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To
Patients of Ukraine Foundation
by e-mail

Dear Sir or Madam,

I am sending you an overview of indications for cannabis in cannabinoids. These are largely taken from a chapter of a book by Professor Dr. Kirsten Mueller-Vahl, Chair of the IACM, and myself, which was published in German in 2019.

Please do not hesitate to contact me if you have any questions.

Yours sincerely

Dr. Franjo Grotenhermen
Exekutive Director

# Indications for cannabis and cannabinoids

**Taken from:**
Müller-Vahl K, Grotenhermen F. (Hrsg.) Cannabis und Cannabinoide in der Medizin. Berlin: Medizinisch Wissenschaftliche Verlagsgesellschaft, 2019.
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The therapeutic spectrum of cannabis and cannabis-based medicines is largely unexplored. Therefore, it is not possible to state exactly in which indications cannabis and cannabis-based medicines are indicated. This is complicated by the fact that cannabis and cannabis-based medicines are thought to have an unusually wide range of indications, much broader than is known for other medicines. This circumstance has recently been referred to as the "cannabis dilemma." Thus, on the one hand, we can look back on a tradition of cannabis medicine that goes back thousands of years, but on the other hand we are confronted with the fact that to date only a few high-quality studies have been conducted with cannabis and cannabis-based medicines. This leads to the "dilemma" that many patients worldwide use cannabis and cannabis-based medicines in very different indications and that patients and their treating physicians report partly astonishing treatment results. On the other hand, however, the scientific data base is very thin and so far only very few substances have been approved under pharmaceutical law in individual countries in a few indications.

## Results from meta-analyses and reviews

Finally, the insufficient database is also reflected in the reviews and meta-analyses that have now been published in greater numbers. In the first comprehensive meta-analysis published by Whiting and colleagues in 2015, the following concluding assessment was made after evaluating all studies published up to that time: There is "moderate-quality evidence" for efficacy of cannabis-based medications for the indications of chronic pain and spasticity. "Low-quality evidence" for efficacy was seen for the indications of nausea and vomiting due to chemotherapy, weight gain in HIV, sleep disorders, and Tourette's syndrome (Whiting et al., 2015).

In a review study published three years later in 2018 by the American "National Academies of Sciences, Engineering and Medicine", the following summary assessment is given: for the indications pain in adults, spasticity in multiple sclerosis (MS) and nausea and vomiting due to chemotherapy, efficacy is clearly proven. Moderate evidence for efficacy is seen for the indications sleep disorders. For all other indications discussed-including appetite enhancement, Tourette's syndrome, anxiety disorders, post-traumatic stress disorder, cancer, irritable bowel syndrome, epilepsy, and various neurodegenerative disorders-the data are

considered insufficient or the evidence low (Abrams, 2018).

In 2017, the summary report of a study commissioned by the Federal Ministry of Health on "Cannabis: Potential and Risks. A scientific analysis (CaPRis)" was published. At the end of 2018, the full expertise was also published in book form ("Cannabis: Potential and Risk: A Scientific Review") (Hoch et al., 2019). In it, the authors conclude that there is benefit for the indications of nausea and vomiting or appetite stimulation in people with chemotherapy-treated cancer and HIV/AIDS. For cannabis-based medications, there is also evidence of "mild pain reduction." On the other hand, there is no "substantial reduction" in pain. For the indication spasticity in MS, only "subjective, but not sufficiently objectifiable evidence" for symptom improvement is available. For all other indications - such as gastrointestinal, neuroinflammatory, neurological and mental diseases - the study situation is classified as "insufficient" and the results as "inconsistent".

Based on these examples it becomes clear that only for very few indications a uniform evaluation is made and even for one of the indications approved in Germany (spasticity in MS) the evidence is evaluated very differently. This is primarily due to the lack of a sufficient number of high-quality studies, but also to the fact that in meta-analyses and reviews a selection is always made beforehand as to which study is classified as suitable at all in order to be considered in the evaluation.

As early as 2016, the Drug Commission of the German Medical Association (AkdÄ) came to the following conclusion in a statement entitled "Cannabinoids in medicine: overview of the study situation on the therapeutic use of cannabinoids":

"For individual patients, the therapeutic use of cannabinoids can be useful - this assessment of the AkdÄ is based on a data situation that has not fundamentally changed compared to 2008. Therefore, the conclusion of the AkdÄ is also still valid: For patients who do not have sufficient relief of symptoms such as spasticity, pain, nausea or vomiting under therapy with approved drugs, the administration of cannabinoids can be considered as an individual therapy trial, especially in palliative care. A combination of THC and CBD is approved as a finished drug for the treatment of spasticity in multiple sclerosis. The use of cannabinoids appears to be limited by the narrow therapeutic window because patients often discontinue treatment, especially with longer-term therapy, because of side effects.

According to the current state of studies, there is no advantage in using hemp cannabinoids ("medicinal hemp") or other substances derived from the cannabis plant over therapy with THC as a prescription drug or the combination of THC and CBD as a finished drug.

In the view of the AkdÄ, a refusal of cost coverage by payers is not justified by reference to insufficient scientific data if it has been confirmed for the patient in an individual healing trial that medication with a

cannabinoid-containing drug is effective and tolerable."

In this chapter, an overview of all possible indications for cannabis and cannabis-based medicines will be presented. Only for a few indications is the data situation good, so that the efficacy in these indications is undisputed. On the other hand, there are numerous indications in which the data base is insufficient or contradictory, and therefore different assessments have been made in the reviews and meta-analyses available (Whiting et al., 2015; Abrams, 2018; Hoch and Schneider, n.d.).. It should not go unmentioned that many physicians and scientists are still generally skeptical or even dismissive of treatment with cannabis and cannabis-based medications, and this may well find expression in the evaluation of the database. In order to ensure an unbiased but at the same time clear presentation, this chapter will first present the indications approved in Germany, followed by indications for which cannabis-based medicines are not approved in Germany but are approved in other countries. Subsequently, indications are presented - sorted according to specialties - for which there are indications for the efficacy of cannabis and cannabis-based medicines, but for which the insufficient data situation does not yet allow a conclusive evaluation.

For all indications currently under discussion, it is still unclear which of the currently prescribable cannabis-based medications is most effective or which form of administration is most effective. If there are indications of superiority of individual substances, this will be explicitly pointed out in the respective sections.

## Indications approved in Germany

### Therapy resistant spasticity in multiple sclerosis: nabiximols (Sativex®)

The efficacy of nabiximols (Sativex®) in the treatment of moderate to severe spasticity in multiple sclerosis (MS) is considered well established. Based on the results of three large controlled trials involving 189 (Collin et al., 2007), 337 (Collin et al., 2010) and 572 patients (Novotna et al., 2011) were approved for this indication in Germany and several other countries in 2011. In the majority of all review articles and meta-analyses, the effect of nabiximols in the treatment of spasticity in patients with MS is considered proven (Whiting et al., 2015; Abrams, 2018). The effect on spasticity is predominantly considered to be mild to moderate. There appears to be an effect particularly when patients respond to treatment from baseline. However, the effects in the studies were more pronounced when the effect of the treatment on spasticity was examined using a scale to be completed by the patients themselves. However, studies are now available that have demonstrated superiority of nabiximols over placebo when using the Ashworth scale, which has been established for objective measurement of spasticity (Leocani et al., 2015). In another recently published large placebo-controlled study of 191 patients, significant improvement in moderate-to-severe spasticity was again demonstrated in patients with MS (Markovà et al., 2018).

There is less agreement on whether other cannabis-based medicines, such as other cannabis extracts, dronabinol and cannabis flowers (with medium to high THC content), have a comparably good effect in the treatment of spasticity in MS. This is primarily due to a much

poorer study record for these substances. The majority believe that there are no significant differences in efficacy between the various THC-containing cannabis-based medications (Whiting et al., 2015; Abrams, 2018).. However, the type of use should also be considered when selecting a medication. For example, for the treatment of permanent spasticity, oral use may be more beneficial, while for example, for shooting-in spasticity before falling asleep, inhaled use with a rapid onset of action may offer advantages.

Numerous preclinical studies have investigated the role of the endocannabinoid system (ECS) in MS and sought explanations for its clinical effects. Currently, modulation of the ECS in MS is thought to result in more than symptomatic improvement. Thus, cannabis-based drugs are also thought to have neuroprotective and anti-inflammatory effects. In animal experiments, reduced disease progression was observed under the effect of cannabinoids. It is unclear which effects are due to the action of THC and which are due to CBD (review in. Chiurchiù et al., 2018).

### Spasticity of other cause

Only a few, mostly uncontrolled studies are available for the treatment of spasticity due to other diseases. There is no marketing authorization. In one small controlled study, nabilone was effective in the treatment of spasticity following spinal cord injury (Pooyania et al., 2010). Overall, it must remain unclear at this time whether cannabis-based medications can be used to treat spasticity in other conditions.

### Nausea and vomiting during chemotherapy: Nabilone (Canemes®)

The second cannabis-based drug approved in Germany is Nabilone (Canemes®), which has been approved since 2017 for the treatment of nausea and vomiting due to chemotherapy for patients who do not respond adequately to other antiemetic treatments. The approval did not require any newly conducted studies. Rather, approval was granted on the basis of "well established use," i.e., proof that nabilone has been "in general medical use" in the EU for more than 10 years and that efficacy and safety are adequately supported by the available data base. Nabilone has been available for the indication of nausea and vomiting associated with chemotherapy in numerous other countries, including the U.S. and the U.K., for decades. Marinol®, a finished product containing dronabinol, has been approved for the same indication in the USA since 1985 - but not in Germany.

As of 2015, 28 studies have been published with a total of 1772 patients. Overall, both nabilone and dronabinol were more effective than placebo and also than older antiemetics that are hardly used today, such as prochlorperazine and chlorpromazine. However, dronabinol also showed comparable efficacy when compared with the newer antiemetic ondansetron (Meiri et al., 2007). The cannabis-based medications resulted in improvement of both acute and delayed-onset nausea and vomiting. Because the majority of pivotal trials were conducted in the 1970s and 1980s, no reliable conclusion can be drawn regarding the efficacy and tolerability of cannabis-based medications compared with current standard antiemetic therapies.

For the treatment of nausea and vomiting due to chemotherapy with cannabis and the cannabis extract nabiximols, there are numerous anecdotal reports or small controlled, but no controlled methodologically high-quality studies. Therefore, a conclusive evaluation is not possible. However, there is little reasonable doubt that cannabis and cannabis extracts are also effective in this indication. In contrast, an effect of CBD is considered unlikely, although this has also not been investigated in studies to date (Whiting et al., 2015; Abrams, 2018). In children, the cannabis-based medications nabilone and dronabinol also appear to be effective for this indication, although data in this age group are much poorer (Phillips et al., 2016).

### Nausea and vomiting from other cause

For the indication nausea and vomiting due to other diseases or therapies - except chemotherapy - cannabis-based medicines are not approved in Germany. The data situation is insufficient. However, there are also - mainly uncontrolled and small - studies with positive reports on the efficacy of cannabis-based medications for the treatment of nausea and vomiting, for example in the context of radiotherapy, postoperatively, as a result of metastatic tumor diseases, in HIV and AIDS, after antiviral therapy for hepatitis C and also in pregnancy vomiting and vomiting as a result of motion sickness. While according to a retrospective chart analysis, prophylactic administration of dronabinol and prochlorperazine was effective in the treatment of postoperative nausea and vomiting (Layeeque et al., 2006), no positive effect was found in a controlled trial of nabilone (n=340) (Levin et al., 2017).

### Orphan drug status for rare forms of epilepsy: Cannabidiol extract Epidiolex®.

On March 30, 2017, the cannabidiol (CBD) plant extract Epidiolex® was granted a so-called orphan drug designation by the European regulatory authorities for the treatment of Lennox-Gastaut syndrome (LGS, also known as Lennox syndrome) - a rare and severe form of childhood epilepsy. Subsequently, orphan drug designation has been granted for several other rare conditions, including tuberous cerebral sclerosis, West syndrome, neonatal hypoxic brain injury, and graft versus host response. In 2018, Epidiolex® was approved in the U.S. for the treatment of epileptic seizures in Lennox-Gastaut syndrome and Dravet syndrome (age two years and older). Currently, approval is also being sought in the EU. For Germany, approval in these indications is expected in 9/2019.

Epidiolex® is not a pure CBD preparation, but a CBD plant extract that also contains other cannabinoids (such as THC) and other ingredients of the cannabis plant in low concentrations. The extent to which these other ingredients contribute to the efficacy of Epidiolex® is currently under discussion. There are indications that the THC contained in Epidiolex® is also relevant for the effect demonstrated in the studies for the above-mentioned epilepsies.

To date, little research has been done to determine whether pure CBD or any other cannabis-based medicine is also suitable for treating epilepsy or whether Epidiolex is effective for other forms of epilepsy.

## Indications approved outside Germany

### Chronic pain

Chronic pain is considered another established indication for cannabis-based medications. Whiting et al. (Whiting et al., 2015) come to the same conclusion in their meta-analysis published in 2015, as does the U.S. National Academies of Sciences, Engineering and Medicine in their report published in 2018 (Abrams, 2018) conclude that cannabis-based medicines are effective in the treatment of chronic pain. However, the effect is predominantly rated as "moderate." The majority of cannabis-based medications are assumed to be effective in the treatment of chronic pain of various etiologies including neuropathic pain, chronic pain in cancer, rheumatic pain, and chronic pain in MS. In the most comprehensive meta-analysis published to date in 2017 on the question of the efficacy of cannabis-based medications for chronic pain, 24 studies out of 42 identified were considered to have high methodological quality and were included in the analysis (Aviram and Samuelly-Leichtag, 2017). The authors again conclude that cannabis-based medications are generally effective in the treatment of chronic pain. However, the strongest effect was shown in neuropathic pain. According to this meta-analysis, inhalation of cannabis-based medications has a stronger pain-reducing effect than peroral treatment (Aviram and Samuelly-League, 2017).

In its position paper published in 2018, the European Pain Federation (EFIC) recommends that treatment with cannabis-based medicines should always be carried out by an expert experienced in the treatment of chronic pain and should be embedded in a multimodal therapy concept. (Häuser et al., 2018). An indication for cannabis-based medications is seen when first- and second-choice treatments do not lead to symptom improvement. Because polypharmacotherapy is often used, special attention should be paid to potential interactions with other central nervous system medications such as opiates and benzodiazepines. At times, the addition of a cannabis-based drug can reduce the dose of other analgesics, thereby reducing side effects while maintaining the analgesic effect. With regard to the various cannabis-based medications that can currently be used, the authors note that there is no evidence of differential efficacy, tolerability, or safety among the substances. For medicinal cannabis, a comparable effect and tolerability is to be assumed for all preparations (such as oily solutions and flowers) (Häuser et al., 2018).

### Chronic neuropathic pain

The best data are available for the treatment of chronic neuropathic pain. The best studied drug in this indication is nabiximols. In several countries - such as Canada, but not Germany - nabiximols (Sativex®) has therefore been officially approved for the treatment of neuropathic pain. Although the data situation for other THC-containing cannabis-based drugs such as dronabinol, nabilone and cannabis is worse, a similar beneficial effect is generally assumed as for nabiximols.

A Cochrane Review published in 2016 considered 16 controlled trials with a total of 1750 patients (Petzke et al., 2016). The duration of therapy ranged from 2 to 26 weeks. The majority of studies investigated the efficacy of nabiximols, with a few studies investigating nabilone, inhaled cannabis, and dronabinol. Four other systematic reviews from 2015 to 2018 found comparable results with a moderate pain-relieving effect. According to these reviews,

the "number needed to treat" for at least 30% pain relief is between 6-11. The authors of the EFIC report therefore classify cannabis-based medications as "third-line therapy" for chronic neuropathic pain (Häuser et al., 2018).

**Tumor pain**

The study situation for tumor-related pain is significantly worse. In a meta-analysis conducted in 2017 (Aviram and Samuelly-Leichtag, 2017) included a total of only three studies. All studies showed superiority of cannabis-based medications over placebo. Therefore, while the authors of this meta-analysis concluded that cannabis-based medications are effective in the treatment of tumor pain, the authors of the EFIC position paper (Häuser et al., 2018) point out that none of the four studies included in their review met the primary study endpoint (pain reduction of $\geq$ 30%). Nevertheless, even these authors recommend a treatment trial with cannabis-based medications for tumor pain when prior treatments with other established analgesics, including opiates, have been insufficiently effective (Häuser et al., 2018).

**Chronic (non-neuropathic and non-tumor related) pain of other cause.**

It is currently unclear whether cannabis-based medications are also effective for other chronic pain conditions such as fibromyalgia. While Avriam and Samuelly-Leichtag did find efficacy of cannabis-based medications in general for chronic pain in their meta-analysis (Aviram and Samuelly-Leichtag, 2017), the authors of the EFIC position paper believe that this study overstates the effects (Häuser et al., 2018).

Based on the results of a meta-analysis examining the influence of cannabis-based medications on pain perception in healthy individuals, it was suggested that cannabis-based medications do not decrease pain intensity, but rather decrease pain perception, making pain perceived as less unpleasant and more tolerable. The authors suggest that cannabis-based medications affect the affective component of pain, but not the pain itself (Vita et al., 2018).

**Acute pain**

To date, few studies have examined the effects of cannabis-based medications on acute pain. In the meta-analysis by Aviram and Samuelly-Leichtag, four studies were classified as methodologically sufficient and included (Aviram and Samuelly-Leichtag, 2017). In all four studies, placebo was more effective than the respective cannabis-based drug. In individual cases, positive effects were reported in migraine and cluster headache.

- For pain disorders of various etiologies, if established therapies have not been sufficiently effective or tolerated, therapy with a cannabis-based drug should be considered.
- Chronic neuropathic pain is considered a well-established indication.
- Good treatment results have also been reported in some cases for

other chronic, as well as acute pain, such as migraine and cluster headache.

- In addition to actual pain reduction, the effect of cannabis-based medications on chronic pain could also be due to an influence on the affective pain component.
- Treatment with cannabis-based medications can often save on other medications (including opioids).
- According to the results of an interim evaluation (3/2019) of the companion survey on off-label and no-label therapy with cannabis-based medicines conducted by the Federal Institute for Drugs and Medical Devices (BfArM), pain is by far the most common indication for prescription, accounting for almost 70%.

  - The most frequent prescription (approx. 30%) was in the age group of 50-59 year old patients.
  - On average, cannabis-based therapy was initiated in pain patients after 8 years of disease duration.
  - No differences were found in therapy between men and women.

**Anorexia with weight loss**

**Aids**

The ready-to-use preparation Marinol® containing dronabinol has been approved in the USA - but not in Germany - since 1992 for the treatment of "anorexia with weight loss in AIDS patients". In a report published in 1999 by the American "Institute of Medicine" with the title "Marijuana and Medicine", the effect of cannabis and other cannabis-based medicines was also classified as proven (Watson et al., 2000). However, only four controlled trials with a total of 255 patients have been conducted in this indication to date, and these were conducted between 1993 and 2003. In all of these studies, the efficacy of dronabinol was investigated and an overall positive effect was found. However, in retrospect, methodological doubts have been raised about the studies (Whiting et al., 2015). Due to the lack of larger and methodologically high-quality studies, current reviews classify the efficacy in the indication of weight loss in AIDS patients as low (Whiting et al., 2015; Abrams, 2018).. Nevertheless, in 2016, the US authorities approved another cannabis-based drug, the oily dronabinol solution Syndros® , for this indication - and additionally for nausea and vomiting due to chemotherapy. In a review published in 2018, an oily dronabinol solution is classified as a useful alternative for the treatment of anorexia in HIV and tumor patients. The easier ingestion of an oil versus swallowing capsules (as with Marinol®) was found to be

advantageous (Badowski and Yanful, 2018).

The appetite-stimulating effect of dronabinol is thought to be due to an agonistic effect at CB1 receptors in brain centers responsible for controlling appetite and vomiting. In addition, it has been speculated that weight gain is due to an increase in body fat percentage, decreased nausea, or a general improvement in mental and physical constitution.

#### Other diseases

In patients with anorexia with weight loss due to other diseases, the data situation is small and inconsistent, so that a conclusive evaluation is not possible. For example, in tumor patients, no positive effect was found for either a cannabis extract or dronabinol in a larger placebo-controlled study of 243 patients. In contrast, small studies in Alzheimer's patients reported improvement in numerous symptoms, including weight gain, with dronabinol treatment. Beneficial effects of cannabis-based medications (mostly dronabinol and nabiximols) with an increase in appetite and consequent facial gain have also been repeatedly reported in other geriatric populations and in palliative care.

## Conditions with currently limited evidence of efficacy of cannabis-based medications.

For all of the conditions listed below, the general consensus, as well as the majority of available meta-analyses and reviews, is that there is only limited evidence for the efficacy of cannabis and cannabis-based medications (Whiting et al., 2015; Abrams, 2018; Hoch and Schneider).. However, this should not be equated with the assumption that cannabis-based medications actually have low efficacy for these conditions. Rather, for the majority of the conditions presented here, there is well-established evidence that cannabis-based medicines actually have very good efficacy in these indications - possibly even better efficacy than established and approved treatments in some conditions - only the data base is currently so thin that no reliable statements can yet be made. Especially in these indications, further methodologically high-quality studies are urgently needed in order to gain further insights into the efficacy and tolerability of cannabis-based medicines.

For many diseases, it is still unknown - due to the lack of long-term studies - whether the positive effects initially observed also persist in the long term. The same applies to tolerability: long-term studies on the question of possible adverse drug effects after years of use are still lacking in the majority of the indications discussed. However, based on the long-term studies on the recreational use of cannabis and initial investigations in patients with MS, there is little reason to believe that in certain indications clinically relevant side effects only occur after a longer period of treatment.

### Mental illness

Evidence of beneficial effects of cannabis-based medications exists for numerous psychiatric

disorders. These are predominantly based on clinical experience and uncontrolled studies and case reports. In addition, based on the psychological effects of cannabis in healthy recreational users, hypotheses have been derived regarding the importance of the ECS in psychiatric disorders and their treatment with cannabis-based medications. However, the hypothesis of a positive effect of cannabis-based medications is also closely related to the fact that cannabinoid CB1 receptors are generally found in high density in the brain, where they are particularly expressed - in addition to the basal ganglia - in the hippocampus and frontal brain, i.e., brain regions associated with numerous mental disorders. The role of cannabinoid CB2 receptors expressed in the brain in the development and treatment of mental illness is still unclear. In contrast to CB1 receptors, the localization of CB2 receptors is limited to a few brain regions, including the brainstem, substania nigra, prefrontal cortex, and hippocampus. Finally, other endocannabinoid-like receptors may be important in mental disorders, such as the GPR55, TRPV1, and PPAR receptors.

Especially in the context of mental illness, there is intense (and controversial) debate as to whether the positive effects described by patients are due to a primary treatment effect - for example, through specific effects at the various cannabinoid receptors. Alternatively, it has been repeatedly speculated that they are merely secondary treatment effects, for example when symptoms such as sleep, anxiety and depression improve after successful treatment of spasticity and pain in MS with cannabis-based medications. Finally, placebo effects cannot be ruled out, which are known to be particularly common in mental illness. Closely related to this question is the hypothesis that some of the diseases described below may be primarily based on a disorder in the ECS. In this case, treatment with cannabis-based medications would represent a causal therapy.

For all the diseases listed below, a conclusive evaluation of the efficacy and tolerability of cannabis-based medicines will only be possible on the basis of further methodologically high-quality clinical studies.

### Tourette's Syndrome

Tourette syndrome is a neurological-psychiatric disorder characterized by so-called motor and vocal tics, i.e. involuntary movements and vocalizations. Tourette's syndrome belongs to the developmental disorders, since the onset is typically in early childhood, the tics reach a maximum in adolescence, and subsequently a spontaneous reduction of symptoms occurs. The majority of patients also have psychiatric comorbidities, such as attention deficit hyperactivity disorder (ADHD), compulsions, anxiety, depression, impulsivity, and sleep disorders. Treatment options are limited to behavioral therapies and psychotropic medications with a goal of 30-50% reduction in tics. The only approved - but no longer commonly used - drug is the classic antipsychotic haloperidol. If clinically relevant psychiatric symptoms exist in addition to the tics, multiple treatment is usually unavoidable.

Against this background, it is not surprising that patients with Tourette syndrome are looking for treatment alternatives. After it was first reported more than 30 years ago that cannabis leads to an improvement of numerous symptoms of the disorder, numerous other anecdotal reports (with a total of about 300 patients) on positive effects of both cannabis, but also dronabinol and nabiximols followed in the following years (for review cf. (Muller-Vahl, 2013; Kanaan and Muller-Vahl, 2017)..

To date, however, only two small controlled trials have been conducted, with 12 and 24 adult patients, respectively, evaluating the efficacy of dronabinol versus placebo. In both studies, efficacy was demonstrated. Due to the overall paucity of data, a conclusive evaluation is not possible. Similarly, in reviews and meta-analyses, the evidence was classified as low (Curtis et al., 2009; Whiting et al., 2015; Abrams, 2018)..

For the first time worldwide, a human study was recently conducted with the drug ABX-1431, a selective irreversible inhibitor of monoacylglycerol lipase (MAGL), which regulates the degradation of the endocannabinoid 2-arachidonoylglycerol (2-AG). In this pilot study in patients with Tourette's syndrome, a significant reduction in both tics and the anticipatory sensation preceding the tics was observed after only a single administration of ABX-1431. Currently, these promising results are being tested in a follow-up study.

Tourette's syndrome can be seen as a typical clinical example of a disorder for which no satisfactory treatment options exist, only one drug is approved at all, but which is no longer recommended for treatment because of frequent side effects, and patients and their treating physicians have repeatedly reported amazing treatment successes with cannabis-based drugs in recent years. In some cases, this also involved patients who had previously been classified as therapy-resistant. Interestingly, in patients with Tourette's syndrome, it has been repeatedly described that treatment with cannabis-based medications leads not only to a reduction in tics - the core symptom of the disorder - but also to an improvement in numerous psychiatric comorbidities. If this broad spectrum of efficacy of cannabis-based medications in patients with Tourette's syndrome is actually confirmed in currently conducted studies, for the first time ever a substance group would be available that improves more than just one symptom of the disease.

On the important question of whether cannabis-based medicines are also suitable for the treatment of children with Tourette's syndrome, no studies are yet available. However, a small number of individual case reports have already found indications of both a positive effect and good tolerability.

Interestingly, there is also evidence that cannabis-based medications may be better tolerated and have fewer adverse effects in patients with Tourette syndrome than in healthy recreational users. For example, one small study reported a lack of cognitive impairment with dronabinol and one case report described an improvement in driving ability after treatment with dronabinol (Müller-Vahl et al., 2003; Brunnauer et al., 2011)..

Finally, there is growing evidence that ECS may play a significant role in the pathogenesis of Tourette's syndrome. In a first study, elevated levels of the endocannabinoids 2-AG and anandamide as well as their metabolites were recently detected.

### Attention Deficit Hyperactivity Disorder (ADHD)

Attention deficit hyperactivity disorder (ADHD) is one of the most common neural developmental disorders. Clinically, the disorder is characterized by the core symptoms of hyperactivity, impulsivity, and lack of attention. The majority of patients also have psychiatric comorbidities, such as depression, antisocial behavior, personality disorders, sleep disorders, substance dependence, and tics. In about half of the cases, the disorder persists into adulthood.

Often, the clinical picture then changes and inattention, disorganization, emotional overreactivity, outbursts of anger, impulsivity, mood swings, and inability to perform tasks become prominent.

Multimodal treatment concepts are available for the treatment of adult patients with ADHD. Methylphenidate, atomoxetine and, more recently, lisdexamfetamine are officially approved for the treatment of ADHD in adults. Nevertheless, many patients are dissatisfied with these established treatment strategies due to lack of efficacy or frequent side effects. Compliance and adherence to therapy are often low in adults with ADHD.

It has been known for many years that adults with ADHD are at high risk for developing substance abuse. It is estimated that up to 30% of patients have an additional substance dependence. The most common additional diagnosis is alcohol or cannabis dependence. The treatment of ADHD according to the guidelines provides for a withdrawal treatment in the case of simultaneous use of cannabis before a drug therapy, for example with stimulants, can be initiated if necessary. Only recently, the question has been increasingly raised whether the use of cannabis in patients with ADHD can alternatively be considered as self-therapy instead of an expression of substance dependence.

It is known from patient surveys that numerous adults with ADHD use cannabis specifically for self-therapy. They report an in part astonishing improvement in numerous symptoms, for example with improved concentration and control ability, lower impulsivity and improved sleep. Accordingly, until 2017, the diagnosis of ADHD was the second most common diagnosis for which the Federal Opium Agency granted an exemption according to Section 3 (2) of the Narcotics Act (BtMG) for legal self-therapy with cannabis. Many of these patients do not meet the criteria for substance dependence. Rather, they often report controlled use over years without dose increase, loss of control, or evidence of habituation with diminishing effects.

To date, however, only one small controlled trial of nabiximols (Sativex®) has been conducted in 30 adult patients with ADHD. This demonstrated significant improvement in hyperactivity and impulsivity and a trend toward improvement in inattention (Cooper et al., 2017).

Similar to patients with Tourette's syndrome, changes in the ECS could also be detected in ADHD. For example, adolescents with ADHD were found to have decreased activity of the enzyme fatty acid amide hydrolase (FAAH), which degrades the endocannabinoid anandamide (AEA). This finding is consistent with the assumption that there is a disturbance in the ECS in patients with ADHD and that this could possibly be compensated for by therapy with cannabis-based medications.

**Post-traumatic stress disorder (PTSD)**

Post-traumatic stress disorder (PTSD) is a mental illness that occurs as a result of a traumatic event of extraordinary scope or catastrophic magnitude and often leads to a shattering of the affected person's understanding of themselves and the world. Typical clinical symptoms of PTSD include intrusive, distressing thoughts and memories, memory lapses, symptoms of hyperarousal such as sleep disturbances, startle response, increased irritability and difficulty

concentrating, avoidance behaviors, and emotional numbness. In the treatment of patients with PTSD, trauma-adapted psychotherapy is considered the treatment of choice. However, there is a high tendency for chronicity.

Similar to ADHD, many patients with PTSD are known to use cannabis as a self-therapy. This topic has also received increasing attention in recent years because cannabis use is widespread among American and Israeli war veterans, many of whom report improvement in symptoms typical of PTSD.

A 2016 systematic review identified a total of 6 studies that examined the efficacy of cannabis, nabilone, and dronabinol in patients with PTSD (Wilkinson et al., 2016). However, this did not include a single randomized controlled trial. Overall, the quality of all studies was considered low. However, all studies reported a positive effect with reduced severity of PTSD, fewer nightmares, improved sleep, fewer flashbacks, improved quality of life, and reduced need for psychotropic medication. These positive effects are countered by evidence that cannabis use is associated with a less favorable long-term prognosis for the disorder, leads to reduced overall mental health, and promotes increased use of other drugs. Therefore, the authors of the review urge that methodologically high-quality studies be conducted.

Based on animal studies, treatment with cannabidiol (CBD) has been suggested as an alternative to treatment of PTSD with dronabinol and THC-containing cannabis flowers and extracts, as this may have fewer side effects (Bitencourt and Takahashi, 2018).

Interestingly, reduced activity in the ECS was detected in patients with PTSD. Thus, on the one hand, decreased levels of the endocannabinoids anandamide and 2-AG were found and, on the other hand, increased binding to the cannabinoid CB1 receptor in the brain. Therefore, in combination with the clinical findings and because of the proven importance of the ECS in stress regulation, it has been suggested that reduced function in the ECS ("endocannabinoid deficieny") may underlie PTSD (Russo, 2016).

### Sleep disorders

In the meta-analysis by Whiting and collaborators published in 2015, sleep disorders were classified as an indication with low evidence of efficacy for cannabis-based medications (Whiting et al., 2015). In the 2018 published assessment by the U.S. National Academies of Sciences, Engineering and Medicine, the evidence for secondary sleep disorders was rated as moderate (Abrams, 2018). At least in the previously published summary report of the CaPRis study conducted in Germany, sleep disorders are not mentioned at all as a separate indication.

It is well known from surveys that cannabis, cannabis-based medicines, but also pure CBD are very often used by healthy people as well as by patients with very different diseases to improve falling asleep and staying asleep or the quality of sleep. To date, however, not a single study has examined the efficacy of a cannabis-based medication for a *primary* sleep disorder. Overall, only 2 studies have been conducted at all investigating the effect of nabilone in patients with sleep apnea syndrome and fibromyalgia, with improvement in sleep as the primary endpoint. Another 19 studies examined the effect of cannabis-based medications (the majority nabiximols) on sleep in different indications (such as MS and chronic pain), but this was only a secondary endpoint in each case. However, in these studies,

treatment with a cannabis-based drug predominantly improved sleep.

### Anxiety disorders

Anxiety disorders are considered the most common mental illnesses of all. The lifetime prevalence is 14-29%. According to ICD-10, anxiety disorders are divided into panic disorder, generalized anxiety disorder, phobic disorder, and mixed disorder with co-existing anxiety and depression. The most common anxiety disorders are generalized anxiety disorder and specific phobias. The course is usually chronic. Various psychotherapeutic procedures are considered effective. Numerous psychotropic drugs are approved for the treatment of anxiety disorders. The goal of available treatments is symptom reduction and relapse prevention.

There is well-established evidence from preclinical and animal studies that CBD, in particular, leads to a reduction in anxiety and panic (reviewed in Blessing et al., 2015). CBD also appears to have a beneficial effect on anxiety symptoms resulting from stress. In healthy subjects, CBD not only reduced anxiety symptoms previously induced by THC, but also experimentally induced anxiety.

To date, however, only two small controlled trials of CBD have been conducted in patients with anxiety disorders. In both studies, CBD was highly effective in treating social anxiety disorder. Numerous other studies investigating the efficacy of cannabis-based medications in other disorders have additionally reported improvement in anxiety, such as in patients with PTSD or Tourette's syndrome (Whiting et al., 2015; Turna et al., 2017; Abrams, 2018)..

However, there is also evidence that cannabis use and dependence can increase the risk of developing an anxiety disorder. Therefore, it seems even more important to investigate whether this effect can be suppressed by CBD. For THC, a biphasic effect is assumed: while low doses lead to a reduction of anxiety, higher doses may induce anxiety.

It is speculated that the anxiety-reducing effects of CBD are caused either by its indirect agonistic action at the cannabinoid CB1 receptor located in the brain - for example, by an increase in the concentration of anandamide due to inhibition of the degradative enzyme FAAH - or by an agonistic action at the TRPV1 receptor (*English*: transient receptor potential cation channel subfamily V member 1, German: Transient receptor potential cation channel of subfamily V (for vanilloid), subtype 1) or, alternatively, through a direct agonistic effect of CBD at the serotonin 1A (5-HT1A) receptor. Finally, these effects are thought to be stress dependent, as endocannabinodies are synthesized on demand ("on demand").

### Depression

It is known from surveys that patients use cannabis as self-medication to improve mood and treat depression. When cannabis and cannabis-based medications are used primarily to treat another condition (such as PTSD, ADHD, Tourette's syndrome, MS, pain), it is not uncommon to report additional mood enhancement. However, it is unknown whether this is a primary treatment effect or a secondary consequence of an improvement in other disease symptoms.

Recreational users also frequently report feeling euphoric after using cannabis. However,

there are also data according to which chronic cannabis use can lead to a deterioration in mood. Whether such effects in healthy recreational users can also be transferred to patients with mental illness is unknown. Thus, it is theoretically conceivable that desirable and undesirable effects of cannabis (and cannabis-based medications) in healthy individuals may differ markedly from those in patients with mental (and neurological) illnesses, as there may be dysfunction in the ECS in these disorders. This in turn could have a significant impact on the clinical effects caused by cannabis and cannabis-based medications.

Also in patients with bipolar disorder (with depressive and manic episodes), beneficial effects of cannabis and CBD on both poles of the disease have been described in individual cases. However, conclusive studies are lacking so far (Whiting et al., 2015; Turna et al., 2017)..

In this context, it is also noteworthy that the approval of the only selective CB1 receptor antagonist ever approved in the EU in 2006, rimonabant (Acomplia®), has been suspended since 2008 due to the frequent occurrence of severe psychiatric side effects with depression, suicidal thoughts and anxiety during treatment.

Based on these clinical observations and animal experiments showing that CB1 knockout mice exhibit depressive symptoms and are more susceptible to stress, it has been speculated that a dysfunction in the ECS may underlie depressive disorders. To date, however, only single-case reports and small, methodologically flawed studies reporting beneficial effects of various cannabis-based medications (including cannabis and dronabinol) are available.

### Schizophrenic psychosis

It has been known for a long time that the use of cannabis increases the risk for the occurrence of psychosis in the case of a corresponding disposition, early onset of use and large amounts of use. However, many patients with schizophrenic psychosis regularly use cannabis. A schizophrenic psychosis is a severe, often chronic psychiatric illness that must be distinguished from a short-term psychotic episode. Patients with schizophrenia report different motives for cannabis use. These range from social reasons and boredom, to an improvement in mood, anxiety and positive symptoms of psychosis (e.g. delusions and hallucinations), to a reduction in side effects of psychotropic drugs.

Based on these clinical observations, it has been repeatedly speculated whether ECS could have a pathogenetic significance at least in a subgroup of patients with schizophrenia. These considerations are supported by imaging studies: for example, a positron emission tomography (PET) study demonstrated that binding to central CB1 receptors is decreased in patients with schizophrenia compared with healthy controls in numerous brain regions associated with the pathogenesis of the disorder, such as the amygdala, caudate nucleus, posterior cingulate cortex, hippocampus, hypothalamus, and insula. Interestingly, both treatment with antipsychotics (neuroleptics) and smoking nicotine led to an increase in receptor availability.

It has been speculated that the beneficial effects reported by patients with schizophrenia may be due to the action of CBD. Analogously, an antipsychotic effect of CBD has been demonstrated in animal models of schizophrenia. This could possibly be due to an increase in

the concentration of anandamide. This in turn could be explained by CBD-induced inhibition of FAAH, the enzyme that degrades anandamide. In addition, CBD antagonizes the effects of CB1 agonists and, in this way, probably exerts effects at dopamine D2 receptors (review in. ((Leweke et al., 2018).

All these findings are consistent with the suggestion that CBD may be an effective drug in the treatment of schizophrenia. Indeed, two controlled randomized trials involving 42 and 86 patients found a significant effect on both positive and negative symptoms of the disorder, as well as a global symptom improvement (Leweke et al., 2012; McGuire et al., 2018). In one of the studies, the effect was comparable to that of the established antipsychotic amisulpride. In addition, interestingly, an increase in serum anandamide concentration was found under CBD treatment, which correlated with clinical improvement (Leweke et al., 2012). Since 2015, a large controlled multicenter study has been conducted in Germany to demonstrate the efficacy of cannabidiol CR (Arvisol®) in patients with schizophrenia.

### Forced anchoring

Obsessive-compulsive disorder is a severe psychiatric disorder characterized by the occurrence of compulsive actions, compulsive thoughts, or a combination of both symptoms. Behavioral therapy and drug treatment with serotonin reuptake inhibitors are considered standard therapies for compulsions. The goal of these therapies is symptom reduction and relapse prevention, but not symptom freedom. The disease often runs a chronic course.

Several reasons give rise to the suggestion that ECS may be important in the development of compulsions or that cannabis-based medications may be effective in therapy. In animal studies, both CBD and CB1 receptor antagonists had positive effects on compulsion-like behavior. Analogous to considerations in anxiety disorders, it has been speculated that CBD may have beneficial effects in obsessive-compulsive disorder through a direct agonistic action at the serotonin 1A (5-HT1A) receptor. In addition to the established serotonin hypothesis for the development of obsessive-compulsive disorder, it has been suggested alternatively that compulsions may underlie a disturbance in the glutamatergic system. Because of the inhibitory effect of ECS from glutamatergic transmission, it has been speculated that cannabis-based medications could lead to symptom improvement in compulsions through this pathway.

To date, there are only individual case reports of positive effects of dronabinol in the treatment of obsessive-compulsive patients. However, evidence was also found in patients with Tourette's syndrome that treatment with cannabis-based medications leads to a reduction in compulsions in addition to an improvement in tics (Kanaan and Müller-Vahl, 2017). In a small controlled study, dronabinol was effective in treating trichotillomania, a disorder classified as obsessive-compulsive disorder and characterized by the compulsive pulling out of one's own hair (Turna et al., 2017).

### Addictive disorders

In Germany, compared to cannabis, almost eight times as many people have "clinically relevant use" of tobacco and almost sixteen times as many have such use of alcohol (Matos et al., 2016). Contrary to frequently expressed assumptions, large epidemiological studies have

repeatedly shown that the risk of developing dependence is significantly greater with the use of nicotine and alcohol than with the use of cannabis (Lopez-Quintero et al., 2011). Therefore, bearing in mind the only low risk of dependence of cannabis and the only mild withdrawal symptoms, it has been repeatedly proposed to use cannabis and other cannabis-based medicines as a substitute drug (substitute) in the context of withdrawal treatment from illicit drugs such as opioids, but also from licit drugs such as nicotine and alcohol (Lucas et al., 2016). This discussion has been further fueled by the current opioid crisis in the USA.

In a small controlled trial, CBD was significantly superior to placebo treatment in tobacco cessation (Morgan et al., 2013). Also, small studies indicate that craving for substances such as alcohol, cocaine, and opiates decreases with cannabis substitution treatment. Conversely, there is evidence that use of alcohol and tobacco increases following abstinence from cannabis (review in Lucas et al., 2016). In the U.S., it was observed that in states that had released cannabis as a medicine, the annual mortality rate due to opioid overdose decreased by 25% (Bachhuber et al., 2014). Similarly, it has been shown that patients with chronic pain disorder can reduce the dosage of opioids and other analgesics after initiating treatment with medical cannabis (Boehnke et al., 2016). Finally, there is evidence that cannabis-based medications such as nabiximols, dronabinol, and nabilone, as well as CBD, reduce withdrawal symptoms in the context of cannabis withdrawal treatment (Allsop et al., 2014).

### Anorexia nervosa

Because of the known appetite-stimulating effect of cannabis, the positive effects of cannabis-based medications in anorexia in AIDS patients, and the weight-reducing effect of cannabinoid CB1 antagonists such as rimonabant, it is reasonable to assume that cannabis-based medications could be effective in the treatment of anorexia nervosa. To date, however, there are only a few case reports and controlled studies with small numbers of cases that have reached contradictory results, so that a conclusive evaluation is not possible at present.

## Neurodegenerative diseases

Because of the great relevance of the ECS for brain homeostasis - including its antioxidant, neuromodulatory, anti-inflammatory, and inhibitory effects - there has always been speculation about a role of this system in the pathogenesis of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS). In addition, the distribution of CB1 and CB2 receptors in the brain suggests involvement. For example, CB1 receptors are found in particularly high density in the basal ganglia output stations (substantia nigra pars reticulata and globus pallidus), hippocampus, cerebellum, and frontal cortex. CB2 receptors, on the other hand, are expressed in the brain especially in the brainstem, substantia nigra, prefrontal cortex and hippocampus. The expression of both receptor types in the basal ganglia suggests an importance in extrapyramidal motor movement disorders such as Parkinson's disease and Huntington's disease - but also dystonia and Tourette's syndrome - while the localization in the prefrontal cortex and hippocampus suggests an involvement in Alzheimer's disease. It is possible that the activation of microglia regulated by CB2 receptors plays a role in neuroinflammatory processes.

Despite numerous plausible hypotheses and promising preclinical findings, no convincing effect of cannabis-based drugs could be found in clinical trials so far, which is why neurodegenerative diseases are not even mentioned in current reviews and meta-analyses. Whether possibly a modulation of the ECS by inhibition of the degrading enzymes FAAH and MAGL or a very early, already in preclinical stages of the diseases starting treatment is effective remains to be clarified.

**Alzheimer's disease**

Numerous preclinical studies have found evidence that the ECS may be important in the development of Alzheimer's disease. Thus, enzymes involved in the synthesis and degradation of endocannabinoids are probably also expressed in microglia and astrocytes. Endocannabinoids are thought to have multiple anti-inflammatory, antioxidant and neuroprotective effects. Animal experiments have shown a functional interaction between the amyloid precursor protein (APP), which is the precursor protein of neurotoxic amyloid, and CB1 receptors.

In patients with Alzheimer's disease, increased binding to CB1 receptors in the hippocampus and frontal cortex was found in early stages of the disease, whereas binding was decreased in later stages. Overall, there appears to be a progressive reduction in CB1 receptor activity in the hippocampus during the course of the disease. Furthermore, in patients with AD, CB2 receptors and FAAH were increasingly enriched in cells associated with beta-amyloid plaques. The proinflammatory effect of beta-amyloid could be counteracted by activation of CB2 receptors. While a decreased concentration of anandamide was measured in the frontal cortex, the concentrations of 2-AG and its degrading enzymes were reduced in beta-amyloid plaques. Overall, numerous findings support reduced ECS activity in AD. Since cannabis-based drugs are thought to have neuroprotective, as well as anti-inflammatory and antioxidant effects, there has been speculation about a possible therapeutic or even protective effect of these compounds in M. Alzheimer's disease (Bedse et al., 2015).

**Parkinson's disease**

Similar to Alzheimer's disease, there is evidence from preclinical studies that the ECS is involved in the development of Parkinson's disease. Thus, alterations in the expression of the cannabinoid CB1 receptor gene have been demonstrated in animal models and in postmortem studies.

Recently, instead of stimulation of CB1 receptors, modulation and activation of CB2 receptors has been proposed as an alternative treatment for PD, as this could have a neuroprotective effect or counteract neuronal damage due to their localization to globus pallidus neurons. Indeed, reduced expression of the cannabinoid CB2 receptor gene was found in the cerebellum and hippocampus of patients with PD compared with healthy controls. In an animal model, overexpression of the CB2 receptor was associated with a reduction in dopaminergic dysfunction and improvement in clinical symptoms. Inhibition of MAGL resulted in neuroprotective effects. A recent study even found complex changes in gene expression of both cannabinoid CB1, cannabinoid CB2, and MAGL genes in the

substania nigra and putamen. In addition, CB2 receptors were increased in expression exclusively on astrocytes in the pars compacta of the substanis nirga.

In an imaging study, CB1 receptor binding was found to be decreased in the substantia nigra of patients with PD compared to healthy controls. In contrast, binding was increased in mesolimbic and mesocortical areas. However, these changes were independent of the presence of levodopa-induced dyskinesia.

As an alternative to the cannabinoid CB1 and CB2 receptors, the 2-AG-degrading enzyme MAGL has been proposed as a pharmacological target in patients with PD. MAGL inhibition had neuroprotective effects in a Parkinson's disease animal model as a result of a regenerative effect on astroglia and microglia and increased release of neuroprotective and anti-inflammatory molecules.

### Huntington's disease

It has been known for many years that even in the early stages of Huntington's disease, there is a loss of cannabinoid CB1 receptors throughout the gray matter of the brain. It has been speculated that this is a consequence of the mutant gene product huntingtin. After anecdotal reports of symptom improvements in patients with Huntington's disease after treatment with CBD and nabilone, no effect was demonstrated in a small controlled study with nabiximols.

### Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with loss of the first and second motor neuron that is still untreatable. Theoretical considerations of the role of ECS in neurodegenerative diseases described above led to the hypothesis that cannabis-based drugs could be used in the treatment of ALS. To date, only one small cross-over study (n=27) has been conducted in which dronabinol did not result in symptom improvement.

In a phase 2 study of 60 patients with motor neuron disease, therapy with nabiximols (Sativex®) resulted in a significant reduction in spasticity. One case report reported a slowing of disease progression with treatment with CBD.

### Other neurological disorders: Dystonia, tremor, restless legs syndrome.

Anecdotally, symptom improvement of dystonias such as blepharospasm has been reported after treatment with CBD. However, in a small controlled study, nabilone was not superior to placebo. In isolated cases, improvements of tremor in MS and restless legs syndrome have been reported.

## Inflammatory bowel disease

Patients with inflammatory bowel diseases such as ulcerative colitis and Crohn's disease unfortunately suffer not only from diarrhea and accompanying pain and fever, but often from weight loss, lack of appetite, joint pain, inflammatory skin changes, and fatigue. It is known from case reports and observational studies that these patients often use cannabis for symptom

relief and report an improvement in quality of life with a reduction in diarrhea, pain, and nausea, increased appetite, and improvement in sleep (review in Swaminath et al., 2018).

In a small controlled study, treatment with cannabis cigarettes resulted in a marked but nonsignificant improvement in numerous symptoms in patients with Crohn's disease (Naftali et al., 2013), while treatment with CBD was ineffective (Naftali et al., 2017). Similarly, in preclinical studies, cannabis-based medications were found to improve inflammation in the gut. However, in clinical studies, no changes in biochemical markers or activity index have been demonstrated so far under treatment with cannabis-based medicines.

Patients with irritable bowel syndrome are also known to frequently use cannabis as self-therapy and report a reduction in bowel mobility and pain. In both healthy individuals and patients with irritable bowel syndrome, dronabinol has been shown to lead to a reduction in intestinal tone and decreased postprandial bowel motility. However, controlled trials of cannabis-based medications in patients with irritable bowel syndrome are still pending (review in Goyal et al., 2017).

### Glaucoma

It has been known for decades that cannabis lowers intraocular pressure. This occurs via direct activation of central cannabinoid CB1 receptors. However, controlled studies systematically investigating the effect of cannabis-based medicines in patients with glaucoma are lacking.

## Palliative therapy and treatment of other severe chronic diseases

In recent years, more and more cannabis-based medicines are being used in palliative care and therapy for the severely chronically ill - for example, in chronic advanced MS. In this context, cannabis-based medicines sometimes prove to be of great value because of their broad spectrum of action. These patients often have many of the symptoms that can be alleviated by cannabis-based medications simultaneously, such as chronic pain, nausea, vomiting, decreased appetite, weight loss, sleep disturbances, spasticity, convulsions, anxiety, and depression. Even if cannabis-based medications do not result in significant improvement for each of these symptoms, the simultaneous improvement of a variety of symptoms can result in significant improvement in quality of life. Even effects otherwise classified as undesirable cannabis-based medications, such as euphoria, may be therapeutically desirable effects in this patient population (Agar, 2018).

The authors of a meta-analysis published in 2018 conclude that the current data situation is insufficient, however, and therefore the use of cannabis-based medications in palliative care cannot (yet) be generally recommended. In addition to the small number of methodologically high-quality studies, this is also attributed to the fact that in only very few studies the presumably most relevant criterion in this indication, namely the improvement of the general quality of life, was investigated at all (Mücke et al., 2018). The authors therefore urgently call

for further studies to be conducted in various indications such as cancer, HIV, and dementia.

For patients with MS, treatment with cannabis-based medications can improve spasticity and chronic pain, as well as numerous other symptoms (Rice and Cameron, 2018). However, the data for this is less clear in terms of, for example, bladder dysfunction, ataxia, tremor, sleep disturbance, overall quality of life, and level of disability (Nielsen et al., 2018).

In MS, but also the majority of studies in palliative care, the efficacy of nabiximols has been investigated. However, based on the available studies, it is not possible to draw a conclusion on which of the THC-containing cannabis-based medications is most effective. However, in a controlled trial of 56 patients with tumors of the head and neck during radiotherapy, nabilone was not superior to placebo treatment in terms of improvement in quality of life, pain, nausea, loss of appetite, weight loss, mood, and sleep (Côté et al., 2016)

## Possible further indications

In addition to the indications mentioned so far, other indications for cannabis-based medicines are also being discussed. However, in some cases only vague indications are available, e.g. based on a single case report. Nevertheless, other possible indications should be briefly discussed at this point, since the case reports sometimes describe astonishing symptom improvements in sometimes very rare diseases or diseases for which no effective therapies are available.

The list of diseases covers practically all medical specialties including neurology, dermatology, ophthalmology, psychiatry, orthopedics and internal medicine. This fact is also illustrated by the fact that patients with more than 50 different diagnoses had received a permit from the Federal Opium Agency according to Section 3 (2) BtMG for the legal purchase of medicinal cannabis flowers until the Cannabis as Medicine Act came into force in 2017 (Grotenhermen and Müller-Vahl, 2016). In addition to the ailments already mentioned, the following additional diagnoses were among them (in alphabetical order): Allergic diathesis, asthma, Barrett's esophagus, bladder spasms after multiple urogenital surgeries, borderline personality disorder, chronic fatigue syndrome (CFS), hyperhidrosis, lupus erythematosus, mitochondriopathy, Still's disease, neurodermatitis, paroxysmal non-kinesiogenic dyskinesia (PNKD), Posner-Schlossmann syndrome, psoriasis, restless legs syndrome, sarcoidosis, systemic scleroderma, thrombangiitis obliterans, tinnitus and urticaria of unknown origin.

## Literature


Abrams DI. 2018. the therapeutic effects of cannabis and cannabinoids: an update from the National Academies of Sciences, Engineering and Medicine report. Eur J Intern Med, 49:7-11 DOI: 10.1016/j.ejim.2018.01.003.

Agar M. 2018. medicinal cannabinoids in palliative care. Br J Clin Pharmacol DOI: 10.1111/bcp.13671.

Allsop DJ, Copeland J, Lintzeris N, Dunlop AJ, Montebello M, Sadler C, Rivas GR, Holland RM, Muhleisen P, Norberg MM, Booth J, McGregor IS. 2014. nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. JAMA Psychiatry, 71(3):281-291

DOI: 10.1001/jamapsychiatry.2013.3947.

Anon. 2017. medical marijuana for post-traumatic stress disorder: a review of clinical effectiveness and guidelines. Canadian Agency for Drugs and Technologies in Health, Ottawa (ON) (CADTH Rapid Response Reports) [accessed: 08/18/2018] URL: http://www.ncbi.nlm.nih.gov/books/NBK442070/.

Anon. www.iqwig.de - [A18-27] Extract of Cannabis sativa (spasticity due to multiple sclerosis) - benefit assessment according to § 35a SGB V (expiry of time limit). [accessed: 10/28/2018b] URL: https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/2018/a18-27-extrakt-aus-cannabis-sativa-spastik-aufgrund-von-multipler-sklerose-nutzenbewertung-gemaess-35a-sgb-v-ablauf-befristung.9646.html.

Aviram J, Samuelly-Leichtag G. 2017. Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Pain Physician, 20(6):E755-E796.

Bachhuber MA, Saloner B, Cunningham CO, Barry CL. 2014. medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. JAMA Intern Med, 174(10):1668-1673 DOI: 10.1001/jamainternmed.2014.4005.

Badowski ME, Yanful PK. 2018. dronabinol oral solution in the management of anorexia and weight loss in AIDS and cancer. Ther Clin Risk Manag, 14:643-651 DOI: 10.2147/TCRM.S126849.

Bedse G, Romano A, Lavecchia AM, Cassano T, Gaetani S. 2015. The role of endocannabinoid signaling in the molecular mechanisms of neurodegeneration in Alzheimer's disease. J Alzheimers Dis, 43(4):1115-1136 DOI: 10.3233/JAD-141635.

Bitencourt RM, Takahashi RN. 2018. cannabidiol as a Therapeutic Alternative for Post-traumatic Stress Disorder: From Bench Research to Confirmation in Human Trials. Front Neurosci, 12 DOI: 10.3389/fnins.2018.00502.

Blessing EM, Steenkamp MM, Manzanares J, Marmar CR. 2015. cannabidiol as a Potential Treatment for Anxiety Disorders. Neurotherapeutics, 12(4):825-836 DOI: 10.1007/s13311-015-0387-1.

Boehnke KF, Litinas E, Clauw DJ. 2016. medical cannabis use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. J Pain, 17(6):739-744 DOI: 10.1016/j.jpain.2016.03.002.

Brunnauer A, Segmiller FM, Volkamer T, Laux G, Müller N, Dehning S. 2011. cannabinoids improve driving ability in a Tourette's patient. Psychiatry Res, 190(2-3):382 DOI: 10.1016/j.psychres.2011.05.033.

Chiurchiù V, van der Stelt M, Centonze D, Maccarrone M. 2018. The endocannabinoid system and its therapeutic exploitation in multiple sclerosis: clues for other neuroinflammatory diseases. Prog Neurobiol, 160:82-100 DOI: 10.1016/j.pneurobio.2017.10.007.

Collin C, Davies P, Mutiboko IK, Ratcliffe S, Sativex Spasticity in MS Study Group. 2007. randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. Eur J Neurol, 14(3):290-296 DOI: 10.1111/j.1468-1331.2006.01639.x.

Collin C, Ehler E, Waberzinek G, Alsindi Z, Davies P, Powell K, Notcutt W, O'Leary C, Ratcliffe S, Nováková I, Zapletalova O, Piková J, Ambler Z. 2010. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurol Res, 32(5):451-459 DOI: 10.1179/016164109X12590518685660.

Cooper RE, Williams E, Seegobin S, Tye C, Kuntsi J, Asherson P. 2016. cannabinoids in attention-deficit/hyperactivity disorder: a randomised-controlled trial. European Neuropsychopharmacology, 26:S130 DOI: 10.1016/S0924-977X(16)30912-9.

Côté M, Trudel M, Wang C, Fortin A. 2016. Improving Quality of Life With Nabilone During Radiotherapy Treatments for Head and Neck Cancers: A Randomized Double-Blind Placebo-

Controlled Trial. Ann Otol Rhinol Laryngol, 125(4):317-324 DOI: 10.1177/0003489415612801.

Curtis A, Clarke CE, Rickards HE. 2009. cannabinoids for Tourette's syndrome. Cochrane Database Syst Rev, (4):CD006565 DOI: 10.1002/14651858.CD006565.pub2.

Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, Scheffer IE, Thiele EA, Wright S, Cannabidiol in Dravet Syndrome Study Group. 2017.Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med, 376(21):2011-2020 DOI: 10.1056/NEJMoa1611618.

Devinsky O, Marsh E, Friedman D, Thiele E, Laux L, Sullivan J, Miller I, Flamini R, Wilfong A, Filloux F, Wong M, Tilton N, Bruno P, Bluvstein J, Hedlund J, Kamens R, Maclean J, Nangia S, Singhal NS, Wilson CA, Patel A, Cilio MR. 2016. cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol, 15(3):270-278 DOI: 10.1016/S1474-4422(15)00379-8.

Devinsky O, Patel AD, Thiele EA, Wong MH, Appleton R, Harden CL, Greenwood S, Morrison G, Sommerville K, GWPCARE1 Part A Study Group. 2018. randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. Neurology, 90(14):e1204-e1211 DOI: 10.1212/WNL.0000000000005254.

Goyal H, Singla U, Gupta U, May E. 2017. role of cannabis in digestive disorders. Eur J Gastroenterol Hepatol, 29(2):135-143 DOI: 10.1097/MEG.0000000000000779.

Grotenhermen F, Müller-Vahl K. 2016. cannabis and cannabinoids in medicine: facts and outlook. Addiction Therapy, 17(02):71-76 DOI: 10.1055/s-0042-100702.

Häuser W, Finn DP, Kalso E, Krcevski-Skvarc N, Kress HG, Morlion B, Perrot S, Schäfer M, Wells C, Brill S. 2018. European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. Eur J Pain DOI: 10.1002/ejp.1297.

Hazekamp A, Ware MA, Muller-Vahl KR, Abrams D, Grotenhermen F. 2013. The medicinal use of cannabis and cannabinoids--an international cross-sectional survey on administration forms. J Psychoactive Drugs, 45(3):199-210.

Hoch E, Friemel CM, Schneider M (eds). 2019. cannabis: potential and risk: a scientific review. Springer-Verlag, Berlin Heidelberg [accessed: 10/28/2018] URL: //www.springer.com/de/book/9783662572900.

Hoch E, Schneider M. Brief report "Cannabis: potential and risks (CaPRis)." Federal Ministry of Health [accessed: 12/10/2017] URL: https://www.bundesgesundheitsministerium.de/service/publikationen/drogen-und-sucht/details.html?bmg%5Bpubid%5D=2650.

Kanaan AS, Müller-Vahl K. 2017. cannabinoid-based medicines for the treatment of Gilles de la Tourette syndrome. In: Handbook of cannabis and related pathologies: biology, pharmacology, diagnosis, and treatment. Academic Press, pp. 1035-1044.

Layeeque R, Siegel E, Kass R, Henry-Tillman RS, Colvert M, Mancino A, Klimberg VS. 2006. prevention of nausea and vomiting following breast surgery. Am J Surg, 191(6):767-772 DOI: 10.1016/j.amjsurg.2005.07.040.

Leocani L, Nuara A, Houdayer E, Schiavetti I, Del Carro U, Amadio S, Straffi L, Rossi P, Martinelli V, Vila C, Sormani MP, Comi G. 2015. Sativex(®) and clinical-neurophysiological measures of spasticity in progressive multiple sclerosis. J Neurol, 262(11):2520-2527 DOI: 10.1007/s00415-015-7878-1.

Levin DN, Dulberg Z, Chan A-W, Hare GMT, Mazer CD, Hong A. 2017. a randomized-controlled trial of nabilone for the prevention of acute postoperative nausea and vomiting in elective surgery. Can J Anaesth, 64(4):385-395 DOI: 10.1007/s12630-017-0814-3.

Leweke FM, Mueller JK, Lange B, Fritze S, Topor CE, Koethe D, Rohleder C. 2018. Role of the Endocannabinoid System in the Pathophysiology of Schizophrenia: Implications for Pharmacological Intervention. CNS Drugs, 32(7):605-619 DOI: 10.1007/s40263-018-0539-z.

Leweke FM, Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, Klosterkötter J, Hellmich M, Koethe D. 2012. cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Transl Psychiatry, 2:e94 DOI: 10.1038/tp.2012.15.

Lim K, See YM, Lee J. 2017. a Systematic Review of the Effectiveness of Medical Cannabis for Psychiatric, Movement and Neurodegenerative Disorders. Clin Psychopharmacol Neurosci, 15(4):301-312 DOI: 10.9758/cpn.2017.15.4.301.

Loflin M, Earleywine M, De Leo J, Hobkirk A. 2014. subtypes of attention deficit-hyperactivity disorder (ADHD) and cannabis use. Subst Use Misuse, 49(4):427-434 DOI: 10.3109/10826084.2013.841251.

Lopez-Quintero C, Pérez de los Cobos J, Hasin DS, Okuda M, Wang S, Grant BF, Blanco C. 2011. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Drug Alcohol Depend, 115(1-2):120-130 DOI: 10.1016/j.drugalcdep.2010.11.004.

Lucas P, Walsh Z, Crosby K, Callaway R, Belle-Isle L, Kay R, Capler R, Holtzman S. 2016. substituting cannabis for prescription drugs, alcohol and other substances among medical cannabis patients: the impact of contextual factors. Drug Alcohol Rev, 35(3):326-333 DOI: 10.1111/dar.12323.

Markovà J, Essner U, Akmaz B, Marinelli M, Trompke C, Lentschat A, Vila C. 2018. Sativex® as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial. Int J Neurosci:1-10 DOI: 10.1080/00207454.2018.1481066.

Matos EG de, Atzendorf J, Kraus L, Piontek D. 2016. substance use in the general population in Germany. SUCHT, 62(5):271-281 DOI: 10.1024/0939-5911/a000445.

McGuire P, Robson P, Cubala WJ, Vasile D, Morrison PD, Barron R, Taylor A, Wright S. 2018. cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. Am J Psychiatry, 175(3):225-231 DOI: 10.1176/appi.ajp.2017.17030325.

Meiri E, Jhangiani H, Vredenburgh JJ, Barbato LM, Carter FJ, Yang H-M, Baranowski V. 2007. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Curr Med Res Opin, 23(3):533-543 DOI: 10.1185/030079907X167525.

Morgan CJA, Das RK, Joye A, Curran HV, Kamboj SK. 2013. cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings. Addict Behav, 38(9):2433-2436 DOI: 10.1016/j.addbeh.2013.03.011.

Muecke M, Weier M, Carter C, Copeland J, Degenhardt L, Cuhls H, Radbruch L, Häuser W, Conrad R. 2018. Systematic review and meta-analysis of cannabinoids in palliative medicine. J Cachexia Sarcopenia Muscle, 9(2):220-234 DOI: 10.1002/jcsm.12273.

Müller-Vahl KR. 2013. treatment of tourette syndrome with cannabinoids. Behav Neurol, 27(1):119-124 DOI: 10.3233/BEN-120276.

Müller-Vahl KR, Prevedel H, Theloe K, Kolbe H, Emrich HM, Schneider U. 2003. Treatment of Tourette syndrome with delta-9-tetrahydrocannabinol (delta 9-THC): no influence on neuropsychological performance. Neuropsychopharmacology, 28(2):384-388 DOI: 10.1038/sj.npp.1300047.

Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM. 2013. cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-

controlled study. Clin Gastroenterol Hepatol, 11(10):1276-1280.e1 DOI: 10.1016/j.cgh.2013.04.034.

Naftali T, Mechulam R, Marii A, Gabay G, Stein A, Bronshtain M, Laish I, Benjaminov F, Konikoff FM. 2017. low-dose cannabidiol Is Safe but Not Effective in the Treatment for Crohn's Disease, a Randomized Controlled Trial. Dig Dis Sci, 62(6):1615-1620 DOI: 10.1007/s10620-017-4540-z.

Nielsen S, Germanos R, Weier M, Pollard J, Degenhardt L, Hall W, Buckley N, Farrell M. 2018. The Use of Cannabis and Cannabinoids in Treating Symptoms of Multiple Sclerosis: a Systematic Review of Reviews. Curr Neurol Neurosci Rep, 18(2):8 DOI: 10.1007/s11910-018-0814-x.

Novotna A, Mares J, Ratcliffe S, Novakova I, Vachova M, Zapletalova O, Gasperini C, Pozzilli C, Cefaro L, Comi G, Rossi P, Ambler Z, Stelmasiak Z, Erdmann A, Montalban X, Klimek A, Davies P, Sativex Spasticity Study Group. 2011. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex(®) ), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. Eur J Neurol, 18(9):1122-1131 DOI: 10.1111/j.1468-1331.2010.03328.x.

Petzke F, Enax-Krumova EK, Häuser W. 2016. [Efficacy, tolerability and safety of cannabinoids for chronic neuropathic pain: A systematic review of randomized controlled studies]. Pain, 30(1):62-88 DOI: 10.1007/s00482-015-0089-y.

Phillips RS, Friend AJ, Gibson F, Houghton E, Gopaul S, Craig JV, Pizer B. 2016. antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. Cochrane Database Syst Rev, 2:CD007786 DOI: 10.1002/14651858.CD007786.pub3.

Pooyania S, Ethans K, Szturm T, Casey A, Perry D. 2010. A randomized, double-blinded, crossover pilot study assessing the effect of nabilone on spasticity in persons with spinal cord injury. Arch Phys Med Rehabil, 91(5):703-707 DOI: 10.1016/j.apmr.2009.12.025.

Rice J, Cameron M. 2018. cannabinoids for Treatment of MS Symptoms: State of the Evidence. Curr Neurol Neurosci Rep, 18(8):50 DOI: 10.1007/s11910-018-0859-x.

Russo EB. 2016. clinical endocannabinoid deficiency reconsidered: current research supports the theory in migraine, fibromyalgia, irritable bowel, and other treatment-resistant syndromes. Cannabis Cannabinoid Res, 1(1):154-165 DOI: 10.1089/can.2016.0009.

Swaminath A, Berlin EP, Cheifetz A, Hoffenberg E, Kinnucan J, Wingate L, Buchanan S, Zmeter N, Rubin DT. 2018. the Role of Cannabis in the Management of Inflammatory Bowel Disease: a Review of Clinical, Scientific, and Regulatory Information: commissioned by the Crohn's and Colitis Foundation. Inflamm Bowel Dis DOI: 10.1093/ibd/izy319.

Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, Lyons PD, Taylor A, Roberts C, Sommerville K, GWPCARE4 Study Group. 2018. cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet, 391(10125):1085-1096 DOI: 10.1016/S0140-6736(18)30136-3.

Turna J, Patterson B, Van Ameringen M. 2017. is cannabis treatment for anxiety, mood, and related disorders ready for prime time? Depress Anxiety, 34(11):1006-1017 DOI: 10.1002/da.22664.

Vita MJD, Moskal D, Maisto SA, Ansell EB. 2018. association of cannabinoid administration with experimental pain in healthy adults: a systematic review and meta-analysis. JAMA Psychiatry DOI: 10.1001/jamapsychiatry.2018.2503.

Watson SJ, Benson JA, Joy JE. 2000. marijuana and medicine: assessing the science base: a summary of the 1999 Institute of Medicine report. Arch Gen Psychiatry, 57(6):547-552.

Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J. 2015. cannabinoids for medical use: a systematic review and meta-analysis. JAMA, 313(24):2456-2473 DOI: 10.1001/jama.2015.6358.

Wilkinson ST, Radhakrishnan R, D'Souza DC. 2016. a Systematic Review of the Evidence for Medical Marijuana in Psychiatric Indications. J Clin Psychiatry, 77(8):1050-1064 DOI: 10.4088/JCP.15r10036.