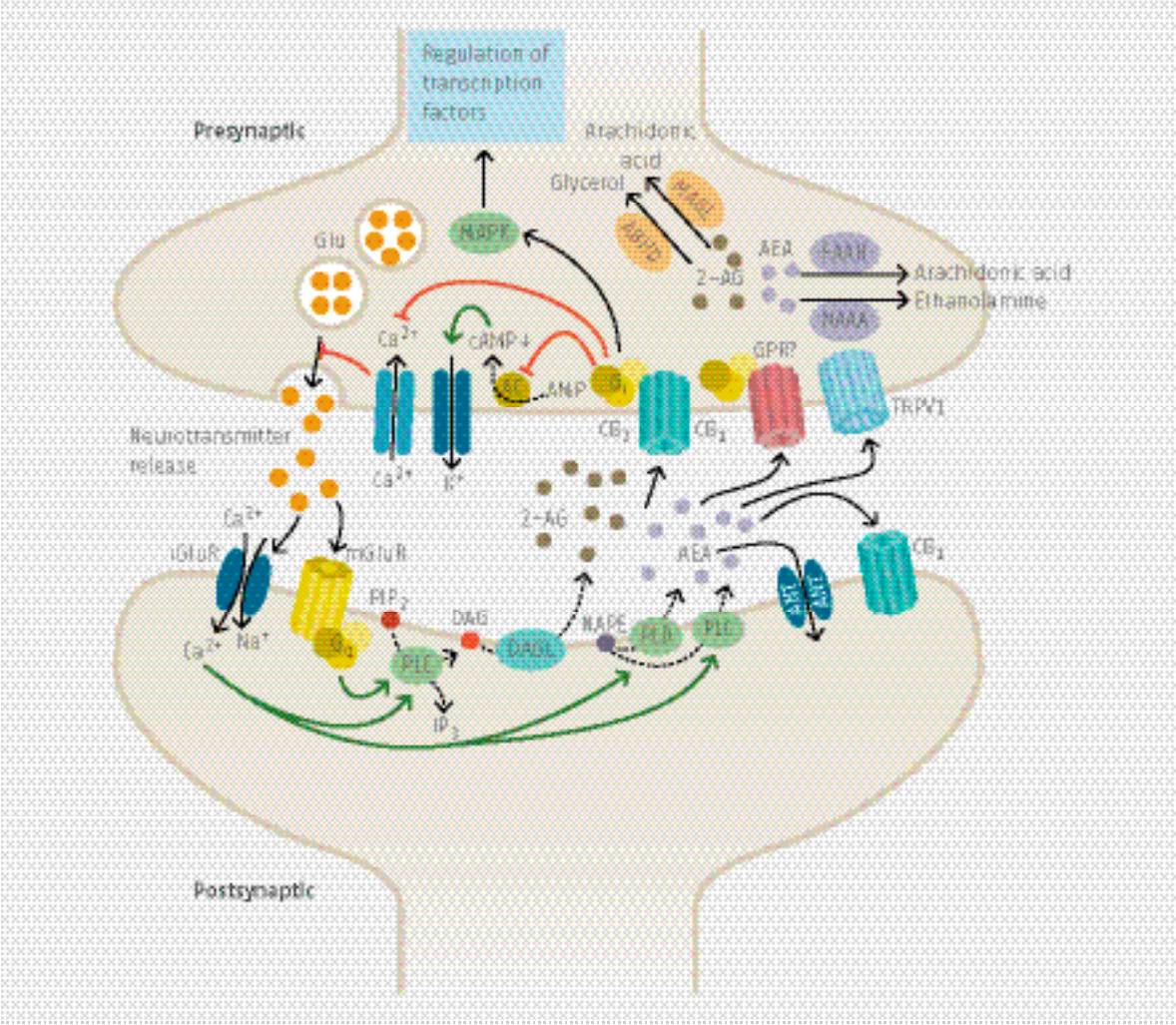


Fig. 6.2 Signaling pathways and metabolism of the endocannabinoids anandamide and 2-arachidonylglycerol. Following synaptic excitation (glutamate, Glu), calcium ions (Ca2+) flow into the postsynaptic cell (bottom left); consequently, anandamide (arachidonoylethanolamine, AEA) and 2-arachidonylglycerol (2-AG) are formed from N-arachidonoyl phosphatidylethanolamine (NAPE) and diacylglycerol (DAG), respectively, and secreted into the synaptic cleft. They then bind to the CB1 receptor of the presynaptic cell and, via several intermediate steps, prevent the release of a neurotransmitter (here as an example glutamate, Glu) into the synaptic cleft. Both endocannabinoids are degraded via fatty acid amide hydrolase (FAAH), N-acylethanolamine amide hydrolase (NAAA) or monoacylglycerol lipase (MAGL) and 2-arachidonoylglycerol hydrolase (alpha/beta hydrolase domain ABHD), respectively. Other abbreviations: iGluR/mGluR: ionotropic/metabotropic glutamate receptor; PIP2: phosphatidylinositol bisphosphate; IP3: Inositol triphosphate; PLC/PLD: phospholipase C/D; DAGL: diacylglycerol lipase; Gi: inhibitory G protein; AC: adenylate cyclase; MAPK: mitogen-activated protein kinase; TRPV1: transient receptor potential vanilloid 1; ANT: anandamide transporter (according to Dingermann and Zündorf 2016).

AEA, the ethanolamide of arachidonic acid, is formed from the membrane-bound precursor molecule N-acylphosphatidylethanolamine (NAPE). NAPE is cleaved by a specific phospholipase D (PLD), NAPE-PLD, to generate AEA. An alternative synthetic pathway in immune cells is the hydrolysis of NAPE by a NAPE-specific phospholipase C (Fig. 6.2).

The affinity of AEA for CB1 is significantly higher than for CB2 (Ki 32 vs 1,930 nmol/l).

AEA is degraded by fatty acid amide hydrolase (FAAH), and it is primarily the increase in AEA associated with inhibition of FAAH that makes FAAH an attractive therapeutic target for ECS enhancement.

Another specific feature of AEA is the high-affinity anandamide transporter (ANT), which transports AEA into neurons and astroglia and thus, analogous to the reuptake transporters for biogenic amines, terminates the (synaptic) effects of AEA.

The importance of AEA arises from its potent CB1 stimulation with THC-like effects, especially with respect to psychiatric homeostasis. A genetic loss-of-function of FAAH with significant increase in AEA

7 Medical applications and their evidence

7.1 General information on dosage and dose finding

Prof. Dr. Kirsten R. Müller-Vahl

Regardless of the indication and the selected cannabis-based drug, treatment should always be slowly uptitrated in to minimize the occurrence of side effects. Since the majority of cannabis-based drugs are used for the treatment of chronic diseases, the top priority is not a particularly rapid onset of action, but the best possible tolerability. If a rapid onset of action is desired, a low dose should also be started initially. Subsequently, a more rapid increase in dose can be attempted.

Slow dosing of cannabis-based drugs not only reduces the number, frequency, and severity of almost all side effects, especially the occurrence of fatigue, dizziness, and drowsiness (o Fig. 7.1), but also prevents early and, above all, avoidable treatment discontinuations due to adverse effects (MacCallum and Russo 2018). Development of tolerance arises with regular use, especially for psychotropic effects and with the most pronounced effect seen for cognitive impairment (Orsolini, Chiappini et al. 2019).

Start low, go slow – but go!
This principle can be used to summarize the dosage of all cannabis-based medicines, regardless of indication, substance and method of use.

7.1.1 Start of treatment

In treatment with cannabis-based medicines, the dosage is primarily based on the THC content, since according to current knowledge, the vast majority of side effects of cannabis-based medicines are due to THC. In contrast, CBD, even as a high-dose therapy of several hundred or even over 1000 mg/day, is considered to be extremely well tolerated. However, to date, there is very little data available for high-dose therapy with pure CBD in adults. Nevertheless, according to the currently available studies, CBD was always well tolerated. Often, no side effects occurred at all. In healthy subjects, single doses up to 6000 mg CBD and repeated doses up to 1500 mg/day were well tolerated (Taylor, Gidal et al. 2018). The most common side effects were diarrhea, nausea, headache and drowsiness. All side

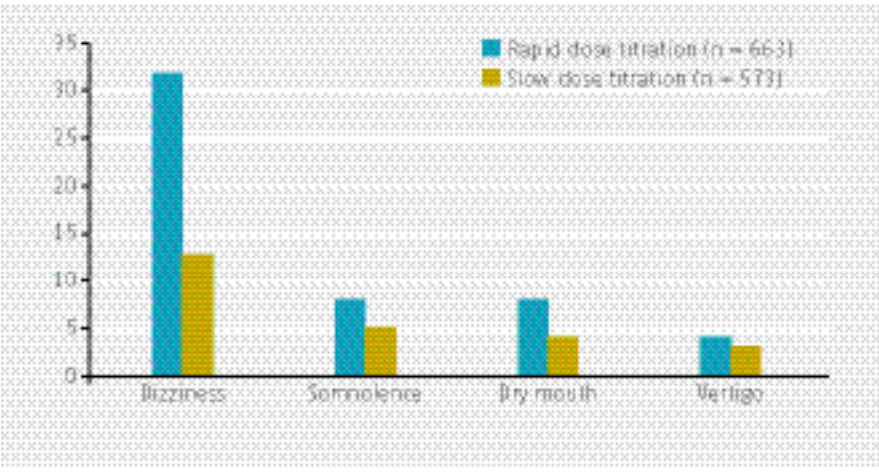


Fig. 7.1 Comparison of side effects (> 3%) of nabiximols in MS patients with rapid dose titration and higher dose (blue) or slow dose titration and a maximum dose of 32.4 mg THC and 30 mg CBD (ocker; MacCallum and Russo 2018)

effects were rated as mild or moderate (Larsen and Shahinas 2020).

For treatment with oral THC-containing cannabis-based medicines, a single dose of 2.5 mg THC/day may be considered a good guide for an appropriate starting dose. This also approximates the amount of THC in one metered dose of the cannabis extract nabiximols (Sativex®), which contains 2.7 mg THC per spray. The clinically required dose of THC may potentially be reduced by the application of a water-soluble extract with novel nanotechnology, i.e. with very small particle size and thus improved oral absorption; however, this must first be verified in independent studies.

For treatment with medicinal cannabis flowers, 25–50 mg of cannabis per day as a single dose, regardless of THC content, is considered a reasonable initial dose (Müller-Vahl and Grotenhermen 2020).

7.1.1.1 Particularly cautious start of treatment

For patients judged to be at high risk of side effects, a more cautious start to treatment with an initial dose of 0.5–1.5 mg THC/day should be chosen. However, this is not possible with all currently prescribable finished medications. For nabiximols (Sativex®), the smallest dose unit is 2.7 mg THC/spray. Nabilone (Canemes®) is available in capsules of 1 mg each, which is equivalent to approximately 7–8 mg THC in terms of potency.

The risk of side effects may be increased for a variety of reasons:

- **Age**:
  - Elderly patients often react more sensitively to cannabis-based drugs, as is the case with other central nervous system drugs.
  - If treatment of children is undertaken, always start with a very low initial dose, again due to the limited data available.
- **Polypharmacy:**
  - If treatment with other drugs is also given, attention should be paid to possible interactions.
  - Of particular clinical relevance are pharmacodynamic interactions with THC, for example, as a result of an increase in dizziness, fatigue or drowsiness. Theoretically, cannabis-based drugs can be combined with all drugs (MacCallum and Russo 2018).
- **Indication:**
  - Although dosing is primarily independent of indication, treatment should be initiated with particular caution for conditions that are already associated with symptoms that may typically also occur as adverse effects of cannabis-based treatment.
- **No previous experience with cannabis:**
  - Patients who have never taken cannabis before should also have their doses escalated more slowly.

Side note

For pain patients currently taking an opioid treatment, one group of experts recommended initiating an additional cannabis-based treatment with the aim of opioid reduction, initially with a CBD-dominant cannabis extract (initial dose: 5–20 mg CBD/day), and then to add THC only if the effect is insufficient (initial dose: 0.5–3 mg THC/day) Sihota, Smith et al. 2020).

7.1.1.2 Start of treatment when there has been previous cannabis use

If an individual has already self-medicated with cannabis before the initial prescription of a cannabis-based drug, then the patient's experience should always be included when establishing the treatment. Inquiries should be made about:

- Duration of self-medication;
- Type of intake;
- Usual dose;
- Number of doses taken per day;
- Positive effects; and
- Adverse effects

The THC content of the street cannabis ingested is unknown to the majority of patients. As pharmacy-grade cannabis usually has higher THC content and greater purity, the initial dose should be reduced initially when switching from street to pharmacy cannabis, and then increased again if necessary.

Case study

If a patient reports previously taking 1.0 g of street cannabis per day, therapy could for example start with a cannabis flower of medium to high THC content (approximately 15–22% THC) and an initial dose of 0.5 g/day. When switching to an oral cannabis extract, a THC dose of 5.0–10.0 mg/day could be used initially and the dose subsequently increased if necessary.

Most patients who have self-medicated with street cannabis for a long time without medical supervision have increased their dose over the years and thus developed increasing tolerance. When initiating a medically supervised and prescribed treatment with pharmacy-grade cannabis, a higher dose is then often necessary than would be the case for a cannabis-naive patient.

7.1.2 Type of use

The type of application is also relevant for the dosage. Apart from rare administrative forms (topical, rectal as suppository), the majority of treatment is oral as oral

spray, oil and capsule or inhalational (▸Chapter 14.1). Individual patients achieve the best treatment outcome with combined oral and inhalational use. However, it is recommended to start treatment initially using only one dosage form. Detailed information on the different routes of administration and dosage forms as well as on the resulting differences in pharmacokinetics can be found in ▸Chapter 14.1.

■ **CAUTION When switching from oral to inhaled treatment, or vice versa, the dose related to the THC content must be adjusted due to the different pharmacokinetics. It is not possible to provide a standard conversion to apply here.**

7.1.3 Dosage titration

The dose is increased slowly, always making adaptations to the individual according to tolerability; it is not possible to provide a standard plan that can be applied generally. For oral intake, a slow dose increase means increasing by 1–2 mg THC once or twice a week (Sihota, Smith et al. 2020). In patients without increased risk of side effects, a dose increase of 2.5 mg THC every 3 (or every 2–5) days is usually well tolerated. The summary of product characteristics for nabiximols (Sativex®) recommends an interval of 2 days for the first two dose increases only, followed by a daily increase of 1 metered dose corresponding to 2.7 mg THC.

By definition, a maximum daily dose is specified only for the approved finished medicinal products nabiximols (Sativex®) at 32.4 mg THC (corresponding to 12 metered doses) and the CBD preparation Epidiolex® (20 mg or 25 mg CBD/kg b. w.). For the THC analog nabilone (Canemes®), the recommendation is to not exceed a dose of 6 mg/day (corresponding to about 42–48 mg THC) distributed across 3 doses.

Based on general experience, daily doses of THC-containing medications are often between 15 and 20 mg THC/day (MacCallum and Russo 2018). However, they can vary significantly in individual cases and, especially in elderly patients, can be as low as 2.5–5 mg THC/day (or even lower), or 40 or 50 mg/day (or even higher) if clinically necessary and tolerated appropriately (Müller-Vahl and Grotenhermen 2020).

Side note

An acute lethal dose for cannabis in humans is not known. According to calculations by the U.S. National Institute of Drug Abuse (NIDA), ingestion of approximately 750 kg of cannabis within 15 minutes would theoretically result in death (Young 1988). This illustrates the broad therapeutic window of cannabis-based medicines.

Since the effects of inhalation occur very quickly, i.e. within a few minutes (in contrast to oral intake) with the maximum effect often being reached after 15 minutes, the dose can be up-titrated more quickly if necessary by assessing the effect and tolerability after each individual inhalation and then increasing the dose by one inhalation every 15–30 minutes until the desired effect is achieved. Common daily doses for inhaled application of cannabis flowers range from 0.5 to 1 g. In general, the daily dose decreases with increasing THC content. Depending on the indication and individual tolerance, very low daily doses of less than 0.05 g can also be effective. In individual cases, however, the dose is also significantly higher. In the majority of cases, maximum daily doses of up to about 5 g of cannabis are considered medically useful (MacCallum and Russo 2018; Müller-Vahl and Grotenhermen 2020).

■ **CAUTION If a treatment involves a CBD-dominant extract or CBD-dominant flowers, the total daily dose of THC taken at the same time should be taken into account in the case of a CBD high-dose therapy at a dose of several hundred or 1000 mg CBD/day, which, depending on the THC content, can then also be in the (upper) therapeutic range.**

7.1.4 Application frequency and distribution throughout the day

The number of doses and their distribution throughout the day do not follow a fixed pattern, but rather are always adapted to the individual. The type of application with its different duration of action plays just as much a role as the indication. If a treatment is to be initiated very cautiously, a single dose in the evening is recommended, so that possible side effects can be slept off if necessary. Subsequently, either the evening dose can be further increased, or a second daily dose can be introduced in the morning. Certain indications (such as sudden spasms or breakthrough pain) may require on-demand treatment.

Tip

The best way to estimate the effect is to increase a morning dose slowly over several days until the onset of effects is seen. Depending on the effect and duration of action, the second step would then be to decide how to distribute doses over the day as well as how many applications to give.

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7.2 Chronic pain

Prof. Dr. Matthias Karst

7.2.1 Preclinical findings

Electrophysiological, neurochemical and behavioral experiments in animals have convincingly shown that activation of both cannabinoid receptor types slows nociceptive transmission (Karst, Wippermann et al. 2010; Lötsch, Weyer-Menkhoff et al. 2018). The recruitment of CB1 receptors in the CNS is not necessarily required to achieve this (Agarwal, Pacher et al. 2007).

Under inflammatory conditions, CB2 receptor activity, which is upregulated on C-fibers and microglia, is also involved in this process (Wotherspoon, Fox et al. 2005; Jhaveri, Sagar et al. 2007), whereby inflammatory processes, among others, are actively terminated (Zurier and Burstein 2016). Interestingly, CB2 receptors are also found on epidermal keratinocytes. Their activation leads to analgesia to noxious temperature stimuli via the production and release of beta-endorphin, an effect that can be blocked by naloxone (Ibrahim, Porreca et al. 2005).

CB1 receptor-mediated CNS pain interference is controlled via activation of pain inhibitory pathways, reduction of the central stress response and initiation of antihyperalgesic mechanisms (long-term depression, LTD) (o Fig. 7.2).

Context-dependent pain relief (placebo effect) is mediated primarily by activation of the endorphin and endocannabinoid systems (Hohmann, Suplita et al. 2005; Carlino and Benedetti 2016). The balance of how much each system is activated varies from individual to individual (Carlino and Benedetti 2016), which may also be a consequence of pharmacological conditioning: if opioids were primarily used for pain relief in the past, the endorphin system may predominate; if cyclooxygenase inhibitors (e.g. ibuprofen) were primarily used, the ECS comes to the fore (Carlino and Benedetti 2016).

The ECS also functions as a buffering system of the central stress response (Morena, Patel et al. 2016). In a yin-yang relationship, a reduction in anandamide (AEA) concentration in the hippocampal and amygdala regions triggered by fatty acid amide hydrolase (FAAH) stimulation triggers activation of the hypothalamic-pituitary-adrenocortical (HPA) axis, as well as anxiety, storage of aversive memory content and other fight-or-flight events, whereas the increase in 2-arachidonylglycerol (2-AG) concentration can terminate this process (o Fig. 7.3). If a collapse of this system occurs under chronic stress (o Fig. 7.4), the allostatic load can no longer be managed with reduced neuroplasticity and disorders (PTSD, depression, anxiety disorder) may emerge (Morena, Patel et al. 2016; Hill and Lee 2016; Karhson, Hardan et al. 2016). There is a broad overlap between the aforementioned disorders and chronic pain (Åkerblom, Perrin et al. 2017).

Moreover, the ECS is also involved in erasing memory content (long-term depression, LTD; Marsicano, Wotjak et al. 2002), for example, by modulating GABAergic transmission in the basolateral amygdala (Fattore, Melis et al. 2010) or by suppressing the activity of supraspinal nociceptive networks in the presence of enhanced CB1 activity in the periaqueductal gray (PAG; Walker, Huang et al. 1999). This finding is particularly relevant because a large part of chronic pain is a consequence of emotional learning of pain mediated by the cortico-mesolimbic system (nucleus accumbens, amygdala, hippocampus, prefrontal cortex) (Vachon-Presseau, Centeno et al. 2016).

The ECS is also linked to the opioid system. CB1-knockout mice, for example, showed an attenuated effect of opioid-dependent stress-induced analgesia (Valverde, Ledent et al. 2000). Synergistic effects between cannabinoid and opioid analgesia have been described (Cichewicz 2004). Animal studies have shown that the combined intake of cannabinoids and opioids can reverse tolerance effects to opioids (Smith,

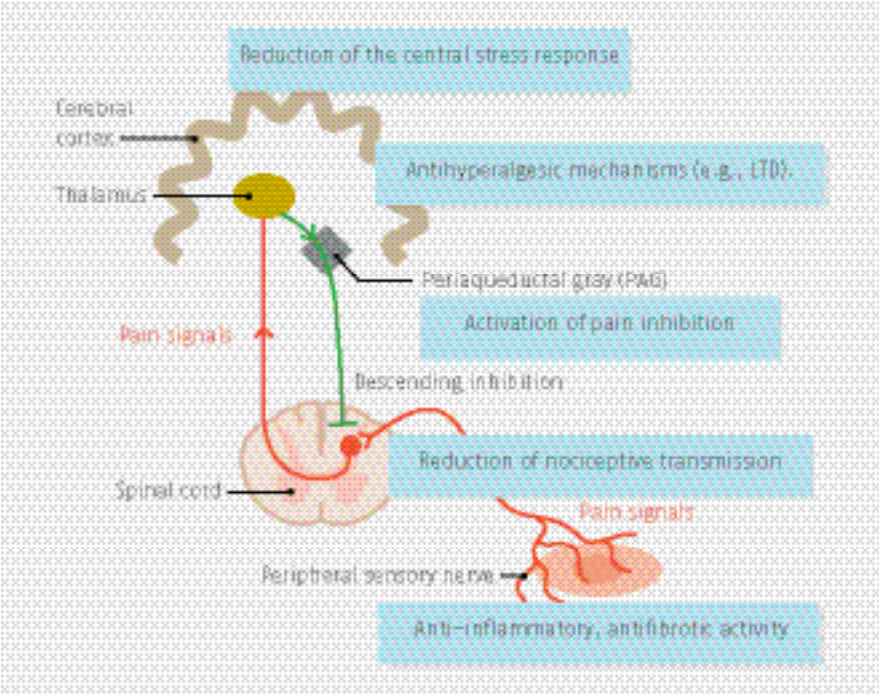

Fig. 7.2 Endocannabinoid system (ECS) activity in the nociceptive system

Selley et al. 2007) and there is a significant opioid saving effect when cannabinoids are administered (Nielsen, Sabioni et al. 2017). In a cross-sectional study of individuals using medical cannabis, it could be demonstrated that particularly opioids, benzodiazepines, migraine medications and sleeping tablets could be used more sparingly (Piper, DeKeuster et al. 2017).

7.2.2 Clinical findings and evidence

To date, it has not been clinically proven that pain relief can be achieved by exclusively activating peripheral CB1 receptors (Agarwal, Pacher et al. 2007). Other approaches to avoid cannabimimetic effects (bypassing CB1 activation) while achieving significant pain relief have also not been confirmed in clinical trials to date. Thus, the (indirect) increase of endocannabinoid tone by using newly developed inhibitors of fatty acid amide hydrolase (FAAH; Fig. 7.5) or monoacylglycerol lipase (MAGL) for this purpose has not been convincing in clinical studies to date (Fowler 2021). It has long been known that some non-opioid analgesics exert effects not only in the arachidonic acid cycle but also in the ECS (Păunescu, Coman et al. 2011). These include, for example, ibuprofen, which also acts as an inhibitor of FAAH, and N-arachidonoylphenolamine, which, as a degradation product of paracetamol, also leads to an increase in AEA concentration in the synaptic cleft as a result of inhibition of the fatty acid-binding transport protein (FABP) (Deutsch 2016; Fig. 7.5). Of the newly developed cannabinoids, only ajulemic acid (=AJA; Burstein 2018) which binds predominantly to peripheral CB2 receptors, showed moderately pronounced

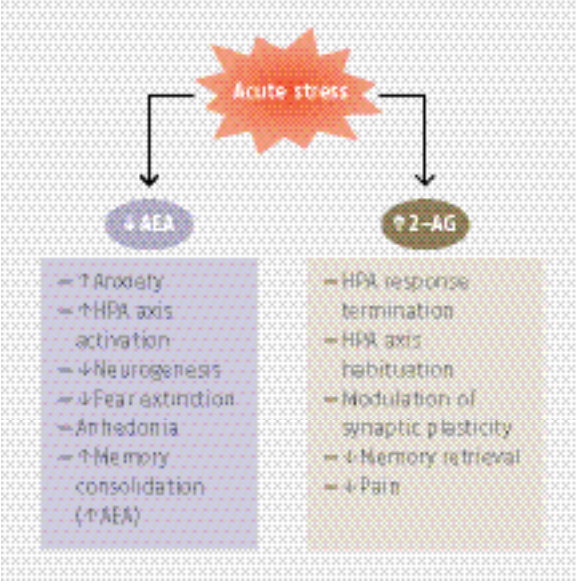

Fig. 7.3 Endocannabinoid system (ECS) activity during acute stress (according to Morena, Patel et al. 2016): acute stress exposure generally leads to bidirectional regulation of anandamide (AEA) and 2-arachidonoylglycerol (2-AG), with AEA reduced and 2-AG increased by stress. The decrease in AEA signaling is thought to be partly responsible for the manifestation of anxiety, activation of the HPA axis, suppression of neurogenesis in the hippocampus and impaired fear suppression. In contrast, the stress-induced increase in 2-AG buffers and limits the effects of stress on the brain, particularly by helping to terminate stress-induced activation of the HPA axis and promoting habituation to stress.

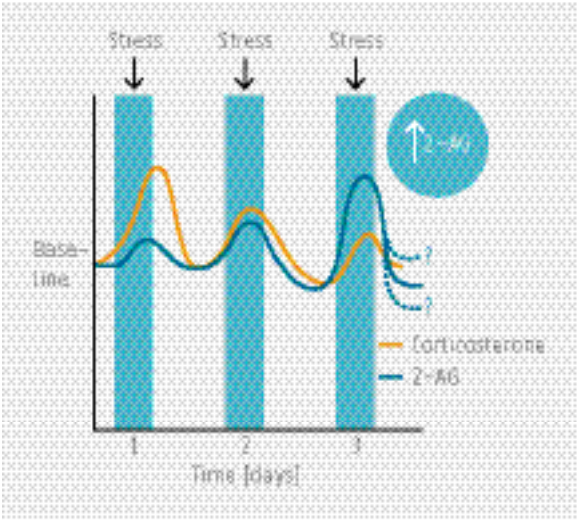

Fig. 7.4 Endocannabinoid system (ECS) dysfunctionality in chronic stress (modified according to Hill, Campolongo et al. 2018): stress exposure increases 2-AG levels in the amygdala and prefrontal cortex, possibly driven by stress-induced corticosterone release. With subsequent stress exposures, the 2-AG response shows sensitization; consequently, 2-AG concentrations are more elevated. This progressive increase in stress-induced 2-AG release in the amygdala correlates with habituation of the HPA axis response to repeated homotypic stress exposure; glucocorticoid concentration tends to remain lower with subsequent stress exposures than with initial exposure; i.e. the ECS becomes dysfunctional with chronic stress.

pain reduction in patients with chronic nerve pain in a small study (Karst, Salim et al. 2003). The compound is currently in clinical development for the anti-inflammatory treatment of various collagenoses (Spiera, Hummers et al. 2020).

Furthermore, in contrast to the preclinical data, no convincing clinical evidence exists that exogenously administered cannabinoids can significantly reduce the intensity of acute pain (Karst, Wippermann et al. 2010; Lötsch, Weyer-Menkhoff et al. 2018). Functional magnetic resonance imaging (MRI) studies in the capsaicin model suggest that the limbic system rather than the sensory system is affected. This fits with the observation that the pain stimulus was perceived as less unpleasant by the test participants, but the pain intensity was unchanged (Lee, Ploner et al. 2013). A meta-analysis conducted on this topic confirmed this finding: while there was a significant reduction in the pain affect, there was no clear effect on pain Intensity (De Vita, Moskal et al. 2018; ○ Fig. 7.6).

In contrast, exogenously administered cannabinoids are effective for chronic pain (National Academies of Sciences, Engineering, and Medicine 2017). This finding results from the results of randomized controlled trials (RCTs) with a total of approximately 2500 patients (Karst, Wippermann et al. 2010; Whiting, Wolff et al. 2015). Systematic meta-analyses published in the following studies also led to similar results (Petzke, Enax-Krumova et al. 2016; Aviram and Samuelly-Leichtag 2017; Meng, Johnston et al. 2017).

The use of cannabinoids for neuropathic pain has been particularly intensively studied. In this context, systematic reviews and meta-analyses (Petzke, Enax-Krumova et al. 2016; Meng, Johnston et al. 2017; Mücke, Phillips et al. 2018) showed that there is external evidence of medium (Meng, Johnston et al. 2017) or low (Petzke, Enax-Krumova et al. 2016; Mücke, Phillips et al. 2018) quality for the use of THC/CBD oral spray (Nabiximols, Sativex®). It was concluded that as an add-on therapy, a cannabinoid approach to neuropathic pain can be tried when satisfactory relief has not been achieved with other methods. In the largest RCT published to date, including over 600 multiple sclerosis patients, more than 50% of patients in the treatment arms (THC or THC/CBD combination) showed pain reduction (Zajicek, Fox et al. 2003). This study was not included in the meta-analyses because the pain was not explicitly defined as neuropathic pain (Petzke, Enax-Krumova et al. 2016), although the lack of efficacy of standard analgesics in many study participants (Zajicek, Fox et al. 2003) and the high prevalence of neuropathic pain (Grau-López, Sierra et al. 2011; Ferraro, Plantone et al. 2018) in patients with multiple sclerosis suggest that neuropathic pain was predominant in the cohort studied. Physical and cognitive impairment in patients with multiple sclerosis exacerbates the affective component of pain (Scherder, Kant et al. 2018), which may explain the high response rate of the patient mostly severely affected by multiple sclerosis to cannabinoid therapy in the study by Zajicek, Fox et al. (2003). In the only meta-analysis that evaluated individual patient data, in contrast to all other meta-analyses, there was significant and more pronounced pain relief with inhaled cannabis as compared to placebo over short observation periods in the 178 patients included who suffered from chronic neuropathic pain (Andreae, Carter et al. 2015).

One review of systematic meta-analyses concluded that a limited evidence-based recommendation for the use of THC/CBD oral spray (nabiximols, Sativex®) can only be made for chronic neuropathic pain (Häuser, Fitzcharles et al. 2017). In contrast, other meta-analyses made that assessment that it was unlikely that cannabinoids are highly effective medications for chronic non-cancer pain (Stockings, Campbell et al. 2018; □ Tab. 7.1). This cautious clinical assessment is also due to the overall small number of available RCTs and the marked heterogeneity of the studies included (Karst and Passie 2018).

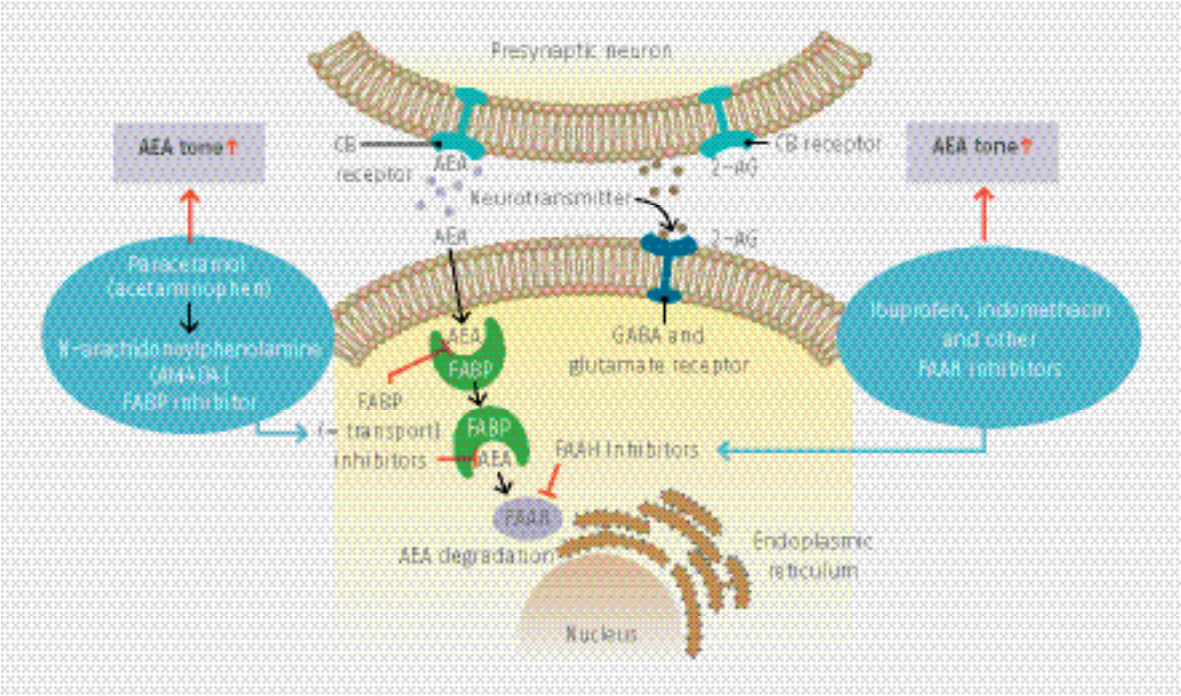

Fig. 7.5 ECS and non-opioid analgesics: Endogenous anandamide (AEA) passes through the cell membrane without the involvement of a protein transporter and reaches the endoplasmic reticulum (ER) in the cytosol by means of fatty acid-binding protein transporters (FABP), where the fatty acid amide hydrolase (FAAH) responsible for AEA degradation is localized. Accordingly, inhibition of FABP or FAAH leads to increased AEA levels or signaling at the receptor by inhibiting AEA degradation (modified according to Deutsch 2016).

As alluded to above, the selection of outcome parameters also seems to have a significant influence on the study results (pain intensity versus pain effect). This is exemplified by a prospective cohort study with chronic pain patients, involving more than 1000 subjects (Aviram, Pud et al. 2021). After 12 months of treatment with a cannabinoid, pain intensity decreased by 20%, but the affective pain component and sleep disturbance both decreased by 33%, and the expression of depression and anxiety decreased by 32% and 40%, respectively (Aviram, Pud et al. 2021). There was a morphine equivalent savings effect of 42% (Aviram, Pud et al. 2021). It is clear that the focus is not exclusively on reducing pain intensity, but on improving a variety of relevant areas of life that are associated with chronic pain.

Cannabinoids are also effective in the painful spasticity associated with multiple sclerosis (Zajicek, Fox et al. 2003), which led to a corresponding approval of the THC/CBD oral spray nabiximols (Sativex®) in Europe in 2011.

Taking an overview, evidence is emerging that cannabinoids can alleviate chronic pain, with benefits found particularly for neuropathic pain and painful spasticity (Whiting, Wolff et al. 2015; Karst and Passie 2018), and less so for nociceptive pain (Fitzcharles, Baerwald et al. 2016). On the other hand, a large meta-analysis on cannabinoids for chronic pain found no significant differences in efficacy between chronic nociceptive and chronic neuropathic pain, or chronic non-cancer and chronic cancer pain (Wang et al. 2021).

In some guidelines for the treatment of chronic neuropathic pain, cannabinoids are mentioned as third-line substances, after antidepressants and anticonvulsants (Mu, Weinberg et al. 2017; Cruccu and Truini 2017). With the involvement of the European Medicines Agency (EMA), ways to conduct benefit-risk analyses in clinical pharmaceutical research have been identified (reviewed in Nutt, Phillips et al. 2021). An international group consisting of pain therapists (with and without experience in the use of cannabinoids), psychiatrists, neurologists and scientists with expertise in the pharmacology of cannabinoids, as well as patient representatives (United Patient Alliance) developed an corresponding decision analysis (Nutt, Phillips et al. 2021). Using 17 criteria weighted by clinical relevance, 12 drugs commonly used for chronic neuropathic pain were evaluated, including cannabinoids, antidepressants, gabapentinoids and opioids. According to these criteria, cannabinoids appear to be more important in terms of improving quality of life than in reducing pain intensity alone (Nutt, Phillips et al. 2021). This is particularly true when compared to duloxetine, gabapentinoids and amitriptyline (Nutt, Phillips et al. 2021). If the side effect profiles are also taken into account, then the

10 Legal framework for the use of cannabis

10.1 International agreements

Dr. Hendrik Greve

The legal use of cannabis is based on the three international United Nations (UN) conventions on narcotic drugs. The conventions were drawn up in the second half of the 20th century and have not undergone any fundamental changes in their regulations since then. However, the respective annexes ("schedules" or "tables") of the conventions have been regularly expanded with regard to additional substances that are subject to international control.

The names of the conventions are always linked to the year in which the individual treaties were concluded:

- "Single Convention on Narcotic Drugs, 1961" United Nations 1961);
- "Convention on Psychotropic Substances, 1971" (1971 Convention on Psychotropic Substances; United Nations 1971);
- "United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988" United Nations 1988).

Cannabis is subject to international control under the Single Convention on Narcotic Drugs, 1961 and is listed in its annexes. Surprisingly, however, the psychoactive ingredient (-)-trans-Δ^9-tetrahydrocannabinol (THC or dronabinol) is listed in the annexes of the Convention on Psychotropic Substances, 1971. This contradicts the principle of the UN conventions which is otherwise applied, which is to control psychoactive metabolites by the same convention as for the associated natural plant material. For example, this is the case for the opioid alkaloids morphine, thebaine and oripavine, and for the coca alkaloids cocaine and ecgonine, which, like their original plant material opium and poppy straw concentrate or coca leaves, are all subject to the Single Convention on Narcotic Drugs, 1961.

The overriding principle of the UN International Conventions on Narcotic Drugs is to limit the use of all narcotic drugs and psychotropic substances, including cannabis (and dronabinol), to exclusively medical and scientific purposes. In addition, the establishment and maintenance of a special administrative service in each UN member state to implement the provisions of the conventions, as well as a system of demand estimates ("estimate" or "assessment") and statistical reporting, form the basic pillars of international monitoring of the legal trade in narcotic drugs and psychotropic substances. In Germany, the Federal Institute for Drugs and Medical Devices (BfArM) carries the tasks of the special administrative service in the sense of the three UN Narcotics Conventions (BtMG). The United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988 plays a minor role with regard to the legal use of cannabis (and dronabinol), as the focus is on preventing illicit traffic in narcotic drugs and psychotropic substances and monitoring so-called precursors (▸ Chapter 10.1.3).

The complex international network between the 1961 and 1971 Narcotics Conventions, the various UN agencies or organs and bodies, and the individual UN member states is illustrated in the simplified diagram in o Fig. 10.1.

Controlled narcotic drugs and psychotropic substances are designated in Schedules I-IV of the 1961 and 1971 Conventions. Apart from a few plant parts and plant constituents, they are mainly chemically defined organic compounds. When amendments are made to the schedules (primarily extensions to include additional substances), the various UN institutions perform different functions. First, a member state or the World Health Organization (WHO) informs the United Nations (UN) Secretary-General if changes are required. The UN Secretary-General then informs all member states, the **Commission on Narcotic Drugs** (CND) and, if the information comes from a member state, the WHO. As a rule, the WHO convenes the

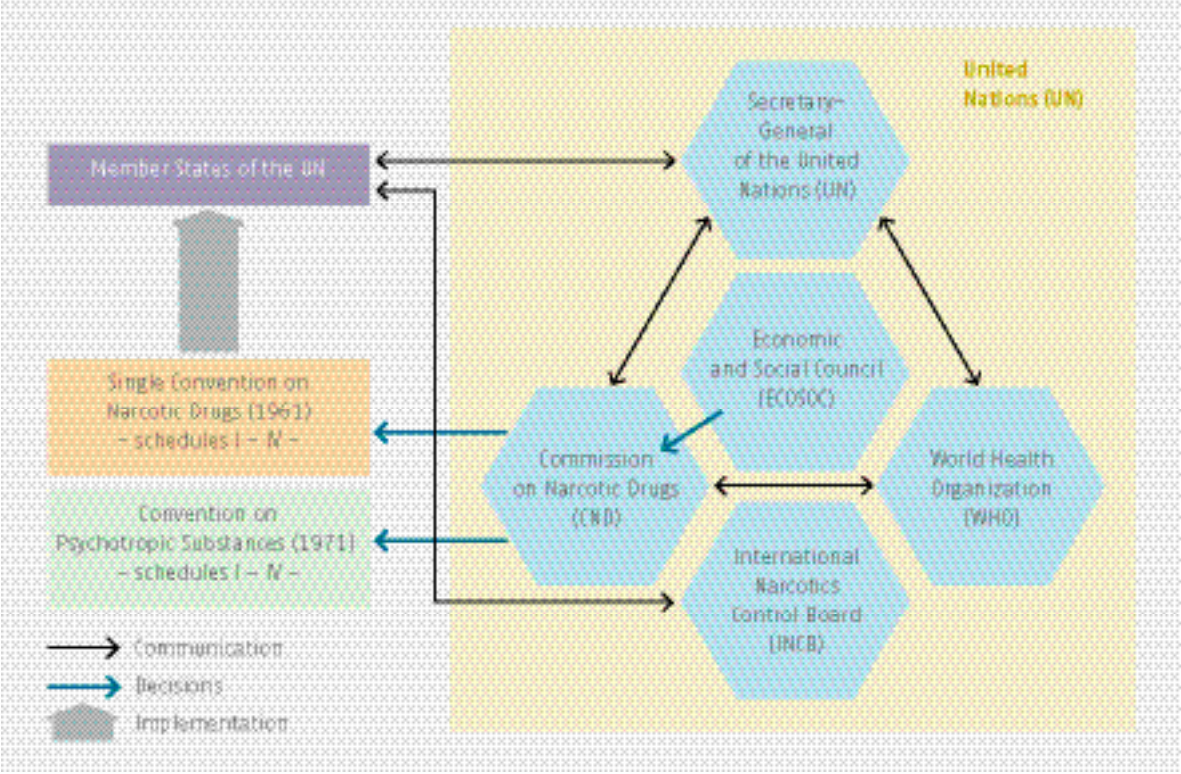

Fig. 10.1 International network of narcotics control

Expert Committee on Drug Dependence (ECDD) once a year (World Health Organization 2020a). The panel makes a scientific assessment of the public health effects of psychoactive substances and makes recommendations on amendments or extensions to the annexes of the conventions. The CND is the decision-making body in this process. It is charged with deciding on possible amendments and extensions to the annexes of the 1961 and 1971 Narcotics Conventions, such as new additions or deletions of compounds. For its part, the CND consists of 53 UN member states, which are elected by the Economic and Social Council (ECOSOC) of the United Nations for a period of four years (United Nations Office on Drugs and Crime 2020a). The Economic and Social Council itself is based in New York and is one of the six main organs of the United Nations (United Nations 2020a). Decisions of the CND do not enter into force until they have been formally communicated to UN member states by the UN Secretary-General. Through this process, new narcotic drugs and psychotropic substances are regularly brought under international control. UN Member States must then implement the decisions of the CND and take the necessary control measures, which may vary in scope depending on the classification in Annexes I-IV of the respective 1961 or 1971 Conventions. The International Narcotics Control Board (INCB) is the monitoring body of the United Nations with regard to the implementation of the requirements from the UN Narcotics Conventions by the individual member states. For this purpose, the INCB maintains a lively exchange with the special administrative services of the member states and is their addressee for the regular needs assessments and statistical reports. It evaluates these and publishes data and reports on its website (www.incb.org). The precise tasks and powers of the INCB are laid down in the individual narcotics conventions.

The item of cannabis and related entries in the 1961 and 1971 UN Conventions on Narcotic Drugs underwent the described annex amendment process in 2019/2020. The process is shown schematically in ○ Fig. 10.2.

The WHO ECDD expert panel had conducted a critical review of the cannabis item at its 41st meeting (Nov. 12–16, 2018), including the related entries cannabis resin, extracts, tinctures, dronabinol (including stereoisomers) and other controlled isomers of tetrahydrocannabinol (World Health Organization 2020b). This resulted in recommendations on amendments to the annexes of the 1961 and 1971 UN Narcotics Conventions, which were transmitted to the UN Secretary-General by notification dated Jan. 24, 2019 (World Health Organisation 2020c). The recommendations included the deletion of the item cannabis and cannabis resin from Annex IV of the Single Convention, 1961, while maintaining these items in Annex I of the same Convention. In addition, a change of the substance dronabinol (including stereoisomers) from Annex II of the

Convention on Psychotropic Substances, 1971 to Annex I of the Single Convention on Narcotic Drugs, 1961 was proposed. Furthermore, the recommendations had provided for various exemptions to certain preparations containing cannabis or dronabinol. During the 62nd meeting of the Commission on Narcotic Drugs (CND) on March 19, 2019, the vote on the WHO recommendations was postponed by decision 62/14 (United Nations Commission on Narcotic Drugs 2019a; United Nations Office on Drugs and Crime 2020b). In the intersessional meetings of the 62nd session of CND during 2019, UN Member States had the opportunity to address questions to WHO on the recommendations, which, including the responses, are also available to the public (United Nations Commission on Narcotic Drugs 2019b, 2020a). At the 63rd session of the CND on March 2–6, 2020, decision 63/14 set the vote to the reconvened session in December 2020 (United Nations Commission on Narcotic Drugs 2020b; United Nations Office on Drugs and Crime 2020c). Finally, at the reconvened 63rd session, on December 2, 2020, only one amendment on cannabis and related items was adopted, namely the deletion of cannabis (and cannabis resin) from Annex IV of the Single Convention, 1961 while maintaining these items in Annex I (United Nations Office on Drugs and Crime 2020d; United Nations Commission on Narcotic Drugs 2020c). This did not lower the international level of control of cannabis, but rather recognized its growing medical use. In Germany, the decision is not expected to lead to any changes in narcotics regulations, because cannabis has already been approved for medical use here since 2017 under the conditions of medicinal products and narcotics law. Whether the decision will lead to more extensive medical use in other countries remains to be seen. The further recommendations of the ECDD of the WHO on cannabis were rejected by the CND on December 2, 2020.

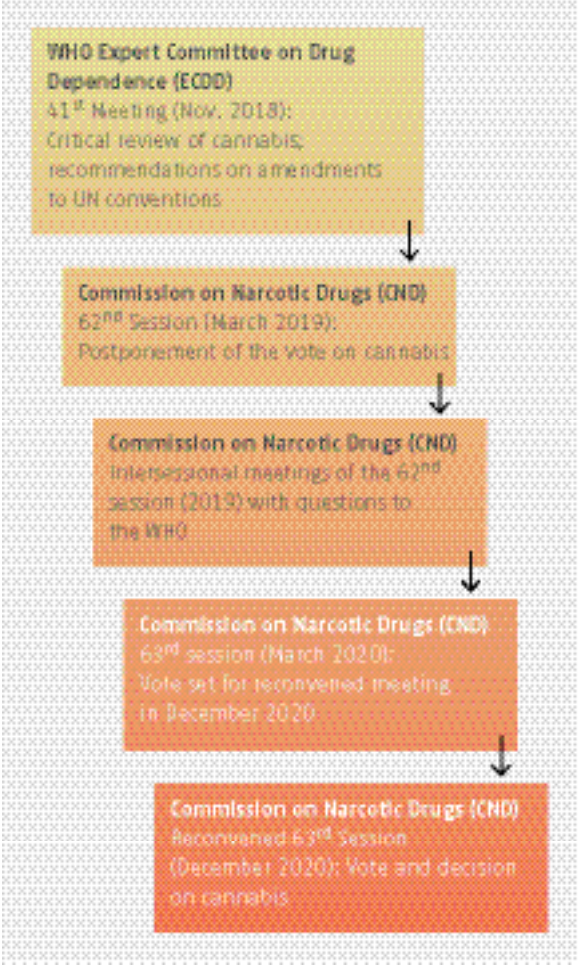

Fig. 10.2 Decision-making pathway of the WHO recommendations on cannabis

10.1.1 Single Convention on Narcotic Drugs, 1961

The Single Convention on Narcotic Drugs was adopted at a United Nations (UN) conference in New York in 1961 (United Nations 2020b). In 1972, the UN conference in Geneva adopted a protocol to amend the convention once, which has since been referred to by its full name: "Single Convention on Narcotic Drugs, 1961 as amended by the 1972 Protocol" (United Nations 2020c). The Single Convention established the International Narcotics Control Board (INCB) and is now applied in 186 UN member states (United Nations 2020d). Germany ratified the Single Convention in 1973 (Hügel, Junge et al. 2018).

Cannabis has been listed in Annexes I and IV since the beginning of the Single Convention. The deletion from Annex IV was made only after the decision of the Commission on Narcotic Drugs (CND) on December 2, 2020. According to the definition of the Convention, cannabis includes the flowering or fruiting tops of plants of the Cannabis genus. The cannabis resin and any preparations, such as extracts and tinctures, are also subject to monitoring. However, leaves are largely exempt, and seeds completely exempt from control. Another exemption from the regulations is when the cannabis plants are grown exclusively for industrial purposes to obtain of fiber or seeds, and for horticultural purposes.

The regulations of the Single Convention on Cannabis form the basis for the respective national regulations, including German narcotics law. For the cultivation of plants for the production of cannabis, a state control body, a so-called Cannabis Agency, must be established in accordance with Articles 23 and 28(1) of the Convention (▸ Chapter 10.5). Furthermore, the Single Convention stipulates that all phases of trade in a narcotic substance (here: cannabis), in particular trade as well as production, must be placed under state con-

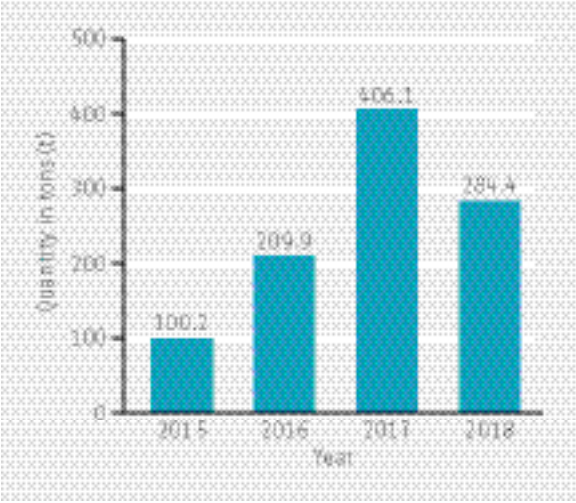

Fig. 10.3 Global legal cannabis production for medical and scientific purposes

trol and may take place only after a state permit has been issued (United Nations Office on Drugs and Crime 2020e). Traders and manufacturers must keep records of all movements. An import or export license is required for each individual cross-border delivery (▸Chapter 5.1 and ▸Chapter 10.4.2). In addition, the Single Convention makes specifications for medical prescribing for medical use. The requirements for the special administrative services in the individual UN member states (in Germany: Federal Institute for Drugs and Medical Devices, BfArM) are also high. First, demand estimates ("estimate") on the expected consumption for medical and scientific purposes for the respective following year have to be submitted to the INCB annually by June 30. Second, statistical data, including actual medical and scientific consumption, stocks, and cultivation of cannabis, must be reported annually to the INCB. The INCB is even to be informed about the imported and exported quantities of cannabis on a quarterly basis. The INCB regularly publishes some of these data in its "Technical Reports" (International Narcotics Control Board 2020a).

INCB technical reports show a steady increase in legal cannabis production for medical and scientific purposes (International Narcotics Control Board 2019, 2020b). After the turn of the millennium, cannabis was increasingly used in medicine and research worldwide. Initially, the demand grew hesitantly, but since 2012, it has grown much more rapidly. Growth in global legal production volumes continued in 2015–2018 (Fig. 10.3). In its 2019 annual report, the INCB explains the comparatively low values for 2018 by the fact that some member states with extensive production had not provided information compared to previous years.

The upward trend is also confirmed by the data on demand estimates under Article 19 of the Single Convention on the Legal Use of Cannabis for Medical and Scientific Purposes (Fig. 10.4). In the statistical reports and demand estimates submitted to the INCB by the UN member states, preparations from cannabis are also presented under the item "Cannabis" in addition to dried flowers. This includes both extracts for the preparation of prescription medicines and finished cannabis-based medicines. To calculate the quantities of cannabis used for the manufacture of preparations, internationally defined conversion factors have been used to date, which the INCB publishes in the List of Narcotic Drugs under International Control (so-called "Yellow List"; International Narcotics Control Board 2020c). This can sometimes lead to inaccuracies in the data presented, since both the dried flowers for direct patient care and use quantities for the production of preparations are included.

10.1.2 Convention on Psychotropic Substances, 1971

The Convention on Psychotropic Substances was adopted at a UN conference in Vienna in 1971 (United Nations 2020e). Germany ratified the convention in 1976 (Hügel, Junge et al. 2018). The International Narcotics Control Board (INCB) also conducts the international monitoring functions here. Since then, a total of 144 different psychotropic substances have come to fall under the scope of the convention (International Narcotics Control Board 2020d). This includes the psychoactive ingredient of the cannabis plant, (-)-trans-Δ^9-tetrahydrocannabinol (THC or dronabinol). A change of the substance to the Schedules of the Single Convention on Narcotic Drugs, 1961 was rejected by the Commission on Narcotic Drugs (CND) in December 2020. The isolation and elucidation of the chemical structure of the natural substance was achieved by Raphael Mechoulam's research group in the 1960 s and 1970 s (Gaoni and Mechoulam 1964, 1971; ▸Chapter 6.1.5.2 and ▸Chapter 15.4.3.1). According to INCB technical report, legal global production of dronabinol has increased significantly over the past five years; in 2018, production totaled 640 kg worldwide (International Narcotics Control Board 2020e). Dronabinol is the International Nonproprietary Name (INN) of the psychoactive (-)-trans-Δ^9-tetrahydrocannabinol. (Dewick 2010; ▸Chapter 15.4.3.1).

The control mechanisms of the 1971 Convention on dronabinol are broadly similar to the provisions of the 1961 Single Convention on cannabis. Under the 1971 Convention, both production and trade must be controlled by use of permits; cross-border movements require import and export licenses for each individual shipment. Manufacturers and traders must keep records of stocks and movements. Requirements are also set down for medical prescriptions. In contrast, require-

ments for periodic statistical reports and needs assessments to the INCB by the national special administrative service (in Germany, the Federal Institute for Drugs and Medical Devices, BfArM) are somewhat less stringent by comparison (International Narcotics Control Board 2020f, 2020g). However, some rules have been subsequently supplemented by means of resolutions of the United Nations Economic and Social Council (ECOSOC) or the Commission on Narcotic Drugs (CND). Such resolutions are less binding than the conventions themselves and are usually implemented on a voluntary basis by UN member states.

10.1.3 United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988

The United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988 supplements the previous UN Narcotic Drugs Conventions of 1961 and 1971. The Convention was adopted as a result of a United Nations (UN) conference in Vienna in 1988 (United Nations 2020f). Germany ratified the Convention in 1993 (Hügel, Junge et al. 2018).

The focus of the Convention is on the **prevention of illicit traffic** in narcotic drugs and psychotropic substances and the monitoring of so-called precursors. In this context, the Convention covers offenses and seizures, as well as international cooperation and training, among other things. The precursors are identified in the two annexes ("Tables I & II"). They are chemicals commonly used in the illicit manufacture of narcotic drugs and psychotropic substances. As an example, acetic anhydride is an internationally monitored precursor that is used in the illicit manufacture of heroin (International Narcotics Control Board 2020h; United Nations 1988; United Nations Office on Drugs and Crime 2020a). The procedure leading to the inclusion of a new substance in the annexes of the 1988 Convention is similar to the procedure for the UN Narcotics Conventions of 1961 and 1971 (▸Chapter 10.1.1 and ▸Chapter 10.1.2). However, with regard to the precursors, the International Narcotics Control Board (INCB) carries out the function of the WHO in this procedure.

Precursors are not relevant with respect to the illegal production of cannabis, as chemicals are not usually required. According to the regulations of the 1988 Convention, **illegally cultivated cannabis plants** have to be destroyed by the UN member states, including the roots. Intentional illicit cultivation of cannabis is to be classified as a criminal offense. This requirement is implemented at the national level by Section 29 (Offenses) of the Narcotics Act.

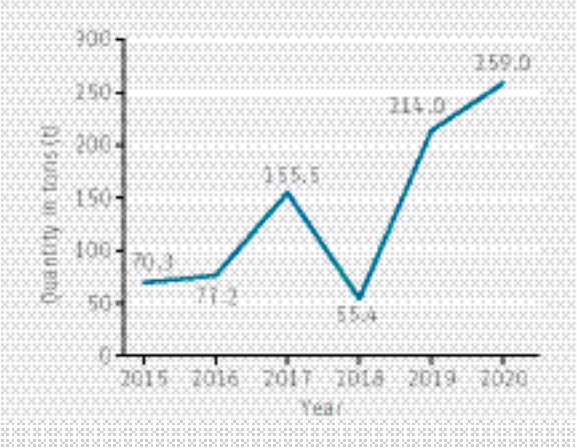

Fig. 10.4 Global demand estimates: cannabis for medical and scientific purposes

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14 Forms and methods of administration

14.1 Dosage forms for medical use

Dr. Andreas S. Ziegler

The administration of drugs containing cannabis is exciting in many respects from both a biopharmaceutical and a galenic perspective. First, cannabis and cannabinoids are used in such a wide variety of different dosage forms, which is almost unknown for any other active ingredient; second, inhalational administration following vaporization provides a mode of administration that is currently almost unique in pharmacy. From a therapeutic point of view, the fact that the various dosage forms differ not only in their administration but also in their pharmacokinetic properties is particularly relevant; the different formulations of otherwise identical dosage forms also play a significant role. In order to obtain a better overview in this respect, the various established dosage forms, as well as some that are still undergoing trials, will be examined in more detail below, together with their biopharmaceutical characteristics and application-specific peculiarities.

14.1.1 Tablets

After administration of a single oral dose, dronabinol is almost completely absorbed (90–95%). However, due to the first-pass effect and high lipid solubility, only 10–20% of the administered dose enters systemic circulation. Both the plasma concentration of dronabinol and that of its main active metabolite (11-OH-THC) reach a maximum (C_{max}) in most cases between 0.5 and 4 hours after oral administration and subsequently decrease over several days. The pharmacokinetics of dronabinol tablets after administration of single (2.5–8 mg) or multiple doses (2.5 mg-7.5 mg twice daily) have been investigated in several studies (▫ Tab. 13.1). When the dose was increased, a slightly disproportionate increase in the mean C_{max} as well as the $AUC_{(0-12)}$ of dronabinol was observed in the investigated range. Concomitant administration of Marinol® with a meal high in fat (59 g fat, corresponding to approximately 50% of the meal's total energy content of 950 calories) resulted in a 4-hour prolongation of mean T_{max} and a 2.9-fold increase in total exposure ($AUC_{0\to\infty}$), with no significant change in C_{max} (AbbVie Inc. 2017).

While the THC in Marinol® tablets is synthetically produced, the preparation Namisol® contains THC of natural origin. However, not surprisingly, the pharmacokinetic parameters hardly differ. Oral administration of Namisol® tablets containing 3–8 mg THC resulted in mean maximum plasma C_{max} levels of 1.42–4.57 ng/ml and a T_{max} of 0.67–2.05 hours (▫ Tab. 14.1). Of note is the fact that sublingual administration at the same dosage resulted in a slightly lower C_{max} and a delayed T_{max} compared with peroral administration (Klumpers, Beumer et al. 2012).

Tablet administration showed a strong correlation between THC dose administered and C_{max} with a Pearson-r of 0.9178 and a coefficient of determination (R^2) of 0.8423 (Poyatos, Pérez-Acevedo et al. 2020).

One advantage of tablets is the simplicity of use of this dosage form. For example, unlike inhalants or flowers, the patient does not have to first convert the dosage form into the administration form by vaporizing or preparing a decoction, nor do they have to divide individual doses on their own. Conversely, however, there are strict limits to individual dose adjustment, since the currently available cannabinoid-containing tablets are exclusively finished medicinal products that are marketed in predefined individual doses and are always taken as a whole. Although the introduction of tablets containing THC or CBD into the field of pharmaceutical compounding has been considered on various occasions, no valid manufacturing specification exists to date that would allow individual dose adjustment, and which could be implemented in the pharmacy. Such kind of a manufacturing instruction for compounded tablets suitable for pharmacy use would represent an improvement to

Tab. 14.1 Pharmacokinetic parameters after oral administration of cannabinoid-containing tablets.

Reference	Study design	Subjects	Mode of administration	Dosage	C_{max} [ng/ml] Mean ± standard deviation or median (range)	T_{max} [h]
Timpone, Wright et al. 1997	Randomized, open-label	7 HIV patients (m/f) with wasting syndrome	Tablets (Marinol®)	2.5 mg THC	**Pooled data of all 20 subjects** **THC:** 2.01 (0.58–12.48) **11-OH-THC:** 4.61 (0.52–37.5)	**Pooled data of all 20 subjects** **THC:** 2.07 (0.66–8.26) **data** 2.07 (0.49–8.00)
		9 HIV patients (m/f) with wasting syndrome		2.5 mg THC; 250 mg megestrol		
		4 HIV patients (m/f) with wasting syndrome		7.5 mg THC; 750 mg megestrol		
AbbVie Inc. 2017	Open-label pharmacokinetics study	34 healthy subjects (m/f)	Tablets (Marinol®)	2.5 mg THC orally 2× daily, fasting	**THC:** 1.32 ± 0.62	**THC:** 1.00 (0.50–4.00)
				5.0 mg THC oral 2× daily, fasting	**THC:** 2.96 ± 1.81	**THC:** 2.50 (0.50–4.00)
				7.5 mg THC oral 2× daily, fasting	**THC:** 7.88 ± 4.54	**THC:** 1.50 (0.50–3.50)
Klumpers, Beumer et al. 2012	Randomized, double-blind, placebo-controlled, double-dummy, cross-over	7 males 7 females (Panel 1) with cannabis experience	Tablets (Namisol®)	5.0 mg THC sublingual	**THC:** 2.30 ± 1.01[1]	**THC:** 1.24 ± 0.65[1]
				5.0 mg THC oral	**THC:** 2.92 ± 1.49[1]	**THC:** 0.93 ± 0.68[1]
		5 males 4 females (Panel 2) with cannabis experience	Tablets (Namisol®)	6.5 mg THC oral	**THC:** 4.43 ± 1.86[1]	**THC:** 0.66 ± 0.13[1]
				8.0 mg THC oral	**THC:** 4.69 ± 2.91[1]	**THC:** 0.73 ± 0.19[1]
Ahmed, van den Elsen et al. 2014	Randomized, double-blind, placebo-controlled, double-dummy, cross-over	6 males 5 females	Tablets (Namisol®)	3 mg THC oral	**THC:** 1.42 (0.53–3.48)	**THC:** 0.92 (0.67–0.92)
				5 mg THC oral	**THC:** 3.15 (1.54–6.95)	**THC:** 0.92 (0.67–0.92)
				6.5 mg THC oral	**THC:** 4.57 (2.11–8.65)	**THC:** 0.67 (0.67–0.92)
Vries, van Rijckevorsel et al. 2016	Randomized, double-blind, placebo-controlled, cross-over	15 males 9 females (no cannabis use in the previous year)	Tablets (Namisol®)	8 mg THC oral	**THC:** 4.01 ± 3.39 **11-OH-THC:** 4.38 ± 1.50	**THC:** 2.05 ± 1.47 **11-OH-THC:** 2.26 ± 1.29

[1] The standard error or coefficient of variation of the mean value given in the original publication was converted into the standard deviation for better comparability.

the scope of dosage forms available for individualized cannabinoid therapy, with improved ease of use; comparatively high levels of drug treatment safety could be expected.

14.1.2 Capsules

Cannabis capsules generally contain synthetic THC (dronabinol), but also ground cannabis flowers or – due to their higher bioavailability – cannabis oil (▸Chapter 14.1.4). If all cannabinoid-containing capsules, irrespective of the active ingredient they contain, are taken together, this is by far the most frequently investigated orally administered form of cannabinoids (▫Tab. 14.2). The single THC doses contained in the cannabinoid capsules studied ranged from 5 to 90 mg, and the mean maximum plasma levels C_{max} thus achieved ranged from 0.42 to approximately 53 ng/ml. T_{max} was 0.78 to 4 hours and 5.59 hours, respectively, when preceded by ingestion of a high-fat meal (Oh, Parikh et al. 2017).

In addition to dose and vehicle system, physiological factors such as different rates of absorption, metabolism and excretion primarily influence THC concentrations in the central compartment, which is why large interindividual variations occur. In particular, significant first-pass metabolism seems to be responsible for the low oral bioavailability of 4–20% (compared to intravenous administration) (Huestis 2007). In addition, a significant dietary effect has been observed: in a study by Oh, Parikh et al. (2017), subjects received capsules containing 5 mg dronabinol either fasting or after ingestion of a standard high-fat, high-calorie meal. Whereas C_{max} values differed only moderately between the two cohorts (▫Tab. 14.2), the $AUC_{0\to\infty}$ of 12.21 ± 4.83 h · ng/ml for THC in the patients with immediately preceding food intake was nearly three times higher than after fasting intake ($AUC_{0\to\infty}$ = 4.33 ± 2.49 h · ng/ml). For the active metabolite 11-OH-THC, the differences were less pronounced (15.59 ± 6.67 h · ng/ml vs. 11.81 ± 6.18 h · ng/ml), but again, capsule ingestion after eating showed higher overall exposure (Oh, Parikh et al. 2017). Perez-Reyes, Lipton et al. (1973) studied the effect of different vehicle systems for oral delivery of THC in gelatin capsules, with glycocholate and sesame oil improving bioavailability; however, there was considerable variability in peak concentrations and absorption rates, even when the same vehicle system was used.

Marinol® is a capsule preparation currently on the market in the USA (▸Chapter 16.1.5.4) that contains synthetic THC and is also pharmacokinetically well-characterized (see also studies in ▫Tab. 14.2). Interestingly, in some studies with Marinol® capsules, two THC peaks were observed, presumably due to enterohepatic circulation (Huestis 2007).

Canemes® capsules, which contain the synthetic THC derivative nabilone, show almost complete oral bioavailability, in contrast to Marinol® or other THC capsules (Tsang and Giudice 2016; Ward and Holmes 1985). The active ingredient undergoes highly significant metabolization, and is converted into numerous active intermediates.

In a comparison of the ingestion of THC capsules with the oromucosal administration of the THC/CBD-containing oral spray Sativex®, Karschner, Darwin et al. (2011) found no significant difference with regard to C_{max} or T_{max}, and the differences in bioavailability were also small (Ude and Wurglics 2020). In this context, a study by Cherniakov, Izgelov et al. (2017) on the improvement of bioavailability of orally administered THC by using liposomes is noteworthy. Thus, administration of equal cannabinoid doses (10.8 mg THC and 10.0 mg CBD) in orally administered capsules using THC-CBD-piperine-pro-nanolipospheres (THC-CBD-PNL) resulted in a threefold increase in C_{max} compared to the oromucosal spray Sativex® (5.4 vs. 1.8 ng/ml THC) as well as faster absorption (○Fig. 14.1).

For orally administered capsules, the correlation between administered dose and C_{max} yielded a Pearson-r value of 0.9271 and a coefficient of determination (R^2) of 0.8596. Accordingly, C_{max} increased largely linearly with an increase in THC doses.

In principle, it should be noted that capsules are a well-suited and well-tested dosage form for cannabinoids. The interindividual variations that occur suggest the need for finely graded dose individualization, not only to take into account the subjectively different minimum effect concentration and side effect threshold, but also the biopharmaceutical characteristics of the individual patient. In Germany, in the absence of approved finished medicinal products, cannabinoid-containing capsules are currently available only as **individual imports** (▸Chapter 16.1.10) or as **individually prepared prescription medicinal products.** Currently, **officinal capsule production** is mostly based on filling capsule shells made of hard gelatin with a lipophilic melt containing dronabinol, which subsequently solidifies at room temperature (▸Chapter 15.6.3.6). From a biopharmaceutical point of view, this formulation is certainly an advantage; however, the processing of a lipophilic melt is complicated and time-consuming, especially considering that it involves individual manual labor. New, innovative manufacturing concepts that are easier to implement in the pharmacy would therefore be desirable. For example, it would be conceivable to fill capsules with powders that have previously been impregnated or coated with THC and/or CBD in a standardized process.

14.1.3 Decoctions („tea")

In connection with aqueous extracts of cannabis flowers, the term "**tea infusion**" is commonly used: this term is, however, **pharmaceutically incorrect**. Since cannabinoids contained in the flowers must first be

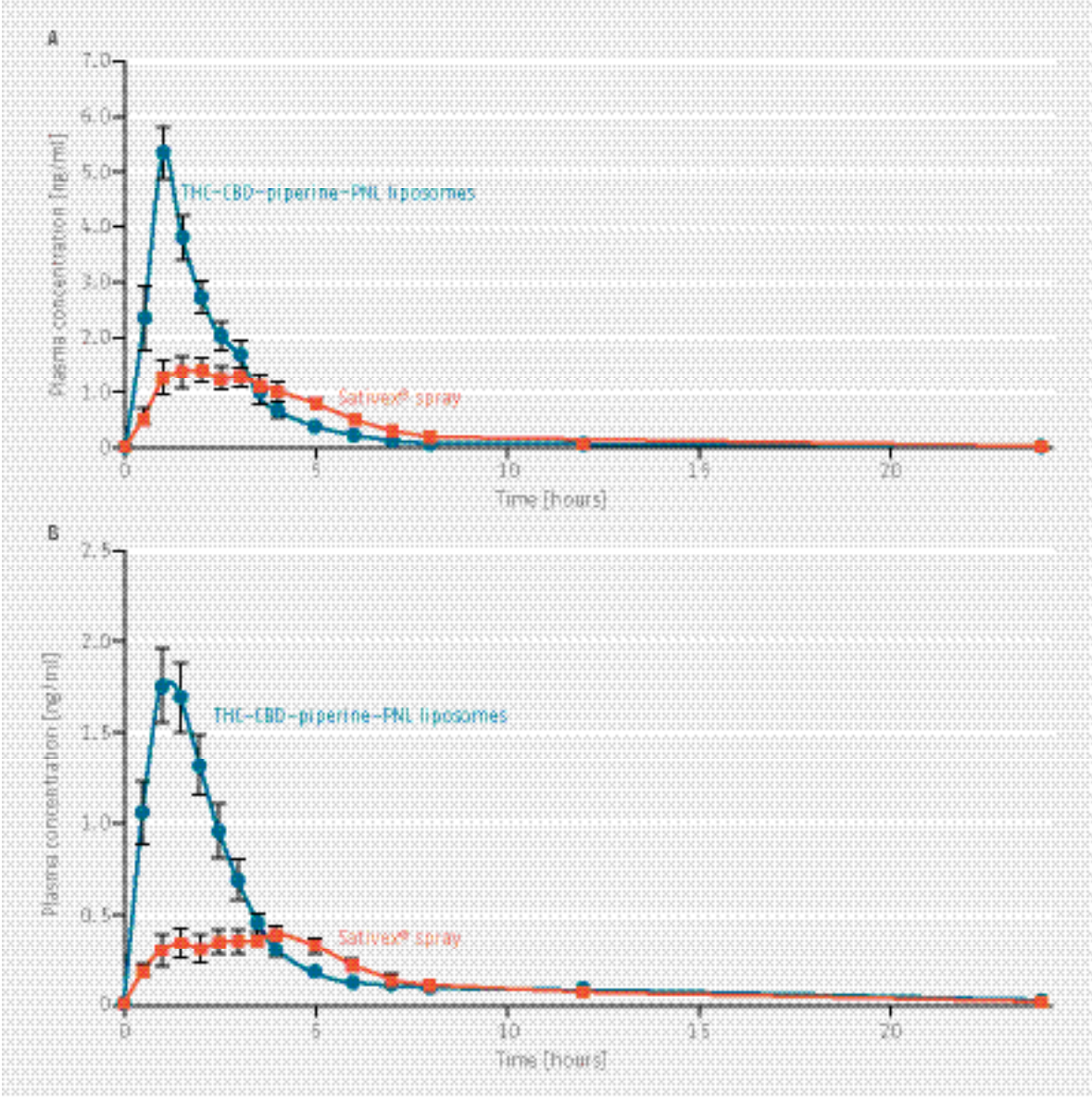

Fig. 14.1 A THC and B CBD plasma levels, respectively, after oral administration of capsules containing THC-CBD-piperin-PNL liposomes compared to oromucosal administration of the same doses (10.8 mg THC and 10.0 mg CBD) using Sativex® spray (n = 9; according to: Cherniakov, Izgelov et al. 2017)

converted from precursors into their active form by thermal decarboxylation, the drug is not poured over with boiling water and left to stand (= infusion), but **heated further for 10–15 minutes** at a low boil (= **decoction**). This is necessary because water cannot become hotter than 100 °C under normal ambient conditions. At this temperature, however, decarboxylation proceeds much more slowly than in the incomparably hotter vaporizer (at 180–210 °C; ▸Chapter 18.3). After boiling flowers with a nominal THC content of about 20% (in the form of the precursor THCA) for 15 minutes, THC concentrations of about 10 mg/l are reached in the decoction, according to NRF, which corresponds to a THC dose of about 2 mg per cup (200 ml) (Hüttemann 2017; DAC/NRF). However, such a blanket statement must be viewed critically, as the extraction rate of cannabinoids in aqueous extracts is fundamentally poor and highly variable (Brunetti, Pichini et al. 2020). This is especially true in direct comparison with oil-based extracts. Thus, the recovery rate of 18.5% ± 8.6% and 13.8% ± 4.7% for THC and THCA, respectively, and 28.1% ± 10.3% and 58.2% ± 21.1% for CBD and CBDA, respectively, in aqueous decoctions (n = 6) was statistically significantly ($p < 0.01$) lower than the comparative values for an oil-based extraction (Pacifici, Marchei et al. 2017; ◘ Tab. 14.3). The range of variation for the individual cannabinoid was also significantly smaller for the oil-based extraction than for the decoction (◘ Tab. 14.3). In addition, the spectrum of constituents shifted in different ways as a result of the prepara-

tion of the decoction or oil-based extract. While the ratio of total THC (= THC + 0.877 · THCA) to total CBD (= CBD + 0.877 · CBDA) in the plant matrix (cultivar not further specified) examined by Pacifici, Marchei et al. (2017) was still 0.71, it was significantly closer to the genuine value in the oil-based extract (0.49) than in the aqueous extract with a total THC : total CBD ratio of only 0.25. Based on the extraction rates in ▫ Tab. 14.3, Brunetti, Pichini et al. (2020) calculated the approximate total THC and CBD amounts contained in aqueous and oil-based extracts, respectively, of various cannabis flowers (▫ Tab. 14.4).

Due to the poor water solubility of cannabinoids, **the decoction should be drunk while it is hot**. After extraction with boiling water, a largely saturated solution is present, from which THC and other cannabinoids precipitate on the cup bottom and wall as it cools. In addition, a THC-rich oil film forms and floats on the water surface (○ Fig. 14.2). Both can be the cause of dose fluctuations, which must be avoided. Against the background of the quasi unavoidable phase separation even at higher temperatures, the statement that cannabis decoctions can be kept warm in a thermos flask for multiple use throughout the day, which can be read in various places, must be assessed critically.

Various pharmacokinetic studies exist on the administration of cannabis decoctions (Pellesi, Licata et al. 2018; Pichini, Mannocchi et al. 2020; ▫ Tab. 14.5), including one that uses milk instead of water as an extractant to better or more exhaustively extract the lipophilic cannabinoids (Ménétrey, Augsburger et al. 2005). After ingestion of 1.85 mg THC and 2.22 mg THCA-A in the form of an aqueous decoction, THC reached a mean C_{max} of 1.38 ng/ml after 1.28 hours (T_{max}), while THCA-A reached a mean C_{max} of 48.92 ng/ml after 1.22 hours (T_{max}) (Pellesi, Licata et al. 2018). In a pilot study with one subject, the subject received 100 ml of a cannabis decoction containing 0.36 mg THC, 1.6 mg THCA-A, 0.42 mg CBD, and 4 mg CBDA. This dose resulted in a C_{max} of 1.0 ng/ml THC and 72.4 ng/ml THCA-A with a T_{max} of 2.0 hours (Pichini, Mannocchi et al. 2020). Milk decoctions with THC doses of 16.5 mg and 45.7 mg resulted in maximum plasma levels (C_{max}) of 3.8 and 8.4 ng/ml, respectively, after one hour (T_{max}) (Ménétrey, Augsburger et al. 2005). Despite the paucity of data, cannabis decoctions showed a strong correlation between THC dose and C_{max} with a Pearson-r of 0.9997 and a coefficient of determination (R^2) greater than 0.99 (Poyatos, Pérez-Acevedo et al. 2020).

14.1.4 Oil

The theoretical basis for the oral application of oil-based cannabis preparations is the assumption that most **cannabinoids are generally not only more**

▫ **Tab. 14.2** Pharmacokinetic parameters after oral administration of cannabinoid-containing capsules (Continuation)

Reference	Study design	Subjects	Mode of administration	Dosage	C_{max} [ng/ml] Mean ± standard deviation or median (range)	T_{max} [h]
Wall, Sadler et al. 1983	Open-label, non-placebo-controlled	6 males	Capsules	20 mg THC	THC: 14 ± 9.7 11-OH-THC: 6.6 ± 3.4	THC: 2.5 11-OH-THC: 2.0
		6 females	Capsules	15 mg THC	THC: 9.4 ± 4.5 11-OH-THC: 5.9 ± 2.8	THC: 1.75 11-OH-THC: 1.75
Haney, Bisaga et al. 2003	Randomized, double-blind, placebo-controlled, cross-over	7 males (cannabis smokers)	Capsules (Marinol®)	30 mg THC	THC: 29.9 ± 9.5 THCA: 121.9 ± 43.5	THC: 4 THCA: 2
				30 mg THC; 50 mg Naltrexon	THC: 21.2 ± 8.6 THCA: 139.0 ± 36.2	THC: 2 THCA: 3
Naef, Curatolo et al. 2003	Randomized, double-blind, placebo-controlled, cross-over	6 males; 6 females (without cannabis experience)	Capsules (Marinol®)	20 mg THC	THC: 7.2 ± 6.9[1] 11-OH-THC: 19.7 ± 6.9[1] 11-COOH-THC: 241.4 ± 73.0[1]	THC: 1–2[1] 11-OH-THC: 2[1] 11-COOH-THC: 2–4[1]
			Capsules	20 mg THC; 30 mg morphine hydrochloride	THC: 6.7 ± 7.3[1] 11-OH-THC: 7.9 ± 8.3[1] 11-COOH-THC: 134.7 ± 65.1[1]	no data

Guy and Robson 2004	Randomized, open-label, cross-over; followed by a non-randomized single dose	6 males; 6 females (with cannabis experience)	Capsules	10 mg THC; 10 mg CBD	**THC:** 6.35 ± 3.12 (3.04–4.55) **CBD:** 2.47 ± 2.23 (0.47–7.55) **11-OH-THC:** 7.87 ± 2.96 (4.79–13.64)	**THC:** 1.05 ± 0.65 (0.5–2.75) **CBD:** 1.27 ± 0.84 (0.5–3) **11-OH-THC:** 1.36 ± 0.63 (0.75–3)
Ménétrey, Augsburger et al. 2005	Randomized, double-blind, placebo-controlled, cross-over	8 males (occasional cannabis smokers)	Capsules (Marinol®)	20 mg THC	**THC:** 2.8 (n. n.–5.6) **11-OH-THC:** 3.9 (1.4–8.5) **THCA:** 27.8 (5.4–55.4)	**THC:** 1 **11-OH-THC:** 4 **THCA:** 5.5
Nadulski, Sporkert et al. 2005	Double-blind, placebo-controlled, cross-over	24 subjects	Capsules	10 mg THC; 5.4 mg CBD	**THC:** 4.05 (1.18–10.27) **CBD:** 0.95 (0.30–2.57) **11-OH-THC:** 4.88 (1.83–12.34) **THCA:** 35.46 (19.2–70.6)	**THC:** 0.93 (0.55–2.08) **CBD:** 0.99 (0.5–2) **11-OH-THC:** 1.67 (0.62–2.17) **THCA:** 1.92 (1.08–3.83)
				10 mg THC	**THC:** 3.20 (0.67–7.99) **11-OH-THC:** 4.48 (1.12–11.14) **THCA:** 32.9 (12.03–57.63)	**THC:** 1.06 (0.5–3.05) **11-OH-THC:** 1.5 (0.5–3.17) **THCA:** 2.07 (0.62–3.92)
Goodwin, Gustafson et al. 2006	Randomized, double-blind, placebo-controlled, double-dummy, multiple-dose (over 5 days)	6 subjects (with cannabis experience)	Capsules (hemp oil)	0.47 mg THC/day	**THC:** $0.0^{2,3,4}$ (0.0–0.0) **11-OH-THC:** $0.0^{2,3,4}$ (0.0–0.0) **THCA:** $1.4^{2,3,4}$ (0.0–2.6)	**THC:** $0.0^{2,3,4}$ (0.0–0.0) **11-OH-THC:** $0.0^{2,3,4}$ (0.0–0.0) **THCA:** $65.3^{2,3,4}$ (11.0–107)
			Capsules (dronabinol)	7.5 mg THC/day	**THC:** $1.5^{2,3}$ (0.6–3.8) **11-OH-THC:** $1.6^{2,3}$ (0.0–2.6) **THCA:** $19.8^{2,3}$ (10.6–43.0)	**THC:** $57.6^{2,3}$ (6.5–107) **11-OH-THC:** $85.9^{2,3}$ (1.5–107) **THCA:** $107^{2,3}$ (107–107)
Schwilke, Schwope et al. 2009	Non-randomized, open-label, non-placebo-controlled, multiple-dose (over 7 days)	6 males (regular smokers with cannabis experience)	Capsules (Marinol®)	Initial 20 mg THC, then a daily increasing dose (40–120 mg) for 7 days	**After the first single dose** **THC:** 12.4 ± 3.4 **11-OH-THC:** 8.2 ± 2.0 **THCA:** 75.8 ± 9.4	**After the first single dose** **THC:** 2.8 (0.33) **11-OH-THC:** 2.5 (0.18) **THCA:** 3.3 (0.56)
Karschner, Darwin et al. 2011	Randomized, double-blind, placebo-controlled, double-dummy	6 males; 3 females (cannabis smokers)	Capsules (dronabinol)	5 mg THC	**THC:** 4.7 ± 0.9; 4.6 (1.4–10.4) **11-OH-THC:** 3.0 ± 0.4; 2.6 (1.8–5.9) **THCA:** 69.3 ± 17.6; 57.1 (15.9–179.7)	**THC:** 3.2 ± 0.3; 3.1 (1.5–4.5) **11-OH-THC:** 3.3 ± 0.4; 3.3 (1.5–5.6) **THCA:** 4.4 ± 0.5; 4.3 (2.7–7.5)
				15 mg THC	**THC:** 14.3 ± 2.7; 11.2 (3.3–28.5) **11-OH-THC:** 11.1 ± 2.0; 9.3 (3.6–19.5) **THCA:** 133.6 ± 36.3; 102.1 (44.5–409.0)	**THC:** 3.4 ± 0.5; 3.4 (1.2–5.5) **11-OH-THC:** 3.4 ± 0.4; 3.6 (1.0–5.5) **THCA:** 4.9 ± 0.5; 5.5 (2.4–7.5)

Tab. 14.2 Pharmacokinetic parameters after oral administration of cannabinoid-containing capsules (Continuation)

Reference	Study design	Subjects	Mode of administration	Dosage	C_{max} [ng/ml] Mean ± standard deviation or median (range)	T_{max} [h]
Karschner, Schwope et al. 2012	Non-randomized, open-label, non-placebo-controlled, multiple-dose (over 7 days)	10 males (regular smokers with cannabis experience)	Capsules (Marinol®)	Initial 20 mg THC, then a daily increasing dose (40–120 mg) for 7 days	After the first single dose **THC:** 8.7 ± 4.8; 6.4 (4.1–17.5) **11-OH-THC:** 4.0 ± 2.1; 3.4 (1.8–7.8) **THCA:** 38.4 ± 15.9; 36.6 (19.7–68.7)	After the first single dose **THC:** 3.0 ± 0.9; 3.0 (2.0–4.0) **11-OH-THC:** 2.8 ± 0.9; 3.0 (2.0–5.0) **THCA:** 3.1 ± 1.0; 3.0 (2.0–5.0)
Martin-Santos, Crippa et al. 2012	Randomized, double-blind, placebo-controlled, cross-over	16 males (with cannabis experience; less than 15 times in life)	Capsules	10 mg THC	**THC:** 0.67 ± 0.66 **THCA:** ≈ 5.64[5] **11-OH-THC:** ≈ 0.73[5]	**THC:** 2
Eichler, Spinedi et al. 2012	Randomized, double-blind, cross-over	9 males (Non-smokers)	Capsules (Marinol®)	20 mg THC	**THC:** 1.03 ± 1,65; 0.48[1,6] **CBD:** 0.00 ± 0.00; 0.0[1,6] **11-OH-THC:** 0.99 ± 0.63; 0.84[1,6] **THCA:** 7.13 ± 5.64; 7.61[1,6] **CBN:** 0.64 ± 0.72; 0.37[1,6]	**THC:** 1.06 ± 0.19; 1.0[1] **CBD:** k. A. **11-OH-THC:** 1,67 ± 0.51; 2.0[1] **THCA:** 1.78 ± 0.96; 2.0[1] **CBN:** 1.06 ± 0.57; 1.0[1]
			Capsules (extract of warmed herbal cannabis)	17.6 mg THC; 27.8 mg CBD	**THC:** 0.42 ± 0.39; 0.25[1,6] **CBD:** 0.30 ± 0.21; 0.27[1,6] **11-OH-THC:** 0.73 ± 0.69; 0.50[1,6] **THCA:** 5.81 ± 7.59; 3.46[1,6] **CBN:** 0.60 ± 0.36; 0.56[1,6]	**THC:** 0.78 ± 0.27; 1.0[1] **CBD:** 0.83 ± 0.51; 0.5[1] **11-OH-THC:** 1.44 ± 0.69; 2.0[1] **THCA:** 2.89 ± 1.05; 2.0[1] **CBN:** 0.94 ± 0.45; 1.0[1]
			Capsules (extract of non-heated herbal cannabis)	10.4 mg THC 14.8 mg CBD	**THC:** 1.02 ± 0.78; 0.71[1,6] **CBD:** 1.24 ± 0.87; 0.96[1,6] **11-OH-THC:** 0.57 ± 0.42; 0.50[1,6] **THCA:** 1.94 ± 1.11; 2.28[1,6] **CBN:** 0.54 ± 0.30; 0.58[1,6]	**THC:** 1.17 ± 0.66; 1.0[1] **CBD:** 1.17 ± 1.17; 1.0[1] **11-OH-THC:** 1.00 ± 0.42; 1.0[1] **THCA:** 2.11 ± 0.78; 2.0[1] **CBN:** 1.00 ± 0.42; 1.0[1]
Lile, Kelly et al. 2013	Single blind, placebo-controlled, cross-over	4 males; 3 females (with cannabis experience)	Capsules (Marinol®)	15 mg THC	**THC:** ≈5[5] **11-OH-THC:** ≈2–3[5]	**THC:** 3[5] **11-OH-THC:** 3[5]
				30 mg THC	**THC:** ≈10[5] **11-OH-THC:** ≈5[5]	**THC:** 3[5] **11-OH-THC:** 3[5]

				45 mg THC	**THC:** ≈17–18[5] **11-OH-THC:** ≈8–9[5]	**THC:** 2,5[5] **11-OH-THC:** 2[5]
				60 mg THC	**THC:** ≈45[5] **11-OH-THC:** ≈11[5]	**THC:** 3,5[5] **11-OH-THC:** 3[5]
				75 mg THC	**THC:** ≈42–43[5] **11-OH-THC:** ≈12–13[5]	**THC:** 4[5] **11-OH-THC:** 4[5]
				90 mg THC	**THC:** ≈53[5] **11-OH-THC:** ≈20[4]	**THC:** 4[5] **11-OH-THC:** 4[5]
Parikh, Kramer et al. 2016	Randomized, open-label, cross-over	51 subjects (m/f; no cannabis exposure in the preceding 90 days)	Capsules (dronabinol)	5 mg THC	**Series 1** **THC:** 2.20 ± 1.51 **11-OH-THC:** 3.28 ± 1.78 **Series 2** **THC:** 2.61 ± 1.69 **11-OH-THC:** 3.98 ± 2.51	**Series 1** **THC:** 1.00 (0.50–6.00) **11-OH-THC:** 1.60 (0.75–6.00) **Series 2** **THC:** 1.50 (0.50–6.00) **11-OH-THC:** 1.50 (0.50–6.00)
Cherniakov, Izgelov et al. 2017	Open-label, cross-over	9 males (no cannabis exposure in the preceding 4 weeks)	Capsules (THC-CBD-piperine-PNL)	10.8 mg THC 10.0 mg CBD	**THC:** 5.4 ± 0.01 **CBD:** 2.1 ± 0.4	**THC:** 1 (1–1.5) **CBD:** 1 (0.5–1.5)
Oh, Parikh et al. 2017	Randomized, open-label, cross-over	27 males; 27 females	Capsules (dronabinol)	5 mg THC; fasting	**THC:** 2.19 ± 1.06 **11-OH-THC:** 3.12± 1.67	**THC:** 1.73 ± 1.74 **11-OH-THC:** 1.91 ± 1.15
				5 mg THCM; after consumption of a high-fat, high-calorie standard meal	**THC:** 2.60 ± 1.74 **11-OH-THC:** 2.16 ± 1.50	**THC:** 5.59 ± 3.24 **11-OH-THC:** 5.95 ± 3.35

[1] The standard error or coefficient of variation of the mean value given in the original publication was converted into the standard deviation for better comparability.
[2] Average values calculated from the individual values of the publication.
[3] **NOTE:** The C_{max} and T_{max} values refer to the highest plasma level reached during the total treatment period of 5 days. Therefore, the value does not refer to a single dose and is not comparable to the other data in the table.
[4] The hemp oil investigated was not used as a placebo in the study. However, the administered THC dose is clearly below the standard therapeutic range, which is also reflected in the fact that neither THC nor 11-OH-THC were detectable in plasma after administration. The reported values should therefore not be compared with pharmacokinetic parameters of preparations containing THC in standard therapeutic amounts.
[5] Values approximated from a graph.
[6] The values given in pmol/ml in the original publication were converted to ng/ml for better comparability.

Tab. 14.3 Comparison of extraction rates and their ranges of variation in aqueous and oil-based extracts of cannabis flowers, respectively (Pacifici, Marchei et al. 2017)

Cannabinoid	Content in the plant matrix [%]		Extraction rate for aqueous extract [%]		Extraction rate for oil-based extract [%]	
THC	3.37 ± 0.66	Ratio total THC : total CBD = 0.71	18.5 ± 8.6	Ratio total THC : total CBD = 0.25	62.4 ± 0.1	Ratio total THC : total CBD = 0.49
THCA	2.82 ± 0.52		13.8 ± 4.7		61.8 ± 9.2	
CBD	2.66 ± 0.52		28.1 ± 10.3		79.4 ± 11.3	
CBDA	6.18 ± 1.06		58.2 ± 21.1		95.8 ± 1.5	
CBN	0.09 ± 0.05		19.6 ± 11.9		34.0 ± 3.3	
CBG	0.06 ± 0.01		16.6 ± 7.7		96.9 ± 2.6	
CBC	0.12 ± 0.03		11.5 ± 7.2		42.3 ± 7.5	

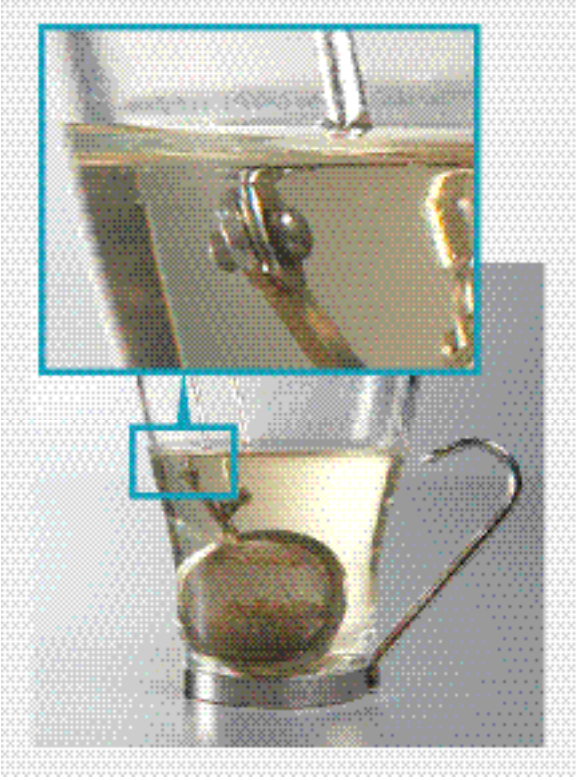

Fig. 14.2 A THC-rich oil film floating on the surface of aqueous decoctions can be the cause of dose fluctuations when the decoction is drunk throughout the day.

exhaustively extracted with oils than with aqueous solvents but are **also better absorbed in lipophilic vehicle systems**, and are thus more bioavailable (Tab. 14.6). This assumption was confirmed by a study by Pellesi, Licata et al. (2018) (Fig. 14.3). Generally, oils and oil-based extracts are administered in capsule or drop form. Whereas the pharmacokinetics of capsules have been relatively well studied (▸ Chapter 14.1.2), little data is available to date for drops, although the intake of oils and oil-based extracts in drop form is widespread. In a corresponding search, only three studies were found in which drops were applied directly; two of these investigated pharmacokinetics after administration of single doses (Pichini, Mannocchi et al. 2020; Pellesi, Licata et al. 2018). In one study, constant doses were administered for five consecutive days (Goodwin, Gustafson et al. 2006). However, the validity of the aforementioned studies is limited for a variety of reasons, especially when it comes to comparison with other dosage forms, some of which were co-studied. These limitations include, among others, the small number of participants, the fact that the administered preparations themselves already exhibited certain variations in content (Pichini, Mannocchi et al. 2020; Pellesi, Licata et al. 2018) and the inadequately described dietary regime of the subjects, which is likely to have a considerable influence on absorption and was sometimes not uniform for all participants within a study (Goodwin, Gustafson et al. 2006). This results in highly variable or sometimes contradictory results, which further complicate a biopharmaceutical characterization of oil-based cannabis preparations. In this respect, it is not surprising that Poyatos, Pérez-Acevedo et al. (2020), including the studies mentioned in Tab. 14.6 were unable to demonstrate a significant correlation between the applied THC dose and the maximum measured plasma concentrations C_{max} for orally administered oils (Pearson-r = 0.38; $R^2 = 0.1448$).

Thus, the studies with orally administered **oil-based cannabis drops** – even more so than the administration of defined quantities of oil in capsules (▸ Chapter 13.1.2) – show pronounced interindividual differences in the plasma level profiles. It should be noted that the capsules investigated (▸ Chapter 13.1.2) were mostly industrially manufactured finished medicinal products, which inherently exhibit a higher degree of standardization than the oil-based preparations investigated in the pharmacokinetic studies considered here. The stan-