Overview: Chronic Pain and Cannabis-Based Medicines

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Authors
Matthias Karst

Affiliations
Anesthesiology, Pain Clinic, Hannover Medical School, Hannover, Germany

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Georg Thieme Verlag, Rüdigerstraße 14,
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Correspondence
Matthias Karst, MD, PhD
Department of Anesthesiology and Intensive Care Medicine
Pain Clinic
Hannover Medical School
Carl-Neuberg-Str. 1
30625 Hannover
Germany
karst.matthias@mh-hannover.de

ABSTRACT

Chronic pain is primarily conceptualized as a disease in its own right when it is associated with emotional distress and functional impairment. Pathophysiologically, dysfunction of the cortico-mesolimbic connectome is of major importance, with overlapping signals in the nociceptive and stress systems. The endocannabinoid system plays an important role in the central processing of nociceptive signals and regulates the central stress response. Clinically, there is moderate evidence that cannabis-based medicines (CBM) can contribute to a significant reduction in pain, especially the associated pain affect, and improvement in physical function and sleep quality in a proportion of patients with chronic pain. The analgesic effect appears to be largely independent of the cause of pain. In this context, CBM preferentially regulates stress-associated pain processing.

Introduction

Chronic pain, i. e., pain lasting longer than three months, is a common health problem that affects quality of life and is a major burden for society [1]. As an epidemiological analysis in Germany has shown, one can speak of an independent pain disease, especially when chronic pain is associated with considerable emotional distress and functional impairment [2]. This definition corresponds to the current ICD-11 classification of chronic primary pain [3].

A recent review found that a wide range of adverse childhood experiences is associated with the development, severity, and impact of chronic pain in adulthood and that the more severe the adverse experiences, the stronger this effect [4].

Stress in early life can interact with genetic factors, especially in vulnerable life periods, and, involving epigenetic mechanisms, creates the basis for permanently impaired responsiveness of allostatic systems and thus increases the likelihood of chronic pain occurring later in life [5–7]. A significant example of such a process is the epigenetic dysregulation of central glucocorticoid receptors, resulting in a disruption of stress processing [8]. Both over- and under-activation of the hypothalamic-pituitary-adrenocortical axis can lead to imbalances in other systems, particularly the endocannabinoid (EC) [9] and cortico-mesolimbic systems [10, 11]. Dysfunction of the cortico-mesolimbic systems can be understood as a central neurobiological correlate of chronic pain [10–12], which may remain active even in the absence of sustained nociceptive input [11]. Trauma in childhood also appears to directly affect pain sensitivity through epigenetic changes in ion channels such as the transient receptor potential ankyrin-1 channel (TRPA1) [13]. This fits with the observation that stress in early childhood is associated with the development of pro-inflammatory responsiveness throughout life [6], e. g., via priming of microglia [14, 15].

Overall, the above-mentioned changes can be understood as an expression of central pain sensitization, which involves intensified neuronal signaling in the central nervous system (CNS), resulting in pain hypersensitivity, clinically manifested in diffuse, widespread pain disproportionate to what would be expected based on

the available presumed source of nociception [16]. A pain intensity above 40 out of 100 on the Central Sensitization Inventory (CSI) is required to determine central pain sensitization [16]. The CSI maps a variety of biopsychosocial aspects, fitting to the multidimensional character of chronic pain, which includes e. g., generalized sensory sensitivity, increased somatic perception, cognitive impairment, and sleep problems [17]. These factors have been included into the new pain classification "nociplastic pain" of the International Association for the Study of Pain [16]. A recent review of studies on central sensitization in chronic low back pain showed that these factors correlate with psychosocial characteristics such as depression, anxiety, and somatization [18]. The development of chronic pain associated with traumatic life events can also be understood based on central pain sensitization [19, 20]. In a cross-sectional study of 202 patients with chronic pain, both traumatic events and PTSD symptoms were significantly associated with clinical indicators of central sensitization, such as pain severity, pain intensity, and polysomatic complaints measured by the CSI [21]. Patients with PTSD who did not report pain showed higher pain scores and significantly increased temporal summation after an intramuscular capsaicin stimulus compared with control subjects, indicating an increased vulnerability to pain sensitization [22]. In a cohort of 914 patients with chronic pain from a German university hospital outpatient clinic, positive correlations were found between observed intensity of trauma and pain area overlap, pain widespreadness, maximum pain, sleep disturbance, pain disability index, stress, anxiety, depression, and somatization [23]. The increased pain area and pain widespreadness, as well as the effects on clinical endpoints such as pain intensity, sleep disturbance, symptom burden disability, and stress, are consistent with the concept of central sensitization in patients with PTSD [23].

Central pain sensitization and the endocannabinoid system (ECS)

Preclinical studies have shown that proinflammatory activation of neurons and microglial cells in the posterior horn of the spinal cord occurs under conditions of sustained nociceptive input. Counterregulatory action upregulates the expression of cannabinoid receptors CBR1 and CBR2 and enhances the activity of EC enzymes. If the system fails to control the pronociceptive and inflammatory processes, the net result is a decrease in EC-tone, increase of glutamatergic transmission of sensory neurons and inflammatory activity of microglial cells, and reduced activity of the endogenous pain control system [24].

An immunohistochemical study of peritoneal tissue from 45 patients with endometriosis and chronic acyclical pain showed signs of peripheral sensitization, in which transient receptor potential vanilloid-1 (TRPV1) channels, among others, were increased in expression in sensory neurons compared to control samples [25]. Since the cloning of TRPV1, at least five additional TRP channels have been discovered in dorsal root ganglia, which are also found in primary somatosensory neurons [26]. These channels are considered sensory transducers that may be involved in the generation of pain sensations evoked by thermal, mechanical, or chemical stimuli. Six of these channels can be modulated by various endogenous, phytogenic, and synthetic cannabinoids [26]. These six channels, TRPV1-TRPV4, TRPA1, and TRP melastatin-8 (TRPM8), are also referred to as ionotropic cannabinoid receptors [26]. For example, the EC anandamide (AEA) shows characteristics of a TRPV1 agonist [27], at least at high concentrations [28]. N-arachidonyl dopamine and AEA were identified as the first endogenous antagonists of TRPM8 [29]. Delta-9-tetrahydrocannabinol (THC) acts most strongly on TRPV2, moderately modulates TRPV3, TRPV4, TRPA1, and TRPM8, but does not appear to interact with TRPV1 [30]. Cannabidiol (CBD) appears to act more through indirect enhancement of EC tone and direct anti-inflammatory effects [30]. CBD has a low affinity for CBR1- and CBR2 but is most effective at TRPV1 and TRPM8 channels [30].

Exposure to different contexts influences pain perception and therapeutic outcome by activating specific neurobiological mechanisms, which have been studied in detail using placebo and nocebo effects as models [31, 32]. A positive and rewarding context can bring about pain relief. An important neurobiological mechanism for this is the activation of the endogenous pain control system, which is primarily based on the endorphin and EC systems. [31, 32]. There are individual differences in the weighting of the respective systems [32], which may also be the result of pharmacological conditioning. If opioids were primarily used for pain relief in the past, the endorphin system might predominate; if cyclooxygenase inhibitors (e. g., ibuprofen) or acetaminophen were primarily used, the ECS is predominant [32]. Both cyclooxygenase inhibitors and paracetamol can increase the tone in the ECS via manipulation of the elimination system of EC (fatty acid amide hydrolase [FAAH] and fatty acid binding protein [FABP]) [33].

In addition, the ECS is also involved in memory extinction (long-term depression, LTD) [34], e. g., by modulating GABAergic transmission in the basolateral amygdala [35] or by suppressing the activity of supraspinal nociceptive networks in the presence of enhanced CB1 activity in the periaqueductal gray [36].

The ECS is also associated with the endorphin system. For example, CBR1-knockout mice showed an attenuated effect of opioid-dependent stress-induced analgesia [37]. Synergistic effects between cannabinoid and opioid analgesia have been described [38]. Animal studies have been able to show that the combined intake of cannabinoids and opioids was able to abolish the tolerance effects to opioids [39], and there is a significant opioid-sparing effect under cannabinoid intake [40]. In a cross-sectional study of individuals using medical cannabis, opioids, benzodiazepines, migraine medications, and sleeping pills, in particular, were found to be reduced [41].

Chronic pain, chronic stress, and the endocannabinoid system

Pain is a complex phenomenon for which mere sensory perceptions and the emotional experiences are significant [12]. Pain and stress are closely linked on several physiological and psychological levels, and this is especially true for chronic pain [10, 12]. Both pain and stress are influenced by psychosocial factors, including, for example, beliefs, life goals, and fears [11]. The brain regions and networks responsible for chronic pain processing and stress regulation show considerable overlap. Most notably, these include areas in the amygdala, hippocampus, and medial prefrontal cortex [11]. Chron-

ic stress increases the perception of pain, which has been discussed in the introduction. Acute stress in chronic pain leads to an increase in pain. This process is also known as stress-induced hyperalgesia (SIH) [42]. Recently, Löffler et al. (2023) demonstrated that in patients with chronic musculoskeletal pain, even a cognitive stressor is sufficient to induce SIH [43]. The brain areas involved in pain and stress processing are densely packed with cannabinoid receptors [44]. Thus, the ECS appears critically involved in cognitive and affective pain processing. This is supported by clinical as well as experimental data, showing that cannabis-based medicines (CBMs) do not so much alter pain intensity but rather the affective component of pain [45, 46].

The ECS represents a buffer system of the central stress response [9]. In a yin-yang relationship, a reduction in the concentration of AEA in the hippocampal and amygdala regions triggered by stimulation of the FAAH activates the hypothalamic-pituitary-adrenocortical axis and thus anxiety, storage of aversive memories and other fight-or-flight events. An increase in 2-arachidonoylglycerol (2-AG) concentration, on the other hand, can terminate this process. If this system collapses under a chronic stress condition, the allostatic load can no longer be coped with and psychiatric comorbidities (depression, anxiety disorder, post-traumatic stress disorder) may manifest [9, 47, 48]. There is a broad overlap between these disorders and chronic pain [23]. Accordingly, experimental and clinical studies show that especially patients with high central stress levels benefit from cannabinoid therapy. Functional magnetic resonance imaging studies suggest that the limbic system, rather than the sensory system, is addressed when 15 mg of THC is administered to volunteers in the capsaicin model, consistent with the observation that participants perceived the pain stimulus as less unpleasant, but pain intensity remained unchanged [49]. In a meta-analysis conducted on experimentally induced pain, this finding was confirmed: while a significant reduction in the pain affect was observed, there was no clear effect on pain intensity [45]. One mechanistic study showed that the more pronounced the dysfunctional cortico-mesolimbic connectome, the greater the pain relief after sublingual administration of the average dose of 15.4 ± 2.2 mg THC in patients with chronic lumbar ischialgia [50]. In patients with chronic pain due to activated osteoarthritis, there were positive correlations in the change of ECS markers and psychosocial symptom expression, such as anxiety and depression [51]. In patients with knee osteoarthritis who were about to undergo knee replacement surgery, postoperative pain, and opioid consumption were significantly increased in those who showed high 2-AG levels in CSF and synovial fluid as an expression of a dysfunctional ECS [52]. A dysfunctional ECS has also been demonstrated in patients with PTSD [53]. In comparison to control groups, patients with PTSD showed decreased serum levels of AEA and a compensatory increase in the concentration of CBR1 in the CNS in positron emission tomography examinations [53].

Clinical evidence for cannabis-based medicines in chronic pain

Over the years, around 60 randomized controlled trials (RCTs) on the efficacy and safety of CBM have been published. To better assess the results, roughly the same number of systematic reviews and meta-analyses (SRMAs) were published from 2010 onwards [54]. This unfavorable ratio, combined with very different statements ranging from clear evidence of efficacy to the complete opposite, has not changed to this day [55]. The main problem with these SRMAs is that the RCTs studied are notably heterogeneous in all respects, especially with regard to the specific CBM used, the galenics, the pain situation, and the outcome parameters [54]. This is also reflected in the reported Number Needed to Treat for Benefit' figures, which show a high degree of dispersion, ranging from 2 to 24 [56]. With this in the background, many SRMAs conclude that the evidence is weak or insufficient, and therefore such meta-analyses do not provide sufficient information about what the best interventions are in terms of patient care [57]. In addition, the strong impression of subjectivity that permeates supposedly objective quantitative methods often remains [57, 58]. For this reason, our research group deliberately avoided a meta-analysis in an early systematic review to avoid misleading results based on the data from these very heterogeneous clinical trials [59]. However, post-hoc analysis of the results of the clinical trials reviewed revealed that apparently, those patients, in particular, benefited from therapy with a CBM who had inadequate stress regulation [59]. Most SRMAs incorporated data from RCTs in which nabiximols (THC and CBD in a 1:1 ratio) and dronabinol (THC) were predominantly used [60]. When studies using inhaled CBM were included, much more pronounced treatment effects were observed, at least in the short term [61]. Previous positive cannabis experiences of patients, which may affect conditioning in pain relief, and pharmacokinetic factors could be the reasons for this. Another factor limiting the validity of these studies is the issue of blinding. When cannabis flowers are inhaled, blinding the study participants is more challenging than with oral administration. In addition, when cannabis flowers are used, the entire constituents (phytocannabinoids, terpenes, flavonoids) are most likely to influence the effect profile, a process known as the "entourage effect" [62].

In an SRMA published in the British Medical Journal in 2021, Wang et al. [63] showed that the use of oral CBM for chronic pain is associated with about a 20 % chance of reducing pain by ≥ 30 % and can also improve physical function and sleep quality [63]. These effects were observed regardless of the type of pain (neuropathic pain vs non-neuropathic pain, tumor pain vs non-tumor pain) [63]. The authors concluded that a trial of non-inhaled CBM can be attempted, particularly in cases of failure of standard therapy [64]. In a concomitant systematic review of mixed-methods studies on claims of patients using CBM, oral preparations with a balanced ratio of THC to CBD or with high CBD content were found to be preferred by patients [65, 66]. In particular, women, inexperienced users, or those who used cannabis only for medicinal purposes tended to choose products with a low THC and high CBD content [66]. However, only 2.6 % of the total population of 1321 participants with chronic pain in this specific online survey in the US reported that they had been advised by a physician, indicating a large discrepancy between medical practice and cannabis product choice among respondents [66].

An SRMA by Bialas et al. [67], which included data from approximately 2500 patients, extends the knowledge of cannabis therapy gained from RCTs by examining long-term observational studies of CBM (predominantly used by inhalation). These showed highly

significant improvements in pain intensity, function, sleep quality, depression, anxiety, and overall quality of life. In addition, approximately 16 % of patients were able to discontinue their opioid medication while receiving CBM therapy [67]. In contrast to nociplastic pain, there is no convincing evidence of the efficacy of CBM in inflammatory pain at the clinical level to date [68]. On the other hand, there seems to be some potential for the anti-inflammatory properties of cannabis constituents (especially CBD, other phytocannabinoids, and terpenes) to be used clinically in the future for certain conditions such as osteoarthritis or collagenosis [69].

Safety of cannabis-based medicines in chronic pain

Medications are judged not only by their efficacy but also by their risk of side effects. An international group of pain therapists with and without experience in the use of CBM, psychiatrists, neurologists, and scientists with expertise in the pharmacology of cannabinoids, as well as representatives of a patient group (United Patient Alliance), have shown by employing a decision analysis that CBM has a greater significance in terms of improving quality of life compared to a reduction in pain intensity alone [70]. This is especially true when compared to duloxetine, gabapentinoids, and amitriptyline. With additional consideration of the side effect profile, all three CBM (THC/CBD 1:1 combination, THC, CBD) showed an advantage over the above-mentioned antidepressants and gabapentinoids [70].

In a recent meta-analysis that included an appreciable number of long-term studies, Zeraatkar et al. [71] reported a prevalence of adverse effects of about 26 %. These are mostly mild and self-limiting side effects such as dizziness, cognitive impairment, vomiting, drowsiness, impaired attention, diarrhea, and nausea. Severe side effects such as syncope or hypotension, adverse events leading to discontinuation of therapy, accidents and injuries, and dependence and withdrawal symptoms are rare and occur overall in < 1 in 20 people treated [71]. With caveats to the overall limited evidence, other pharmacologic treatments for chronic pain, such as gabapentinoids, antidepressants, and opioids, has been suggested to be potentially associated with more (and more serious) adverse events [71].

Cannabis hyperemesis syndrome (CHS), which overlaps with cyclic vomiting syndrome in adults and whose occurrence appears to depend on the composition and quantity of cannabis consumed, was first described in the 2000s [72]. The prevalence of CHS in recreational cannabis use was calculated at 0.01 % – 0.05 % in the Rome Foundation Global Study [73]. Data on the prevalence of CHS in medically prescribed CBM are not available. Accordingly, the package insert for Sativex Oromucosal Spray does not mention CHS as an undesirable side effect of this CBM [74].

In a cross-sectional study in the database of the US Veterans Health Administration, which investigated the influence of the introduction of medical cannabis laws on the prevalence of cannabis use disorder (CUD), the prevalence of CUD increased by 0.135 % in patients with chronic pain and by 0.037 % without chronic pain [75]. Neither the International Classification of Diseases (ICD) of the World Health Organization nor the Diagnostic and Statistical Manual of the American Psychiatric Association has developed the definition of CUD specifically for the medical application of CBM in a clinical setting [76]. To date, no specific measurement tool exists to assess dependence or CUD when using CBM as a therapy [76]. In general, 10 % of all people who have ever used cannabis meet the criteria for lifelong cannabis dependence [77]. Nearly 50 % to 60 % of the variance in CUD is associated with an addictive genetic effect [77]. Severe depression compared to no depression may increase the risk of developing dependence on medical marijuana in chronic pain patients, as shown in a regression analysis of 324 chronic pain patients treated with medical marijuana [78].

Because cannabinoids are likely to have an opioid-sparing effect, the use of CBM may reduce those risks posed by opioids (e. g., occurrence or exacerbation of sleep apnea syndrome) [79, 80]. However, only preclinical and observational studies demonstrate the potential opioid-sparing effects of cannabinoids in the context of pain management, as opposed to higher-quality RCTs that did not provide evidence of opioid-sparing effects [81]. On the other hand, the uncontrolled recreational use of cannabis is considered a risk for opioid abuse (“gateway hypothesis”), for which Wilson et al. [82] presented an SRMA of six studies from the USA, Australia, and New Zealand, in which they calculated an odds ratio (OR) of approx. 2.8 and 2.5 for the use of opioids and the development of an opioid use disorder (OUD) with cannabis use. However, they cautioned against the low quality of evidence with a moderate risk of bias in their analysis [82]. Furthermore, only 6 % of young adults start using cannabis before alcohol and tobacco, as shown by the results of the Population Assessment of Tobacco and Health study, which included data from 8062 young adults [83]. A prospective Dutch study showed that in light cannabis users, cannabis intoxication does not affect implicit and explicit tobacco or cocaine motivations [84]. In general, the transfer of data from uncontrolled recreational cannabis use to the use of CBM in the context of medical treatment is not readily transferable.

In children and adolescents who have an individual or familial predisposition to schizophrenia and other psychoses, cannabis products containing THC may increase the risk of psychosis [85]. Therefore, CBM should not be used in this group, if possible, or with extreme caution. In general, the indication should be strict in individuals aged < 21 years. This caution relates in particular to preclinical data suggesting neurodevelopmental impairment from early and heavy cannabis use [86]. In humans, further in-depth studies are needed to determine whether an earlier age of onset and a more intensive pattern of use play a causal role in neurodevelopmental impairment and increase the risk of persistent, if not permanent, adverse effects on mental health and cognition later in life [86]. Likewise, the indication should be restrained in pregnant women, nursing mothers, and persons with severe cardiovascular diseases.

In principle, smoking cannabis flowers can also lead to bronchial damage. The risk of serious complications such as chronic obstructive pulmonary disease or bronchial carcinoma seems to be lower than with smoking tobacco [87]. In general, a vaporizer should be used when inhaling CBM. Vaporizing cannabis has been shown to reduce the risk of respiratory disease compared to smoking, as it produces fewer or no unwanted toxic pyrolytic compounds or by-products (e. g., carcinogenic polynuclear aromatic hydrocarbons) and reduces exposure to carbon monoxide [88]. The epidemic of lung injuries associated with the use of e-cigarettes or vaping

products in various US states was primarily associated with the use of cannabis-containing cigarettes [89]. However, the prevalence of cannabis vaping at the state level was not positively associated with the prevalence of lung injury. This indicates that the occurrence of these lung injuries may not simply be due to the prevalence of cannabis vaping at the state level but rather the use of contaminated or illegally acquired vapor products such as vitamin E acetate, which are more likely in states with restrictive cannabis laws [88, 89]. Differentiated sublingual formulations are currently under development to avoid risks to the respiratory tract [90].

Practical Considerations

For CBM, the best balance between efficacy and risk of adverse events is usually achieved in the low to moderate dose range [91, 92]. For pharmacokinetic considerations, oral preparations are often preferred as they have a longer-lasting effect compared to inhaled cannabis [93], which can be beneficial for persistent chronic pain. To improve oral bioavailability, ingestion should occur after meals. The presence of high-fat food has been shown to increase the time to peak plasma concentration and the area under the curve of THC, implying increased mean absorption of THC compared to fasting pharmacokinetic data, which could be due to the slowed transit time through the gastrointestinal tract when fat is present [94]. However, since head-to-head studies are scarce, there is no clear external evidence to date that cannabis flowers and oral CBM differ in terms of efficacy, tolerability, and drug safety [95]. Ingestion via the lungs (with a vaporizer) or sublingually might have the advantage that the highly psychoactive metabolite 11-OH-THC is formed to a lesser extent [93, 96]. The much faster onset of action could have an advantage in the treatment of symptom attacks [97].

Dosage should be based on the principle: start low, go slow, stay low. The initial daily dose of cannabis flowers is 25–75 mg. For this purpose, patients should use a precision scale. Dronabinol (THC) administration can be started with 0.8 mg (1 drop) and oromucosal cannabis extract with 2.7 mg (1 spray). Nabilone is only available as a 1 mg capsule, which is equivalent to the effect of approximately 7–8 mg of THC. For oral forms of use, THC daily doses of a maximum of 30 to 40 mg (with CBD addition) should usually not be exceeded [92, 98]. There is much greater dose variation in the daily dose of cannabis flowers due to the variable form of ingestion and the different constituents; mean doses are usually less than 1 g per day, and in exceptional cases under the supervision of an experienced medical cannabis clinician, 3 g per day should generally not be exceeded. There is evidence from cohort studies and observation of everyday clinical practice that the use of multiple constituents of the cannabis plant may have advantages over single substances in terms of efficacy and tolerability. This could be explained within the concept of polypharmacy in terms of, for example, synergistic interactions and bioenhancement [99]. This approach fits with the general observation that in pharmacological pain treatment, the combination of different agents is the rule rather than the exception. In addition, many substances used for pain relief often act through various mechanisms. One example is amitriptyline, which is used as a multi-mechanistic agent for all types of chronic pain [100].

Challenges and cautions

Chronic pain is highly individual and dependent on genetic, epigenetic, and biographical factors in terms of gene-environment interactions [101]. In this context, large interindividual differences in the expression of the ECS are also found [102]. Avoidance behaviors, catastrophizing, perseveration principles, or perfectionism are harmful coping strategies that can increase pain. The inability to learn and use mindfulness-based practices or relaxation techniques for oneself can be considered a barrier to pain control. All of these factors contribute to the fact that the response to CBM can be completely different for each individual.

After decades of cannabis outlawing and the associated lack of information and actual treatment experience with CBM, expectations of CBM effects are very high, especially with inadequate effects under standard chronic pain treatment. Expectations significantly trigger the neurobiological mechanisms that produce placebo effects. This may lead to an overestimation of the intrinsic effect of CBM and an underestimation of the risks of cannabis use.

Another source of confusion is that the extent of the dysfunctional central networks associated with more intense pain perception in patients with chronic pain treated with CBM in clinical trials is generally unknown. Accordingly, findings such as that CBM is most commonly used for osteoarthritis pain [103] may lead to unreliable conclusions, as it is not an anti-inflammatory mechanism of CBM but an effect on the central stress and pain processing networks responsible for symptom relief.

Finally, there are different weightings about what exactly patients benefit from when taking CBM. In clinical trials in pain patients, pain intensity is usually chosen as the primary outcome parameter. Pain patients, on the other hand, are often more likely to benefit from CBM in terms of their overall quality of life [104, 105], which can be understood as an indication of the pleiotropic effects of CBM.

Conclusions

Chronic pain must be viewed holistically and can be considered as a disease in its own right in cases of high emotional distress and functional impairment. The pathophysiological correlate for this is a dysfunction of the cortico-mesolimbic system. Clinical and experimental evidence suggests that CBM can exert positively influence these maladaptive brain functions and thus contribute to a reduction in symptom burden. Accordingly, there is moderate evidence that CBM can contribute to significant improvements in pain, physical function, and sleep quality in some patients with chronic pain while being well tolerated with only a low risk of severe side effects, such as the development of dependence.

Conflict of Interest

MK has received speaker honoraria from Federal Association of Pharmaceutical Cannabinoid Companies (BPC), Demecan, EVER Pharma, Grunenthal, Hormosan, IUVO Therapeutics, Lilly, Medical Service of the Health Insurance Funds, Novartis, Stadapharm, Teva, and Tilray. He has received consultancy fees from Almirall. He has received expert opinion fees from several local and social courts. He is member of the ad-hoc commission cannabis in medicine of the German Pain Society and the Science Network Cannabinoids in Medicine (WCM).

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