Cannabinoids in the Treatment of Selected Mental Illnesses: Practical Approach and Overview of the Literature

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ABSTRACT

Although an increasing number of patients suffering from mental illnesses self-medicate with *cannabis*, current knowledge about the efficacy and safety of *cannabis*-based medicine in psychiatry is still extremely limited. So far, no *cannabis*-based finished product has been approved for the treatment of a mental illness. There is increasing evidence that cannabinoids may improve symptoms in autism spectrum disorder (ASD), Tourette syndrome (TS), anxiety disorders, and post-traumatic stress disorder (PTSD). According to surveys, patients often use cannabinoids to improve mood, sleep, and symptoms of attention deficit/hyperactivity disorder (ADHD). There is evidence suggesting that tetrahydrocannabinol (THC) and THC-containing *cannabis* extracts, such as nabiximols, can be used as substitutes in patients with *cannabis* use disorder.

Preliminary evidence also suggests an involvement of the endocannabinoid system (ECS) in the pathophysiology of TS, ADHD, and PTSD. Since the ECS is the most important neuromodulatory system in the brain, it possibly induces beneficial effects of cannabinoids by alterations in other neurotransmitter systems. Finally, the ECS is an important stress management system. Thus, cannabinoids may improve symptoms in patients with mental illnesses by reducing stress.

Practically, *cannabis*-based treatment in patients with psychiatric disorders does not differ from other indications. The starting dose of THC-containing products should be low (1–2.5 mg THC/day), and the dose should be up-titrated slowly (by 1–2.5 mg every 3–5 days). The average daily dose is 10–20 mg THC. In contrast, cannabidiol (CBD) is mainly used in high doses > 400 mg/day.

Introduction

Currently, *cannabis*-based medications are well established in the treatment of chronic pain, spasticity in patients suffering from multiple sclerosis, nausea and vomiting, and – to a lesser extent – in palliative care [1]. In contrast, physicians in many countries rarely prescribe cannabinoids to patients suffering from mental illnesses. This is attributed to different factors, including only limited evidence suggesting the beneficial effects of cannabinoids in psychiatric disorders due to a tremendous lack of well-designed studies and limited access to *cannabis* programs [2–5]. Furthermore, psychiatrists more or less automatically associate the use of *cannabis* with *cannabis* use disorders (CUD), which may result in special caution in using cannabinoids as a medicine. To date, no finished *cannabis*-based product has been approved for the treatment of a mental illness.

Despite these facts, for many years, a substantial number of patients have been widely known to use *cannabis* as a form of self-medication for a variety of psychological symptoms and mental ill-

nesses or report "dual motives use," which means combined medical and recreational *cannabis* use. According to surveys performed at different time points in different geographical regions, mental illnesses, including attention-deficit/hyperactivity disorder (ADHD), depression, sleep disorders, anxiety, and post-traumatic stress disorder (PTSD) are among the most common reasons for taking *cannabis* as medicine [6–9]. However, until today, data for none of these indications is sufficient to have confidence that *cannabis*-based medicine is more likely to reduce symptoms than placebo. According to recent systematic reviews and meta-analyses specifically investigating the effects of *cannabis*-based medicines on mental illnesses, a larger number of well-designed and sufficiently powered studies is not available [2–4].

Against the background that mental illnesses represent a significant global burden and a considerable number of patients experience inadequate relief or intolerable side effects after the use of conventional treatments, including psychotherapy and pharmaceutical medications, *cannabis*-based medicines may represent a promising new treatment approach, particularly for otherwise therapy-resistant patients suffering from psychiatric disorders such as CUD, autism spectrum disorder (ASD), Tourette syndrome (TS), PTSD, anxiety disorders, sleeping disorders, ADHD, and depression. Furthermore, it has been suggested that cannabinoids and substances that potentiate endocannabinoid neurotransmission may augment the effects of behavioral therapy in different conditions, such as obsessive-compulsive behavior (OCB) and traumatic stress-induced behavior [10, 11].

Currently available *cannabis*-based medicines

The classification of *cannabis*-based medicines is primarily based on the content of the two most important and best-characterized cannabinoids, tetrahydrocannabinol (THC) and cannabidiol (CBD). Currently, only very few *cannabis*-based approved medicines are available (for an overview, see ▶ **Table 1**). The majority of products currently used are prescription drugs. *Cannabis*-based medicine can be taken orally (as oil, spray, or capsules), by inhalation, or rarely for topical use. Except for pure CBD and the plant-derived, purified pharmaceutical-grade CBD medication Epidiolex (in German-speaking countries: Epidyolex), *cannabis*-based medicines are included in the category of narcotic drugs. Depending on national laws and indications, in some countries, costs for *cannabis*-based medicines are reimbursed by health insurance. However, in particular, for patients with mental illnesses, health insurances often refuse to cover the costs, resulting in (illegal) self-medication with recreational *cannabis* unsupervised by a physician. This, in turn, limits the practical experience of psychiatrists in using *cannabis*-based medicines for patients with mental illnesses.

In many countries today, more than one hundred different chemotypes of *cannabis* with different concentrations of THC and CBD can be prescribed. Depending on the THC:CBD ratio, *cannabis* flowers and extracts can be classified as THC dominant (THC > CBD), CBD dominant (CBD > THC), and balanced (THC = CBD) products. However, *cannabis* flowers and full-spectrum extracts may contain, in addition to the two most well-known and best-studied "major" cannabinoids Δ9-THC and CBD, further so-called "minor" cannabinoids such as Δ8-THC, cannabigerol, cannabichromene, and cannabinol (CBN). Altogether, in the *cannabis* plant, more than 100 different cannabinoids have been identified, as well as about 400 further non-cannabinoid constituents, including phenols, flavonoids, terpenes, and alkaloids [12–14]. Up to now, it is still unclear whether the combination of all these ingredients of *cannabis* is more effective in the treatment of certain illnesses compared to the use of pure THC and CBD, respectively. According to the so-called "entourage effect", the combination of different cannabinoids and non-cannabinoid ingredients of *cannabis* leads to synergistic effects, boosting and complimenting those of THC and CBD [15].

There is still an ongoing debate on how to best classify *cannabis*. While some researchers prefer to treat all varieties as one diverse species, others describe up to three or four different species, including *Cannabis sativa*, *C. indica*, *C. ruderalis*, and *C. afghanica*. Alternatively, a classification based on the content of cannabinoids and THC is suggested describing, respectively, three or five different chemotypes ranging from high Δ9-THC content to fiber hemp containing no cannabinoids. However, currently, most experts believe that *cannabis* is best characterized as a single species, *C. sativa* L., with three different varieties being *C. sativa* L. var. *sativa*, *C. sativa* L. var. *indica*, and *C. sativa* L. var. *ruderalis*[16, 17]. *Cannabis* users often describe distinct or even opposite psychoactive effects of *C. indica* – as being relaxing and calming – and *C. sativa* – as being uplifting and energetic – although these effects are not based on scientific evidence. Accordingly, there is a suggestion to abandon a nomenclature that differentiates between *C. sativa* and *C. indica* and instead only declare cannabinoid and terpenoid profiles of the different *cannabis* chemotypes [16].

▶ **Table 1** Currently available *cannabis*-based medicines.

Drug		Ingredients	Finished medicinal product*	Prescription drug
Pure substance	Dronabinol	THC	Marinol, Syndros	dronabinol
	Nabilone	Nabilon	Canemes#, Cesamet#	–
	CBD	CBD	Epidyolex#, Epidiolex#	CBD
Cannabis flowers		Standardized for THC and CBD	-	> 100 strains*
Cannabis extracts	Nabiximols	Standardized for THC:CBD (1:1)	Sativex	–
		Standardized for THC and CBD	-	> 50 full spectrum extracts*

#spelling and trade name, respectively, differ from country to country, *availability differs from county to country, CBD = cannabidiol, THC = tetrahydrocannabinol.

Different modes of action of tetrahydrocannabinol and cannabidiol

Before initiating a *cannabis*-based treatment, treating physicians should know that THC and CBD – although both belonging to the group of natural cannabinoids in the *cannabis* plant – have very different effects on the endocannabinoid system (ECS) and also different molecular targets. THC is a potent orthosteric agonist for cannabinoid CB1 and CB2 receptors. However, as a partial agonist, THC has a mixed agonist-antagonist effect depending on the cell type and receptor expression, as well as the presence of endocannabinoids or other full agonists. In contrast, CBD has multiple molecular targets. CBD acts as an inverse agonist at cannabinoid receptors and, therefore, may reduce the activity of the ECS. However, CBD also inhibits the degradation of endocannabinoids, including anandamide, through the enzyme fatty acid amide hydrolase (FAAH), resulting in an increase in endocannabinoid levels and thus may cause cannabinoid receptor activation. In addition, CBD is a full agonist at 5-hydroxytryptamine 1 A serotonin receptors and transient receptor potential vanilloid 1 (TRPV1) channels. It is believed that most of the effects associated with CBD are mediated through these two receptors. However, CBD has been demonstrated to also act as a partial agonist at D2 dopamine receptors, a full agonist at adenosine A1 receptors, a negative allosteric modulator of μ opioid receptors (MOR), an agonist of intracellular peroxisome proliferator-activated receptor gamma, and has an overall inhibitory effect on sodium and calcium channels [18, 19].

It has been hypothesized that the addition of CBD to THC may not only enhance the clinical effects of THC but also reduce adverse events. According to the "entourage effect", it has been speculated that not only CBD but also other cannabinoids and non-cannabinoid components of *cannabis*, such as terpenoids, may attenuate the effects of THC [15, 20]. Assuming a synergistic activity when combining CBD, other cannabinoids, and terpenoids with THC, some researchers suggested the use of full-spectrum *cannabis* extracts or *cannabis* flowers in clinical therapy instead of isolated THC [20]. However, until today, it is unclear whether such an "entourage effect" exists and how such synergistic (or additive) effects could occur. By inhibiting FAAH activity, the addition of CBD to THC may result in increased levels of *N*-arachidonoylethanolamine (AEA), resulting in turn in increased agonistic effects on cannabinoid receptors. Furthermore, there is evidence that some effects of THC are biphasic depending on dose and that presumed synergistic effects are dependent on the relative ratios between the cannabinoids. However, it is important to note that besides possible synergistic effects, the combination of THC and CBD may also result in antagonistic effects, since CBD binds to CB1 receptors as an allosteric negative modulator and can influence the pharmacokinetic of THC by inhibiting the metabolism of THC into its more potent psychoactive metabolite 11-hydroxy-THC (11-OH-THC) [21]. Accordingly, THC and CBD may have opposite clinical effects, for example, with respect to appetite, cognition, and behavior.

Common side effects of *cannabis*-based medicines and contraindications

In general, *cannabis*-based medicines are considered well-tolerated and safe [22, 23]. Independent of the specific indication, the most common side effects of THC-containing *cannabis*-based medicines are drowsiness, fatigue, dizziness, and dry mouth. All side effects – and in particular psychological effects such as anxiety as well as psychoactive and cognitive effects – are subject to tolerance development. Accordingly, in any case, a "start low, go slow" dosing strategy is recommended. Special caution is recommended in children and older patients, *cannabis*-naïve patients, patients with clinically relevant somatic diseases such as cardiovascular diseases, pregnant and breastfeeding women, and patients with substance use disorder (SUD). Absolute contraindications are known sensitivity and acute psychosis. So far, no cases of deaths due to overdose of *cannabis* have been reported [23–25].

Pure CBD is extremely well-tolerated, causing almost no side effects after acute administration of doses up to 900 mg. Chronic administration of high doses up to 1500 mg/d causes only mild to moderate side effects such as diarrhea, nausea, headache, and somnolence [26]. While THC has only a few interactions with other drugs, CBD may have clinically relevant and serious interactions with several drugs, including ketoconazole, warfarin, clobazam, tamoxifen, and several other substances [26, 27].

Therapeutic doses of *cannabis*-based medicines

Since the balanced *cannabis* extract nabiximols is officially licensed for the treatment of spasticity in adults with multiple sclerosis in several countries, for this finished medicinal product – in contrast to all prescription drugs – expert information is available, including dosage instructions. For nabiximols, a starting dose of 1 spray containing 2.7 mg delta-9-THC and 2.5 mg CBD from *Cannabis sativa L*. is recommended. In general, up-titration should be slow to avoid side effects, for example, by one spray every 3–5 days. The maximum approved dose of nabiximols is 12 sprays, corresponding to 32.4 mg THC.

In line with this dosage instruction, in most indications and for all THC-containing oral products, a starting dose of about 2.5 mg THC is recommended. On average, the total daily dose of pure THC and THC-containing *cannabis* extracts is between 10 and 20 mg THC/day [22]. In the elderly, children, patients with polypharmacy, and other vulnerable groups of patients, a lower starting dose of about 1 mg THC/day is recommended [23].

With respect to pure CBD, in all current indications (including intractable childhood epilepsies), high oral doses of CBD (e. g., 10–50 mg/kg in children and > 400 mg/day in adults, respectively) are recommended. So far, it is uncertain whether lower (i. e., < 300 mg/day) oral doses of CBD have therapeutic potential [28].

In *cannabis*-naïve patients, treatment with *cannabis* flowers should also be up-titrated slowly, for example, starting with 10–25 mg/day. On average, daily doses of *cannabis* flowers range between 0.5 and 1.0 g/day. However, in individual cases, doses may be lower than 0.05 g/day but also higher than 4 g/day. For inhalation of *cannabis* flowers, the use of a vaporizer is recommended.

Possible underlying mechanisms for beneficial effects of *cannabis*-based medicine in mental illnesses

Since there is preliminary evidence that cannabinoids might be effective in a wide spectrum of mental illnesses with different underlying pathophysiology, different hypotheses have been proposed on how these effects can be best explained. Since the database is still weak, currently, it cannot be ruled out that at least some of the beneficial effects obtained from open uncontrolled or small-scale studies are due to placebo effects. Also, blinding in studies using THC-containing substances can be difficult because of the psychoactive effects of THC. Finally, cannabinoids – and in particular THC – have sedating and calming effects, which also can have positive effects on various symptoms in patients with mental illnesses.

However, it also can be speculated that cannabinoids may improve symptoms in different psychiatric disorders because of their effects on stress reduction since it is well-known that several psychiatric symptoms may increase with stress, such as anxiety, PTSD, sleeping problems, depression, and tics and at the same time it has been shown that the ECS is the most important stress regulatory system in the body [29]. Endocannabinoids are released "on demand." Accordingly, concentrations can be influenced by several different factors that may alter the synthesis or degradation of the endocannabinoids. However, the two most important endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG), as well as the activity of the FAAH enzyme and the CB1 receptor, are regulated by stress. Thus, the ECS is highly stress-responsive, resulting in altered synaptic activity and modulation of the sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis. This, in turn, may have beneficial effects on clinical symptoms that are stress-responsive [29].

Furthermore, it is well established that the ECS is the most important neuromodulatory system in the brain, influencing all important neurotransmitter systems, including the dopaminergic, glutamatergic, GABAergic, norepinephrinergic, acetylcholinergic, and serotoninergic systems [30]. For example, it has been demonstrated that there is a complex interaction between the ESC and the dopaminergic system: (i) vanilloid TRPV1 receptors modulate dopaminergic transmission, (ii) stimulation of dopamine D2-like receptors increases the levels of AEA, and (iii) endocannabinoids may counteract the effects of dopamine D2 receptor stimulation and control directly dopaminergic neurotransmission. The key role of the ECS in neuromodulation and its influence on several neurotransmitter systems provides a plausible explanation for the possible beneficial effects of cannabinoids on different conditions with different underlying pathologies and different transmitters involved [31].

Finally, it has been suggested that different disorders, including some mental illnesses, might be caused by a dysfunction or deficiency in the ECS [32]. Accordingly, the term "clinical endocannabinoid deficiency" has been suggested, describing clinical features as sequelae of a deficiency in the ECS. It has been speculated that such a deficiency may be caused by genetic or congenital defects, or occur secondarily due to infections, injuries, or other diseases. As described in more detail below, in some psychiatric disorders, including ADHD, depression, PTSD, and TS, alterations in levels of endocannabinoids or related enzymes, changes in CB1 receptor signaling, and associations with specific cannabinoid receptor alleles have been described, suggesting that changes in the ECS may be related to the underlying cause of the diseases.

Cannabis-based medicines in selected psychiatric indications

In the following, available data on *cannabis*-based treatment for different mental illnesses is summarized. All those disorders were included, with at least minimal data from small controlled or uncontrolled studies or case series available. All data included report results in adults besides a small number of studies and single case reports, respectively, in ASD and TS. Data is presented in alphabetical order. For studies reporting the effects of cannabinoids in dementia and psychosis, please refer to Dammann et al. and Broers et al. in this issue.

Anxiety disorders

In healthy subjects, it has been shown that CBD reduces anxiety symptoms [33–35]. Due to the prominent role of the ECS in stress regulation [29] and the close relationship between stress and anxiety, it has been speculated that beneficial effects on anxiety may be related to stress reduction [36]. According to epidemiological studies, anxiety disorders, including generalized anxiety disorder, social anxiety disorder, and panic disorder, but also other anxiety-related conditions, are a common reason for the use of *cannabis* [6, 37–39]. Data obtained from medical *cannabis* registry programs in Australia and Canada showed that *cannabis* is commonly prescribed for the treatment of anxiety disorders [37, 40]. So far, no randomized controlled trials (RCTs) have been performed investigating the effect of THC-containing cannabinoids on anxiety disorders.

In three small RCTs (N = 10, N = 24, N = 37), treatment with medium to high dose CBD (300–600 mg/day) resulted in a significant improvement in social anxiety disorder [41–43]. In a recently published RCT (N = 80), researchers investigated whether additional treatment with CBD enhances the effects of exposure therapy in treatment-refractory patients with panic disorder with agoraphobia or social anxiety disorder. However, single doses of 300 mg CBD had been administered only once weekly before therapist-assisted exposure in vivo sessions. This only once weekly medium dose of CBD did not result in any difference in treatment response compared to placebo [44].

According to a recent systematic review and meta-analysis, there is low-quality evidence suggesting that CBD reduces anxiety. In addition, the authors found some indication of publication bias and concluded that further clinical trials are needed [45].

A first study investigating the effect of JNJ-42165279, a selective inhibitor of FAAH, the enzyme responsible for the degradation of fatty acid amides (FAA) including anandamide, palmitoylethanolamide (PEA), and N-oleoylethanolamide (OEA), in social anxiety disorder demonstrated non-significant improvements of this endocannabinoid modulator [46].

Attention deficit/hyperactivity disorder (ADHD)

From surveys and retrospective studies, it is well known that patients with ADHD often self-medicate with *cannabis* and report an

amelioration in a broad spectrum of symptoms, including inattention, hyperactivity, impulsivity, depression, anxiety, sleeping problems resulting in improved psychosocial performance and quality of life [6, 47–49]. According to an online survey performed in Germany in 2020 with N = 1028 participants indicating the use of medicinal *cannabis* flowers prescribed by a physician, ADHD was the diagnosis most frequently indicated as a current indication for *cannabis*-based treatment [50]. According to case studies including one and three patients, respectively [51, 52], and a case series including N = 30 patients [53], THC-containing *cannabis*-based medicines (pure THC, *cannabis* flowers) improve concentration, sleep, impulsivity, depression, anxiety, quality of life, and enhance the driving performance of the patient.

So far, only one small controlled study examined the efficacy of the *cannabis* extract nabiximols in adults with ADHD (N = 30). The mean dose was 4.7 sprays (range, 1–13), corresponding to 12.6 mg THC. Although the primary endpoint was not reached, several secondary endpoints showed significant improvements in hyperactivity, impulsivity, and cognitive measure of inhibition and a trend towards improvement in inattention and emotional lability [54].

There is some evidence for an involvement of the ECS in ADHD pathology since a reduced activity of the enzyme FAAH was found in the serum of boys with ADHD [55]. In addition, differences in allele frequency and genotype distribution of the FAAH rs2295633 gene were detected in children with ADHD [56].

Autism spectrum disorder (ASD)

Increasing evidence suggests that cannabinoids might be effective in the treatment of behavioral problems in patients with ASD, such as rage attacks, impulsivity, and aggression [57]. In a case study, PEA plus the flavonoid luteolin resulted in symptom improvement, including stereotypies, in a 10-year-old boy with ASD [58]. In a retrospective study in children and adolescents (N = 60), treatment with a full-spectrum CBD dominant *cannabis* extract (CBD:THC between 20:1 to 6:1, mean daily dose: 3.8 ± 2.6 mg/kg/day CBD and 0.29 ± 0.22 mg/kg/day THC) improved "behavioral outbursts." The higher the THC dose, the stronger the effects were [59]. In a prospective uncontrolled study (N = 53), pure CBD (median daily dose = 90 (45–143) mg) resulted in an improvement of different behavioral symptoms, including angry outbursts, autoaggression, hyperactivity, sleeping problems, and anxiety [60]. According to another open-label study, longer-term treatment with CBD-rich *cannabis* (individually adjusted dose: maximum 10 mg/kg/day or total of 400 mg/day of CBD and 0.5 mg/kg/day or total of 20 mg/day of THC) over 6 months resulted in the majority of N = 82 children and adolescents with ASD in improvements in social communication abilities as well as restricted and repetitive behaviors [61].

In a large controlled study, N = 150 children and adolescents were included, and the efficacy of full-spectrum *cannabis* extracts (CBD:THC = 20:1) and purified THC and CBD in the same ratio were compared with a placebo. The dose depended on body weight up to a maximum of 420 mg CBD and 21 mg THC per day. While the primary study endpoint ("change in overall behavior") was not met, treatment with the full-spectrum extract resulted in a significant improvement in disruptive behavior compared to placebo or the full-spectrum extract [62]. Overall, cannabinoids were well tolerated, with only mild adverse effects. These promising effects were corroborated in another recent RCT, including N = 60 children with ASD demonstrating significant improvements in social interaction, anxiety, psychomotor agitation, number of meals a day, and concentration after treatment with a CBD-rich *cannabis* extract at a concentration of 0.5 % (5 mg/mL) in a 9:1 ratio of CBD:THC (daily dose ranged from 6 to 70 drops) [63].

Cannabis use disorder (CUD) and other substance use disorders (SUD)

A limited number of studies have explored the potential of *cannabis*-based medicine as an adjunctive or alternative treatment for specific SUDs. Doses most often used ranged from 5–40 mg THC/day and 400–800 mg CBD/day, respectively. According to a small number of RTCs, including between N = 16 and N = 154 patients, there is preliminary evidence suggesting that orally taken THC and, in particular the *cannabis* extract nabiximols can improve symptoms associated with CUD such as severity and time course of *cannabis* withdrawal symptoms, overall health, and quality of life and may reduce *cannabis* craving and use of smoked *cannabis* [64–67]. In a randomized clinical trial (N = 84), in addition, pure CBD was more efficacious than placebo at reducing *cannabis* use in patients with CUD [68]. Finally, in a single center RTC in N = 70 men, the FAAH-inhibitor PF-04457845 was superior compared to placebo in reducing symptoms of *cannabis* withdrawal as well as *cannabis* use [69].

There is limited evidence suggesting that THC may decrease the severity of opioid withdrawal symptoms [70, 71] and that CBD may reduce opioid craving [72]. It is well-known that *cannabis* is frequently used as a substitute for prescription drugs, including opioids [73]. There is no convincing data available suggesting that cannabinoids reduce symptoms associated with cocaine use disorder [74, 75] or with other substances such as tobacco [76]. Although cannabinoids, including THC and CBD demonstrate potential for treating SUDs, the available evidence is limited and larger well-designed studies are needed.

Depression

Data obtained from epidemiological studies and surveys including large samples has shown that people self-medicating with *cannabis* and patients taking prescribed *cannabis*-based medicines, respectively, often report an improvement in mood and that depression is one of the most common reasons for cannabinoid therapy [6, 49, 77–80]. Interestingly, in one of these studies that included N = 1,819 individuals, the THC concentration of *cannabis* flowers was the strongest independent positive predictor for the improvement of depressive symptoms [80].

Remarkably, until today, well-designed RTCs investigating the effect of cannabinoids on major depression are missing. Controlled studies investigating the efficacy of nabiximols and smoked *cannabis* flowers with varying THC levels (0–9.4 %), respectively, in other conditions such as multiple sclerosis, cancer pain, CUD, and neuropathic pain failed to demonstrate a significant improvement of depression as a secondary endpoint [2, 81].

On the other hand, there is no evidence suggesting that recreational use of *cannabis* is an independent risk factor for the onset of mood disorders [78]. A recent genetic study suggested that car-

riers of the cannabinoid receptor 1 (CNR1) A-allele are more susceptible to developing depression [82].

Obsessive compulsive disorder (OCD)

While numerous animal studies have suggested that *cannabis*-based medicines may improve obsessive-compulsive symptoms (for review, see [83]), clinical studies are limited. In a large internet survey from the US, the majority of patients with OCD self-reported that using *cannabis* medicinally resulted in an improvement of OCD [84]. According to a small number of single case studies, dronabinol, and *cannabis* flowers improve compulsive behaviors and obsessive thoughts [83, 85, 86]. In a small RCT (N = 11), co-medication with nabilone (up to 2 mg/day, corresponding to 14–16 mg THC/day) augmented exposure-based behavioral psychotherapy for OCD, while monotherapy with nabilone had no significant effect [10]. In a small placebo-controlled single-dose study (N = 12), no acute effects of low-dose smoked *cannabis* with different THC:CBD ratios (about 400 mg of *cannabis* with either 7.0 % THC and 0.18 % CBD or 0.4 % THC and 10.4 % CBD) were detected [87].

While in a small open-label study (N = 14), dronabinol was effective in reducing trichotillomania [88], in one randomized, double-blind, placebo-controlled, parallel-group follow-up study over 10 weeks in a mixed population with trichotillomania (N = 34) or skin picking disorder (N = 16), dronabinol (5–15 mg/day) did not significantly separate from placebo on any efficacy measure [89].

Post-traumatic stress disorder (PTSD)

The title of a recent editorial by Abizaid et al., "*Cannabis*: A potential efficacious intervention for PTSD or simply snake oil?" [90] strikingly illustrates the controversial debate about the sense or nonsense of *cannabis* in the treatment of PTSD. Similar to other mental illnesses, from epidemiological studies, it is well-known that patients with PTSD often self-medicate with *cannabis* [6]. In some observational studies, negative effects have been reported in patients with PTSD when using *cannabis*, such as overall worsening of symptoms, more violent behavior, more alcohol use [91], an increase in trauma-associated intrusions [92] as well as suicidal thoughts and behavior [93]. Other surveys suggested the contrary, showing the use of *cannabis* resulted in more than 50 % improvement in all recorded PTSD symptoms, including intrusive thoughts, flashbacks, irritability, anxiety [94] as well as a significantly lower risk of a major depressive episode and the presence of suicidal ideation [95].

From a small number of case reports and uncontrolled studies, beneficial effects on different symptoms in patients with PTSD have been reported after use of *cannabis* [96–98], THC, nabilone [99–101], and pure CBD [102, 103], respectively.

Up to now, there are only three small controlled studies (including between N = 10 and N = 33 patients) available reporting significantly improved nightmares and overall clinical impression after treatment with 0.5 mg nabilone [104] and improved anxiety and cognitive impairment after a single dose of 300 mg CBD [105, 106]. In the largest RCT published so far in this indication, treatment with three different concentrations of smoked *cannabis* (THC/CBD = 12 %/ < 0.05 %, THC/CBD = 0.50 %/11 %, and THC/CBD = 7.9 %/8.1 %) in N = 80 military veterans with PTSD was not superior compared to placebo [107].

Limited data suggest that the ECS is involved in the pathogenesis of PTSD, as indicated by a globally increased binding to central cannabinoid CB1 receptors as well as decreased blood levels of the endocannabinoid anandamide [108].

Sleeping disorders

Anecdotally, it has been reported several times that patients often use *cannabis* and *cannabis*-based medicine, respectively, to improve sleeping problems [6, 7, 37, 77, 109]. In patients with chronic pain, the beneficial effects of *cannabis*-based medicines on sleep as a secondary outcome measure have been demonstrated [110]. In a small controlled study (N = 19), it was found that nabilone (mean dose = 0.86 mg/day (corresponding to 6–7 mg THC), range, 0.25–1.75 mg/day) improves – among other non-motor symptoms – night-time sleep problems in patients with Parkinson's disease [111].

However, the database supporting the use of medicinal *cannabis* as an effective and safe treatment option for sleep disorders is still very weak [112]. So far, only two small RCTs have been performed investigating the efficacy of *cannabis*-based treatment in patients with sleep disorders. In the first study, N = 24 patients with chronic insomnia (symptoms ≥ 3 months) received up to 1 mL of the cannabinoid extract ZTL-101, which contains 20 mg/mL THC, 1 mg/mL CBD, 2 mg/mL CBN, and naturally occurring terpenes or placebo for two weeks [113]. Insomnia symptoms and sleep quality significantly improved after treatment with the *cannabis* extract. In the second study, including N = 29 patients with insomnia, medicinal *cannabis* oil containing 10 mg/mL THC and 15 mg/mL CBD (up to a maximum dose of 15 mg THC/22.5 mg CBD per day) over 2 weeks also resulted in an improvement of time and quality of sleep. In addition, midnight melatonin levels improved significantly [114].

Tourette syndrome (TS)

Thirty-five years ago, in 1988, an anecdotal report suggested for the first time that smoked *cannabis* may improve symptoms in patients with TS [115]. Thereafter, several similar case reports and open-label studies have been published reporting not only a sustained reduction of tics and premonitory urges, but also an improvement of a broad spectrum of psychiatric comorbidities, including ADHD, sleeping problems, self-injurious behavior, impulsivity, OCB, and depression after use of smoked *cannabis* [116–120] and oral *cannabis*-based medicines such as THC, THC plus CBD, THC plus PEA, and nabiximols, respectively [121–128]. In addition, one case study reported an improvement in the driving performance of the patient after the use of THC [123]. Beneficial effects of *cannabis*-based treatments (THC, nabiximols, and inhaled *cannabis*) were also been reported in four children and adolescents aged 7 to 16 years with improved tics, ADHD, depression, and insomnia [120, 126, 129–131].

To date, four controlled trials have been published investigating the effects of different cannabinoids in adults with TS. In two small-scale studies including N = 12 (single dose of THC up to 10 mg) and N = 24 patients (up to 10 mg THC/day for 6 weeks), respectively, THC resulted in a significant improvement of tics [132, 133] without causing impairment in neuropsychological performance [134, 135]. Another small RCT (N = 12) suggested that vaporized

single doses of 0.25 g of medicinal *cannabis* containing 10 % THC and 9 %/9 % THC/CBD – but not 13 % CBD – reduce tics and premonitory urges [136].

Only recently, results from the first large, well-designed RCT investigating the efficacy and safety of the *cannabis* extract nabiximols have been reported [137, 138]. Although this study, including N = 97 patients with TS, formally failed to demonstrate superiority for nabiximols (mean dose = 7.21 ± 3 · 42 puffs/day for 13 weeks) over placebo in the primary endpoint, the results showed clear trends for improvements in tic severity, depression, and quality of life after treatment with nabiximols.

While in a small controlled single-dose single-center phase 1b cross-over study (N = 20), the endocannabinoid modulator Lu AG06466 (formerly known as ABX-1431) that reduces the degradation of the endocannabinoid 2-AG by inhibiting the monoacylglycerol lipase (MAGL) was effective in reducing tics and premonitory urges in patients with TS [139], in a follow-up RCT including N = 49 patients, Lu AG06466 was not effective in reducing tics or related symptoms in patients with chronic tic disorders [140].

Preliminary data suggests a dysfunction in the ESC in TS, since levels of different endocannabinoids (anandamide, 2-AG, the endocannabinoid-like molecule PEA, and arachidonic acid (AA)) were found elevated in cerebrospinal fluid (CSF) [31]. Results of genetic studies were inconsistent and showed either no genetic variations of the CNR1 gene in patients with TS [141] or a relationship between variants of the CNR1 gene and an increased risk for TS [142].

Summary

Future studies will show whether the ECS is pathophysiologically involved in mental illnesses. Because of its paramount role as a neuromodulatory system in the brain, it can be speculated that stimulation of the ECS influences symptoms of mental illnesses, even if they are caused by alterations in other neurotransmitter systems. Finally, agonists at central cannabinoid CB1 receptors, such as THC-containing cannabinoids, can reduce stress, which may ameliorate a wide spectrum of psychopathological symptoms.

Although a substantial number of patients with various mental illnesses self-medicate with *cannabis*, current knowledge about the efficacy and safety of *cannabis*-based medicine in psychiatry is still in its infancy. There is limited evidence that THC-containing substances may improve tics in patients with TS as well as different symptoms in ASD and PTSD. From a small number of studies it is suggested that CBD improves social anxiety disorder. Although cannabinoids are often used in these indications, based on current literature, it is still unclear whether they may be effective in sleep disorders, depression, and ADHD. It should be noted that all data presented refer to data in adult patients besides a small number of studies on ASD and TS. Accordingly, in children, *cannabis*-based medicine should be used with particular caution, because only very little data is available on efficacy and safety in patients with various psychiatric disorders in this age group.

Against the background that *cannabis*-based medications are safe and, in most cases, well tolerated, this group of substances may provide a new treatment strategy in otherwise treatment-resistant patients suffering from psychiatric disorders, including CUD, ASD, TS, PTSD, anxiety disorders, sleeping disorders, ADHD, and depression. Currently, different cannabinoid modulators that either inhibit the degradation or the reuptake of endocannabinoids are under development and might be further alternative options for the treatment of mental illnesses in the future.

Conflict of Interest

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