REVIEW ARTICLE

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Role of Cannabinoids in the Treatment of Pain and (Painful) Spasticity

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Abstract

Both the discovery of the endocannabinoid system (ECS) and its role in the control of pain and habituation to stress, as well as the significant analgesic and antihyperalgesic effects in animal studies, suggest the usefulness of cannabinoids in pain conditions. However, in human experimental or clinical trials, no convincing reduction of acute pain, which may be caused by a pronociceptive, ECS-triggered mechanism on the level of the spinal cord, has been demonstrated. In contrast, in chronic pain and (painful) spasticity, an increasing number of randomized, double-blind, placebo-controlled studies have shown the efficacy of cannabinoids, which is combined with a narrow therapeutic index. Patients with unsatisfactory response to other methods of pain therapy and who were characterized by failed stress adaptation particularly benefited from treatment with cannabinoids. None of the attempts to overcome the disadvantage of the narrow therapeutic index, either by changing the route of application or by formulating balanced cannabinoid preparations, have resulted in a major breakthrough. Therefore, different methods of administration and other types of cannabinoids, such as endocannabinoid modulators, should be tested in future trials.

1. Cannabinoids

1.1 Constituents of the Endocannabinoid System

In the early 1990s, cannabinoid receptors of the subtypes cannabinoid 1 (CB1) and CB2 were discovered and described. While CB1 receptors were found to be expressed in both the CNS and the peripheral nervous system,[1] CB2 receptors were primarily identified on keratinocytes, immune cells, cells of the peripheral nervous system and microglia, as well as on spinal cord dorsal horn neurons.[2,3] Together with the subsequently characterized endogenous ligands (the endocannabinoids, primarily anandamide[4] and 2-arachidonylglycerol [2-AG])[5] and the ligand-metabolizing enzymes, these receptors form the endocannabinoid system (ECS). Key enzymes of the ECS include the anandamide-metabolizing fatty acid amide hydrolase (FAAH) and the monoacylglycerol lipase (MGL), which cleaves 2-AG to produce arachidonic acid.[6-8] The regulation of the overall activity of the ECS, governing processes associated with perception, movement, memory and concentration, as well as anti-inflammatory, cytoprotective and neuroprotective effects, is primarily attributed to FAAH activity.[8] Endocannabinoids are retrograde messengers with agonistic activity on presynaptic CB1 receptors, slowing down neurotransmission. Since CB1 receptors are found on both excitatory and inhibitory neurons, they simultaneously suppress GABAergic and glutamatergic transmission, causing so-called 'depolarization-induced suppression of inhibition' (DSI) and 'depolarization-induced suppression of excitation' (DSE).[9] The net effect of this process is determined by the ratio of DSI to DSE and represents the 'fine tuning' of neurotransmission in the CNS and the peripheral nervous system; in addition, the release or uptake of other neurotransmitters, such as dopamine and serotonin, is also influenced. In this context, further cannabinoid receptors are postulated. Recent evidence suggests that the orphan G-protein-coupled receptor GPR55, which is involved in processes of inflammatory and mechanical hyperalgesia in mouse models of adjuvant-induced inflammation and partial nerve ligation, might be a third cannabinoid receptor.[10] Furthermore, there is evidence that receptors not primarily associated with cannabinoids, such as serotonin 5-HT_3, 5-HT_{1A} and transient potential receptor vanilloid 1 (TRPV1) receptors, may also be stimulated by exogenous or endogenous cannabinoids.[11,12] In addition, there is strong evidence to suggest that some cannabinoids can act on peroxisome proliferator-activated receptors through either direct or indirect pathways, indicating possible effects on different metabolic pathways and inflammation.[13,14]

1.2 The Endocannabinoid System and Pain

A 10-fold higher concentration of anandamide was detected in the brains of FAAH-knockout (KO) mice compared with wild-type controls. These mice were characterized by a significantly lower sensitivity to pain induced by an inflammatory reaction in the paw. However, animals pre-treated with a CB1 receptor antagonist exhibited the same behaviour as wild-type mice.[15] The observation that the inhibition of cyclooxygenase (COX)-2 increased anandamide concentration when a COX2 inhibitor or a nonselective COX inhibitor was used highlights the close relationship between the ECS and the arachidonic acid cycle.[16,17] Animal studies have demonstrated that the anti-inflammatory effect of indomethacin and flurbiprofen is dependent on functioning CB1 receptors, although there is no direct CB1 receptor interaction.[18]

Electrophysiological and neurochemical animal studies have provided convincing evidence that endocannabinoids and exogenous cannabinoids suppress nociceptive transmission, especially peripherally and at the level of the posterior horn of the spinal cord.[7] The observation that no analgesic effect was elicited by the release of endocannabinoids or the administration of cannabinoids in mice with normal CB1 receptor density in the CNS but significantly reduced CB1 receptor density in the peripheral nervous system (SNS-CB1-KO mice) has highlighted that cannabinoid-induced analgesia is mediated to a considerable extent by the intrinsic activity at CB1 receptors

located in the peripheral nervous system.[19] CB2 receptors are expressed on peripheral nerve fibres as well as in microglia and astrocytes where they are upregulated after nerve injury or during inflammation.[3,20,21]

Detailed studies at the level of the periaqueductal grey, the rostral ventromedial medulla and the posterior horn of the spinal cord have shown that the coordinated release of 2-AG and anandamide triggers the activation of descending pain-inhibiting pathways and leads to stress-induced analgesia (SIA; reduced pain sensation after an electrical stimulus), which is not identical to opioid-dependent SIA.[22] While this effect was mainly increased by the inhibition of MGL, the blockade of CB1 receptors did not result in a complete suppression of SIA, indicating the presence of additional mechanisms not involving cannabinoid receptors.[20] In fact, many data suggest that the ECS serves to facilitate habituation to stress by restraining hypothalamic-pituitary-adrenal (HPA) axis response and maintaining homeostasis of the body.[23]

These findings resulted in the idea of modulating the endocannabinoid degrading enzymes, thus producing elevated endocannabinoids levels. In several preclinical models, promising results of this approach could be demonstrated, mainly by using FAAH or MGL inhibitors.[24-26] Interestingly, neither inhibitor elicited general cannabinoid effects, which may be explained by different endocannabinoid tissue levels as a result of altered physiological conditions in sensitized and inflamed tissue areas[8,24,25] or by analgesic mechanisms limited to peripheral sites.[26]

1.3 Exogenous Cannabinoids and Routes of Administration

Some 66 different cannabinoids, chemically defined as C_{21} terpenophenols, can be isolated from hemp (*Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*). In the 1960s, the isolation and synthesis of Δ^9-tetrahydrocannabinol (Δ^9-THC; dronabinol) and cannabidiol (CBD) as the major psychoactive and nonpsychoactive cannabinoids, respectively, was achieved.[27] Subsequently, various other cannabinoid receptor agonists and antagonists have been described and developed, which are described in depth in another review.[28]

Smoking cannabis causes a rapid elevation in plasma Δ^9-THC concentration with a peak Δ^9-THC concentration being reached within 9 minutes. The concentration quickly decreases as a result of rapid tissue distribution.[29] The total amount of drug absorbed depends on the inhalation technique but combustion, side stream smoke and incomplete absorption restrict the total amount of Δ^9-THC absorbed to 10–30%.[30] However, absorption and bioavailability of oral preparations are much more variable mainly due to first-pass effects. Accordingly, the overall delivery of Δ^9-THC to the bloodstream may not exceed 10%.[30] In addition, 11-hydroxy-Δ^9-THC, one of the major metabolites of Δ^9-THC formed in the liver, contributes at least as much as Δ^9-THC to the overall drug effect.[30] Oromucosal preparations of cannabinoids such as the Δ^9-THC-CBD buccal spray (Sativex®) have sought to avoid these constraints. In fact, when administered buccally, blood concentrations of Δ^9-THC and other cannabinoids are lower than with inhalation of smoked cannabis. The resultant concentrations in the blood are lower than those obtained by inhaling the same dose because absorption is slower, redistribution into fatty tissues is rapid and, additionally, some of the Δ^9-THC (which has been swallowed) undergoes hepatic first-pass metabolism to 11-hydroxy-Δ^9-THC. Following a single buccal administration of Δ^9-THC, maximum plasma concentrations of both CBD and Δ^9-THC typically occur within 2–4 hours. However, the pharmacokinetics of this route of administration also shows a high degree of inter-subject variability.[31]

2. Methods of Literature Review

This article reviews the most current and relevant data available on the antinociceptive properties of cannabinoids for their potential or already established use in clinical settings. The search was made electronically in MEDLINE/PubMed, EMBASE and the Cochrane Controlled Trials Register of all literature published from

1975 to November 2010, using the following search terms: 'cannabis', 'cannabinoids', 'marijuana', 'THC', 'tetrahydrocannabinol', 'pain', 'chronic pain', 'spasticity', 'animal models' and 'clinical trials'. All reviewers independently reviewed the titles and abstracts for relevance according to the search terms. Based on the aim of this review, the basic science information was intended as an introduction to the clinical findings. Therefore, only key results were reported and, where appropriate, the reader is referred to other relevant review articles. For the clinical trials, we included non-randomized, observational, and randomized, double-blind, placebo-controlled trials (RCTs) in clinical and experimental settings. The validity of the RCTs was evaluated independently by all reviewers using the Jadad scale of the Oxford quality scoring system.[32]

3. Preclinical Evidence of Cannabinoid-Mediated Analgesia

3.1 Antinociceptive Effects in Animal Models of Pain

There are numerous published studies investigating the antinociceptive properties of cannabinoids in animal models of pain. The efficacy of cannabinoid receptor agonists in pain management has been widely demonstrated. Ernest Dixon was the first investigator describing the antinociceptive effects of cannabinoids in an animal model. In 1899 he showed that dogs that had inhaled cannabis smoke failed to react to pin pricks.[33] Different animal models have been used to investigate the antinociceptive effects of cannabinoids. However, systemic administration of cannabinoids can produce profound motor effects in animals (immobility or catalepsy), which can limit interpretation of studies involving a motor response.[34] Thus, some studies also used electrophysiological and neurochemical methods for the investigation of specific neuronal pathways.

The following sections briefly review cannabinoid effects in animal models of acute and chronic pain.

3.2 Cannabinoid Modulation of Acute Pain in Animal Models of Pain

There are many more studies investigating the effects of cannabinoids in animal models of chronic pain than in models of acute pain. However, cannabinoid receptor agonists have long been known to exhibit antinociceptive activity in animal models of acute pain. Thermal and mechanical stimuli or incision to the hindpaw of rats are used to simulate acute or postoperative pain.

The most widely studied cannabinoids are Δ^9-THC and its analogues. They show antinociceptive effects in a wide range of animal models when administered orally, systemically or directly into the brain or spinal cord.[35-38] Other cannabinoid receptor agonists that show activity in rats or mice in acute pain models include WIN 552122, CP55940 and the endogenous cannabinoid anandamide. The majority of cannabinoids so far investigated in animal models of acute pain act via CB1 receptors. This putative mechanism was concluded from the observation that in the presence of highly selective CB1 receptor antagonists, such as rimonabant (SR141716) or AM251, or in CB1 KO mice, antinociceptive effects were completely abolished.

Antinociceptive effects in models of acute pain have also been shown for the selective CB2 receptor agonists such as AM1241, HU308, GW405833 and JWH133. However, findings are less consistent compared with the CB1 receptor-mediated analgesia. Discrepancies in the pain-reducing effects of the different compounds may arise from differences in experimental methodology, the distribution of the drugs within the body, different doses of receptor-selective antagonists, different receptor selectivity of the used compounds, activity on receptors other than CB1 or CB2, and confounding factors inherent to genetically altered mouse models.[39]

In summary, there is good evidence that the production of antinociception by cannabinoid receptor agonists in acute pain models is not a consequence of motor impairment or hypothermia. Beneficial effects on experimental acute pain are induced by several CB1 and CB2 receptor agonists.

3.3 Cannabinoid Modulation of Chronic Pain in Animal Models of Pain

Animal models for the investigation of cannabinoid effects in chronic pain states are well established in preclinical research. This section gives a short overview of frequently used models for the induction of inflammatory and neuropathic pain in animals and commonly used cannabinoids.

Several CB1 and CB2 receptor agonists suppress inflammatory pain and paw oedema induced by carrageenan injection. It was shown that locally administered WIN 552122 reduced carrageenan-induced allodynia and mechanical hyperalgesia, and that the CB2 receptor antagonist SR144528 or the CB1 receptor antagonist rimonabant could block this action. This suggests that both CB1 and CB2 receptors were involved in this effect. CBD, the major non-psychoactive component of marijuana, exhibited time- and dose-dependent antinociceptive effects in acute inflammation induced by intraplantar injection of carrageenan in the rat. A single dose of CBD reduced oedema in a dose-dependent manner and subsequent daily doses caused further time- and dose-related reductions.[40] Studies using the same animal model revealed anti-inflammatory effects of the synthetic cannabinoid nabilone. Nabilone, given 1 hour before carrageenan, reduced the development of oedema and the associated hyperalgesia in a dose-related manner.[41]

The cannabinoid receptor agonist AM1241 reduced mechanical and thermal hypersensitivity following intraplantar injection of carrageenan.[42-44] These effects seem to be mediated by CB2 receptors because they were blocked by the selective CB2 receptor antagonists AM630 and SR144528.[42] Spinal Fos protein expression reflects increased neuronal activity;[45] AM1241 also reduced the expression of spinal Fos protein in carrageenan-induced inflammatory pain.[42] Electrophysiological studies brought evidence that the neuronal sensitization in nociceptive spinal neurons, which develops as a consequence of carrageenan inflammation, is suppressed by AM1241.[46] The suppression of neuronal sensitization is also blocked by the CB2 receptor antagonist SR144528 and not by the CB1 receptor antagonist rimonabant.[46] However, in a rodent model of inflammatory pain, topical application of the endocannabinoid anandamide suppressed both the development and maintenance of carrageenan-evoked thermal hyperalgesia, which was blocked by the CB1 receptor antagonist rimonabant.[47] In contrast to these results, anandamide was reported to reduce mechanically evoked responses of dorsal horn neurons of rats with carrageenan-induced hindpaw inflammation via CB2 receptors.[48]

Local administration of JWH 133 showed inhibitory effects on mechanically evoked responses of dorsal horn neurones in rats with carrageenan-induced inflammation.[3] This effect of JWH133 was blocked by the CB2 receptor antagonist SR144528 and not by the CB1 receptor antagonist rimonabant.[49] HU210 attenuated established inflammatory hypersensitivity and swelling in the carrageenan model of inflammatory pain,[50] and systemic administration of JWH133 and GW405833 abolished the decreased weight bearing of the inflamed paw in the same model.[50]

In the capsaicin-induced inflammation model, peripheral administration of the endocannabinoid anandamide attenuated hyperalgesia via interaction with the CB1 receptor, as indicated by the reversal of the effect by the CB1 receptor antagonist rimonabant. Additionally, peripheral administration of anandamide inhibited oedema formation. Peripherally administered anandamide also interacted with CB1 receptors to inhibit capsaicin-evoked plasma extravasation into the hindpaw.[47] The effects of AM1241 in capsaicin-induced inflammation seem to be mediated by CB2 receptors because they were blocked by the CB2 receptor antagonists AM630 and SR144528. Both systemic and local administration of AM1241 reduced capsaicin-evoked thermal and mechanical hyperalgesia and hypersensitivity.[43,51]

In another study investigating the effects of the cannabinoid receptor agonist HU210 in a rat model of inflammatory pain, intrathecal administration of HU210 reduced the mechanical allodynia and thermal hyperalgesia induced by intraplantar injection of complete Freund's adjuvant (CFA). The effects of HU210 were reduced by the cannabinoid CB1 receptor antagonist AM251.[52]

Peripheral oedema and hypersensitivity to thermal or mechanical stimuli evoked by local application of CFA in rodents is also influenced by the selective CB2 receptor agonist GW405833. Systemic administration of GW405833 reduced allodynia and mechanical hypersensitivity in rats and mice.[53,54] It is likely that these effects were mediated by CB2 receptors because hypersensitivity was reduced in CB2+/+ mice but not in CB2–/– mice.[53,54] Systemic administration of the cannabinoid ajulemic acid (AJA) and the nonselective cannabinoid receptor agonist HU210 reduced mechanical allodynia in the CFA-induced model of inflammatory pain.[55]

CB2 receptors are present in the immune system and their expression level is higher under conditions of inflammation. Thus, cannabinoids that preferentially target CB2 receptors exhibited analgesic effects in different models of inflammatory pain. For an overview of cannabinoids selectively addressing CB2 receptors, the reader is referred to the comprehensive review by Guindon and Hohmann.[56]

Several models are used to induce neuropathic pain in animals. The most common models are chronic constriction injury, partial sciatic nerve ligation (Seltzer model) and spinal nerve ligation. Many different cannabinoids, including natural cannabinoid ligands, endocannabinoids, as well as CB1 and CB2 receptor-selective agonists, have been evaluated for suppression of neuropathic pain. The modulation of neuropathic pain by cannabinoids is reviewed in detail by Rahn and Hohmann[28] and by Guindon and Hohmann.[56]

Chronic constriction injury induces thermal and mechanical allodynia as well as hyperalgesia in the paw of the test animal. The main components of cannabis, the psychoactive Δ^9-THC and the nonpsychotropic CBD, have been tested in this model. Administration of CBD reversed thermal or mechanical hyperalgesia.[57] However, there are hints that these effects might be mediated via TRPV1.[57] The TRPV1 is a nonselective cation channel that is chemically activated by capsaicin and endogenous cannabinoid receptor activators such as anandamide.[58] The synthetic cannabinoids CP55940 and WIN 552122, both agonists at CB1 and CB2 receptors, showed influence on neuronal sensitization and hypersensitivity in neuropathic pain states via spinal wide dynamic range neurons.[59] The CB2-receptor selective agonist GW405833 reduced mechanical allodynia in the chronic constriction injury model.[60] Modulators of the ECS such as AM404 attenuated the symptoms of neuropathic pain by different molecular mechanisms and reduced mechanical hyperalgesia and allodynia.[61,62]

Partial sciatic nerve ligation induces mechanical allodynia and mechanical as well as thermal hyperalgesia (for details see Seltzer et al.[63]). The endocannabinoids anandamide and 2-AG showed anti-allodynic and anti-hyperalgesic effects. Anandamide mediated its effects via CB1 receptors, whereas the effects of 2-AG were mediated via CB1 and CB2 receptors.[64-66] The synthetic cannabinoids AJA, HU210, WIN 552122 and CP55940 attenuated mechanical hyperalgesia and allodynia by CB1 and CB2 receptor-dependent mechanisms.[55,67-69] Intraplantar injection of WIN 552122 has been shown to reduce mechanical hyperalgesia in rats with partial sciatic nerve ligation. The effect of WIN 552122 was blocked by systemic, but not spinal, administration of the CB1 receptor antagonist rimonabant, indicating a peripheral site of action for WIN 552122. The selective CB2-receptor agonists GW405833 and JWH133 suppressed neuropathic pain in the Seltzer Model and reduced mechanical allodynia and hyperalgesia.[53,54,70]

Spinal nerve ligation induces mechanical allodynia and thermal hyperalgesia. CP55940 and WIN 552122 attenuated mechanical hyperalgesia in the test animals[71,72] and additionally WIN 552122 influenced thermal hyperalgesia.[71] The selective CB2 receptor agonists AM1241 and GW405833 suppressed the development of mechanical allodynia in the spinal nerve ligation model of neuropathic pain.[73,74]

Most studies investigating the effects of cannabinoids on experimentally induced neuropathic pain focused on Δ^9-THC and the natural and synthetic components of Δ^9-THC. The synthetic cannabinoid WIN 552122 has been shown to be effective in the chronic constriction injury, the spinal nerve ligation and the partial sciatic nerve ligation models. The effects of other substances

have been investigated in only one model of neuropathic pain.

Again, some of these studies have shown that selective activation of CB2 receptors produces antinociceptive effects in persistent pain states. This observation is important since CB2 receptor-selective agonists lack centrally mediated adverse effects, which may increase their therapeutic potential.[56]

4. Cannabinoids in Human Studies

In total, 156 articles were found that reported on the effects of cannabinoids against pain and spasticity in human trials. Among them were 58 clinical or experimental trials, 13 on acute pain and 45 on chronic pain. These included 11 RCTs on acute pain, 10 on chronic nociceptive pain, 18 on pain of neuropathic origin, including 6 RCTs that addressed spasticity, and 8 RCTs on cannabinoids primarily for (painful) spasticity; the list is added to by 11 observational studies.

The neuropathic pain studies were divided into patients with multiple sclerosis (MS) and studies on other causes of neuropathic pain mainly of peripheral origin. This subdivision was considered meaningful since about half of the studies in MS patients focused primarily on spasticity and almost all of the rest on both neuropathic pain and spasticity. Furthermore, the neuropathic pain in the MS patient is of central origin, while the vast majority of the studies classified in the neuropathic pain group focused on neuropathic pain of peripheral origin.

4.1 Cannabinoids in Acute Pain

The few studies investigating the use of cannabinoids in experimentally induced or acute postoperative pain – comprising 238 volunteers/patients in 11 RCTs with a mean quality score of 3.9 and 85 in non-randomized trials – showed no or, at best, weak analgesic effects irrespective of the cannabinoid and method of administration used (table I). Far from it, in three experimental studies[79,85,86] and in four RCTs on postoperative pain,[75,78,81,84] capsules of Δ^9-THC 20 mg and Δ^9-THC/CBD 20 mg/10 mg, marijuana cigarettes containing 8% Δ^9-THC, intravenous Δ^9-THC 0.044 mg/kg, oral Δ^9-THC 5 mg as a single dose or three times daily, and oral nabilone 2 mg exerted hyperalgesic effects. On the other hand, marijuana cigarettes containing 4% Δ^9-THC[85] and the Δ^9-THC-morphine combination (Δ^9-THC 5 mg orally plus morphine 0.02 mg/kg intravenously)[75,78,79,81,83-86] showed additive analgesia to electrical stimulation or heat stimulation. In addition, Jain et al.[76] identified significant benefits of the synthetic cannabinoid levonantradol administered in four doses ranging from 1.5 to 3 mg. In an open-label, dose-escalation study on moderate to severe postoperative pain, all patients receiving Δ^9-THC 5 mg (combined with small amounts of CBD) requested rescue analgesia in contrast to 25% of patients treated with 15 mg, who also showed significantly less pain at rest.[82] However, the study was terminated prematurely because of a serious vasovagal adverse reaction in one patient receiving a 15 mg dose of the study medicine. Furthermore, following a dose 1 mg of nabilone, temporal summation of pain intensities during tonic heat pulse stimulation was significantly reduced in women but not in men.[87] HU210 administered topically to capsaicin-induced painful skin showed analgesic and antihyperalgesic effects in a small trial.[80]

In general, adverse effects were common in those trials but usually mild to moderate, although marked vasovagal and psychotropic effects were noted,[79,86] some to the extent of acute psychotic symptoms[86] and adverse event-related withdrawals.[77,82] An earlier study highlighted the increase in pain detection thresholds without simultaneous effects on pain thresholds.[75] Furthermore, this study showed the connection between psychotropic and hyperalgesic effects of Δ^9-THC in six of ten subjects who reported an increased pain level in the presence of elevated anxiety levels.[75]

In summary, except for two studies,[80,82] all trials on cannabinoids for acute pain in humans were RCTs displaying an average quality score of 3.9 based on the Jadad criteria.[74] At best, a small analgesic and antihyperalgesic effect was found in a medium dose range, which was mildly increased by the addition of opioids in the experimental

Table I. Trials of cannabinoids (CBs) in experimentally induced and clinical acute pain

Study (year)	Study design	Quality score	Patients, indication	CB/dosage	Route of administration	Efficacy	Adverse effects and events
Raft et al.[75] (1977)	RCT	3 (randomization and blinding scheme not described)	10 healthy volunteers, before four subsequent dental extractions	0.022 mg/kg vs 0.044 mg/kg Δ^9-THC vs diazepam 0.157 mg/kg vs placebo, single dose each	IV	Significant increase in pain detection thresholds but no evidence of effect on pain tolerance thresholds for diazepam and both Δ^9-THC doses; experience after high-dose Δ^9-THC premedication was described as most painful, after diazepam as least painful; for low-dose Δ^9-THC three pts described positive, six negative experiences (more anxiety)	Dose-related tachycardia, severe anxiety in one case
Jain et al.[76] (1981)	RCT	3 (randomization and blinding scheme not described)	56 pts, moderate to severe acute postoperative, fracture or trauma pain	Levonantradol 1.5 vs 2 vs 2.5 vs 3 mg vs placebo, single dose each	IM	Significant effect compared with placebo for all dosages, no statistically significant difference between the active treatment groups	Generally mild, mainly drowsiness, also dizziness, dry mouth, 'weird dreams', mild hallucinations, nervousness, apprehension and confusion, minor changes in resting heart rate
Greenwald[77] (2000)	RCT, co	3 (randomization not related to cannabinoid inhalation)	13 volunteers, only regular marijuana users	Cannabis cigarettes containing 3.55% Δ^9-THC vs 0%, nine cumulative puffs each	inh	Dose-dependent increase in antinociception of relatively weak amount (19% MPE), no effect of naltrexone on analgesia	Eight withdrawals due to intolerable adverse effects
Buggy et al.[78] (2003)	RCT	5	40 women, elective abdominal hysterectomy	Δ^9-THC 5 mg vs placebo, single dose each	PO	No significant differences in summed pain intensity between Δ^9-THC and placebo at 6 h, or in time to rescue analgesia	Increased awareness of surroundings
Naef et al.[79] (2003)	RCT, co	4 (randomization procedure not described)	12 cannabis-naive volunteers	Δ^9-THC 20 mg vs morphine 30 mg vs both combined, single dose each	PO	Additive analgesia for Δ^9-THC-morphine to electrical stimulation; no analgesic effect for THC or Δ^9-THC-morphine to pressure or heat stimulation; hyperalgesia of Δ^9-THC to cold stimulation	Psychotropic and somatic adverse effects common, but usually mild
Rukwied et al.[80] (2003)	pc	NA	20 healthy volunteers, capsaicin model	HU210 (selective CB1 and CB2 receptor agonist) vs placebo	top	Significant reduction of pain sensation, heat pain thresholds and allodynia. No effects on pin-prick hyperalgesia. No effect on heat pain thresholds in non-sensitized skin. Effects no longer than 30 min	None reported

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Table I. Contd

Study (year)	Study design	Quality score	Patients, indication	CB/dosage	Route of administration	Efficacy	Adverse effects and events
Seeling et al.[81] (2005)	RCT	3 (randomization and blinding procedures not described)	105 pts, elective abdominal prostatectomy	Δ^9-THC 5 mg vs placebo tid beginning at the evening before the operation day and last dose at the morning of the second postoperative day each	PO	No significant differences in piritramide (PCIA) consumption or analgesia	More vasovagal reactions and less PONV, in one pt early termination of drug intake due to visual symptoms
Holdcroft et al.[82] (2006)	ol, dose escalation	NA	65 pts; moderate to severe postoperative pain	Δ^9-THC/CBD (1 : 0.3 and 1 : 0.5) containing Δ^9-THC 5, 10 or 15 mg single dose; n = 11 vs 30 vs 24 after PCIA period for 6 h	PO	Rescue analgesia under 5 mg in 100%, under 10 mg in 50%, under 15 mg in 25%; NNT 2.0 for incidence of rescue analgesia under 10 mg and 1.3 under 15 mg	AEs in 1 of 9 under 5 mg, 6 of 30 under 10 mg and 12 of 24 under 15 mg; 1 vasovagal episode
Roberts et al.[83] (2006)	RCT, co	4 (randomization procedure not described)	13 volunteers	Δ^9-THC 5 mg + morphine 0.02 mg/kg vs THC 5 mg + placebo vs placebo + morphine 0.02 mg/kg vs PO placebo + IV placebo, single dose each	PO (Δ^9-THC, placebo), IV (morphine, placebo)	No sensory response with either of the study drugs to heat stimulation; no affective response with either of Δ^9-THC or morphine, but significant affective response of the Δ^9-THC-morphine combination to heat stimulation	Variety of mild euphoric or dysphoric effects
Beaulieu et al.[84] (2006)	RCT	5	41 pts, gynaecological and orthopaedic operations	Nabilone 1 mg (n = 11) vs nabilone 2 mg (n = 9) vs ketoprofen 50 mg (n = 11) vs placebo (n = 10), 1 h before induction of anaesthaesia and tid for 24 h each	PO	Pain at rest and movement significantly higher in the nabilone 2 mg group, no difference in cumulative 24-h morphine consumption	Most common dry mouth, nausea, vomiting, respiratory depression, sedation and pruritus. No serious AE; calculated sample size (n = 19 per group) not obtained
Wallace et al.[85] (2007)	RCT, co	5	15 healthy volunteers	Cannabis cigarettes containing 0% vs 2% vs 4% vs 8% Δ^9-THC single dose each (standardized cued-smoking procedure)	inh	In comparison with placebo significantly decreased pain at 4%, but significantly more pain at 8% in capsaicin pain model	Mild to moderate adverse effects primarily at the highest dose, increase in heart rate, no significant differences in performance on neuropsychological tests
Kraft et al.[86] (2008)	RCT, co	5	18 healthy female volunteers	Δ^9-THC/CBD (2 : 1) containing Δ^9-THC 20 mg vs active placebo (diazepam 5 mg), single dose each	PO	No significant analgesic or antihyperalgesic effects, reduced electrical pain thresholds (sunburn and capsaicin model)	Significantly more drowsiness, sedation, dry mouth, and vertigo in Δ^9-THC/CBD group
Redmond et al.[87] (2008)	RCT, co	3 (randomization and blinding scheme not described)	20 healthy volunteers	Nabilone 0.5 vs 1 mg vs placebo, single dose each	PO	No reduction of tonic heat pain; no strengthening of descending inhibitory responses; in women significant reduction of temporal summation (1 mg)	Mild dry mouth, red eyes, sedation, dizziness and euphoria; three withdrawals due to organizational reasons

Δ^9-THC = Δ^9-tetrahydrocannabinol; **AE** = adverse event; **CBD** = cannabidiol; **co** = crossover; **IM** = intramuscular; **inh** = inhalation; **IV** = intravenous; **MPE** = maximum percentage effect; **NA** = not applicable; **NNT** = number needed to treat; **ol** = open-label; **pc** = placebo-controlled; **PCIA** = patient-controlled intravenous analgesia; **PO** = oral; **PONV** = postoperative nausea and vomiting; **pt(s)** = patient(s); **RCT** = randomized, double-blind, placebo-controlled trial; **tid** = three times daily; **top** = topical.

studies,[79,83] but not in the clinical studies.[81,84] However, even though pain detection thresholds were increased similarly to the common experience of marijuana users,[88] many of the participants seemed to experience the noxious stimuli more intensely. In general, no analgesic or even hyperalgesic effects were observed with significantly higher doses, which were also associated with more adverse effects. This dose-related biphasic pattern was also demonstrated for the endocannabinoid anandamide.[89] In addition, in a very recent publication it could be demonstrated that spinal endocannabinoids and CB1 receptors act as mediators of heterosynaptic pain sensitization on inhibitory dorsal horn interneurons.[90] The administration of a dose of rimonabant 20 mg, a CB1 receptor antagonist/inverse agonist, decreased the sizes of hyperalgesic and allodynic skin areas induced by electrical stimulation, while no effect on acute pain ratings was found.[90] However, analgesic effects of cannabinoids may emerge and may be much more pronounced in clinical settings, in which the state of the ECS is altered and sensitized to cannabinoids.[91]

4.2 Cannabinoids for Chronic Nociceptive Pain

Numerous clinical studies on the efficacy of cannabinoids for chronic pain have been published, and their results have been compiled in several review articles.[92-99]

Summarizing the data of Noyes et al.[100,101] and two other RCTs[102,103] investigating benzopyranoperidine (nabitan), a synthetic analogue of Δ^9-THC, with a total of 128 cancer pain patients, an early review article reported that in cancer pain the analgesic effect of Δ^9-THC 10 and 20 mg is approximately equivalent to codeine 60 and 120 mg, respectively; higher doses were frequently associated with significant adverse effects, such as drowsiness and cognitive impairment.[92] In fact, adverse effects of benzopyranoperidine have been observed so frequently that no further clinical studies were conducted because it was felt that the substance was not clinically useful,[102,103] and this may be the main reason why it was never developed for clinical use. From the results of these research studies it was concluded that Δ^9-THC and other cannabinoids have a low analgesic potency and a narrow therapeutic range in chronic nociceptive pain.[92] A standardized cannabis-based medicinal extract (CBM) containing doses of Δ^9-THC 5 or 10 mg taken orally was used in a patient with familial Mediterranean fever, resulting in a reduced demand for morphine compared with placebo.[104]

More recently, seven RCTs with a quality score of 3.7 and including a total of 398 patients reported the effects of Δ^9-THC, CBM, a Δ^9-THC-CBD combination or nabilone on mixed chronic noncancer pain, pain due to rheumatoid arthritis, fibromyalgia syndrome (FMS) or cancer pain not completely relieved by strong opioids (table II). In comparison with placebo, significant reduction of pain,[105,107-109,111,113] anxiety,[111] and a significant improvement of sleep either in comparison with amitriptyline[112] or placebo[105,108] was observed. Some studies also described significant functional improvement.[108,111] Twenty-eight of the original 30 noncancer pain patients in the Narang et al.[109] study who were taking stable doses of opioids and who experienced significant pain reduction after a single oral dose of either 10 or 20 mg Δ^9-THC also showed a significant decrease in average pain scores compared with baseline in the open-label, 4-week extension study, in which Δ^9-THC was administered in doses of up to 20 mg three times daily. However, the maximum study duration was 4 weeks and adverse effects were common, although they were generally mild in nature. Another open-label study showed beneficial effects in 5 of 13 patients with chronic noncancer pain after oral Δ^9-THC administration (maximum daily dose of 15 mg), even over a period of up to 36 months, but 6 patients experienced adverse events, 2 of whom were for that reason unable to continue the medication.[110] Similarly, another open-label study on nine patients with FMS receiving up to 15 mg Δ^9-THC per day showed a significant reduction of spontaneous pain and electrically induced pain, but no effect on the axon reflex flare; however, five patients withdrew during the study due to adverse events.[106] Interestingly, only one study indirectly showed superiority of CBM over

Table II. Clinical trials of cannabinoids for chronic nociceptive pain

Study (year)	Study design	Quality score	Patients, indication	Cannabinoid/dosage	Route of administration	Efficacy	Adverse effects and events
Noyes et al.[101] (1975)	RCT	3 (randomization and blinding procedures not reported)	10, cancer pain	Δ^9-THC 5 vs 10 vs 15 vs 20 mg vs placebo, one single dose respectively, 6-h observation period	PO	Significantly more pain relief with higher Δ^9-THC doses (15 and 20 mg) than with placebo and lower doses (5 and 10 mg); in one pt with sharply localized pain no pain relief at all	Considerable drowsiness at 15 mg, heavily sedated at 20 mg
Noyes et al.[100] (1975)	RCT, compared with placebo and codeine	3 (randomization and blinding procedures not reported)	36, cancer pain	Δ^9-THC 10 vs 20 mg vs codeine 60 vs 120 mg vs placebo, one single dose respectively, 7-h observation period	PO	Significantly more pain relief caused by Δ^9-THC 20 mg and codeine 120 mg than with placebo	Dizziness, sedation, dry mouth, blurred vision, mental clouding; extreme anxiety in five pts (in one pt caused by 10 mg, in four pts caused by 20 mg Δ^9-THC), two AE-related withdrawals
Holdcroft et al.[104] (1997)	RCT, co	3 (randomization and blinding procedures not reported)	1, chronic abdominal pain due to Mediterranean fever	Δ^9-THC 50 mg/d in cannabis extract in five daily doses vs placebo for 3 wk each	PO	Significantly less morphine consumption	Not reported
Notcutt et al. (2004)[105]	RCT, co after excessive individualized run-in of 2 wk	3 (randomization and blinding procedure not described)	34, mixed pain	CBM (Δ^9-THC/CBD 1 : 1; one pump action = 2.5 mg/2.5 mg) vs Δ^9-THC alone vs CBD alone vs placebo for 1 wk each	OM	PP set of 24 pts (without use of rescue medication [CBM]): compared with placebo significant pain reduction for CBM and Δ^9-THC (37.5% >50% pain reduction); significant improvement of sleep for CBM, Δ^9-THC, and CBD	Dry mouth, dizziness and euphoria/dysphoria common in the beginning (run-in phase) but decreasing during study time, one vasovagal episode during dosing
Schley et al.[106] 2006	ol	NA	9, fibromyalgia syndrome	Δ^9-THC 2.5–15 mg/d	PO	Significant pain reduction, electrically induced pain significantly reduced (with Δ^9-THC 10–15 mg/d), no effect on the axon reflex flare	Five dropouts due to AE
Pinsger et al.[107] (2006)	RCT, co	3 (inappropriate randomization)	30, chronic pain in musculoskeletal system	Nabilone 0.25–1 mg/d vs placebo for 4 wk each	PO	Significant reduction of pain in one case (back pain at interview), no significant effects on headache and quality of life scores	Significantly more dizziness, one nabilone-related fall

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Table II. Contd

Study (year)	Study design	Quality score	Patients, indication	Cannabinoid/dosage	Route of administration	Efficacy	Adverse effects and events
Blake et al.[108] (2006)	RCT	4 (blinding procedure not described)	56, rheumatoid arthritis	CBM (Δ^9-THC/CBD 1 : 1; one pump action = 2.5 mg/2.5 mg) with on average 15 mg/d vs placebo for 4 wk each	OM	Significant pain reduction, improvement of sleep and DAS-28	Dizziness in 26%, dry mouth 13% and light-headedness 10% vs 4%, 0% and 4%, respectively, in the placebo group. General mild intensity
Narang et al.[109] (2008)	RCT (phase I), co	4 (randomization procedure not reported)	30, chronic noncancer pain, stable doses of opioids for >6 mo, pain at least NRS 4	Δ^9-THC 10 vs 20 mg vs placebo, single dose each	PO	Significantly more TOTPAR, SPID, ESPID, and global satisfaction, and less pain bothersomeness by both doses	Most frequent drowsiness, sleepiness, dizziness and dry mouth
Narang et al.[109] (2008)	ol (phase II), multi-dose (extension from the phase I RCT)	NA	28, chronic noncancer pain, stable doses of opioids for >6 mo, pain at least NRS 4	Δ^9-THC from 5 mg/d up to 20 mg tid for 4 wk	PO	Significant decrease in average pain scores from baseline	Most frequent dry mouth, tiredness, sleepiness and drowsiness (especially at the 20 mg dose), two AEs relating to heightened anxiety
Haroutiunian et al.[110] (2008)	ol, add-on	NA	13, chronic noncancer pain unresponsive to conventional pharmacotherapy	Δ^9-THC 5 mg bid or tid	PO	In five pts adequate response, in eight pts no or inadequate response	AE reported in six pts, two AE-related withdrawals
Skrabek et al.[111] (2008)	RCT	4 (randomization procedure not described)	40, fibromyalgia syndrome	Nabilone 0.5–1.0 mg bid vs placebo for 4 wk each	PO	Significant reduction of pain and anxiety, significant functional improvement	Significantly more generally mild adverse effects (mainly drowsiness, dry mouth, vertigo, ataxia)
Ware et al.[112] (2010)	RCT, active-controlled (amitriptyline), co	5	31, fibromyalgia syndrome	Nabilone 0.5–1 mg vs amitriptyline 10–20 mg for 2 wk each	PO	Nabilone superior to amitriptyline regarding improvement of sleep. No effects on pain, mood or quality of life between treatments	Mild to moderate dizziness, nausea, dry mouth, more common with nabilone
Johnson et al.[113] (2010)	RCT	3 (blinding and randomization procedure not described)	177, cancer pain not fully relieved by strong opioids	CBM (Δ^9-THC/CBD 1 : 1; one pump action = 2.5 mg/2.5 mg) vs Δ^9-THC vs placebo with 48 actuations in any 24-h period for 2 wk each	OM	Significantly more pain relief only by CBM (not by Δ^9-THC) than with placebo	Significantly more nausea and vomiting with CBM than with placebo, other adverse effects mild to moderate, 17 AE-related withdrawals in active groups vs 3 in placebo group

Δ^9-THC = Δ^9-tetrahydrocannabinol; **AE** = adverse event; **bid** = twice daily; **CBD** = cannabidiol; **CBM** = cannabis-based medicine; **co** = crossover; **DAS-28** = disease activity score, 28 for judging disease activity and follow-up controls in rheumatoid arthritis; **ESPID** = evoked pain differences; **NA** = not applicable; **NRS** = numeric rating scale; **ol** = open-label; **OM** = oromucosal; **PO** = oral; **PP** = per protocol; **pt(s)** = patient(s); **RCT** = randomized, double-blind, placebo-controlled trial; **SPID** = sum of pain intensity differences; **tid** = three times daily; **TOTPAR** = total pain relief, sum of integral relief scores ranging from 0 = no relief of pain to 10 = complete relief of pain.

Δ^9-THC. In this three-arm study, treatment with CBM alone resulted in significantly more responders (30% pain reduction) than with placebo, while no difference in the numbers of responders between Δ^9-THC and placebo was observed.[113] In this study, about 19% of the patients in the active groups terminated the study early due to adverse events.

In summary, recent RCTs on mixed pain, rheumatoid arthritis, FMS or cancer pain with a quality score of 3.7 based on the Jadad criteria have confirmed the results of the earlier studies, indicating a significant reduction of pain and/or significant improvement of quality of life and/or improvement in sleep, no matter what cannabinoid and route of administration was used. However, only 398 patients in total were included in these studies, pain characteristics were heterogeneous (e.g. according to the modern concept of FMS it might not be classified as nociceptive pain), the prevalence of adverse effects was high, and study durations did not exceed 4 weeks. Altogether, these results suggest that cannabinoids exert some pain-reducing effects in patients with chronic nociceptive pain, but are associated with a small therapeutic window and substantial interpatient variability in analgesic response. Further suggestions were that cannabinoids would be more useful in pain syndromes characterized by a more altered ECS and/or difficult-to-treat pain conditions, such as neuropathic pain, e.g. in MS.

4.3 Cannabinoids for Chronic Neuropathic Pain and Spasticity in Multiple Sclerosis

From the 18 clinical trials on chronic neuropathic pain and spasticity in MS, 15 were RCTs.[114-128] They included 1722 patients in total (however, 80% of the 502 patients in the second Zajicek study[123] had already participated in the first Zajicek et al.[118] study) and reached a mean quality score of 3.8 (table III). The study durations ranged between the one-off administration of a single dose and 12 months. In nine RCTs, a clearly significant effect of cannabinoids on either spasticity[114,116,119,120,123,125] or pain[116,118,119,121,123,124] or both was found, while mixed results were found in one study regarding pain reduction,[127] in three studies regarding different measurements of spasticity[115,118,122,126,128] and in two studies regarding the findings in the intention-to-treat and per protocol populations.[122,128] Two studies showed a negative outcome regarding reduction of spasticity[117,127] and one study regarding reduction of pain.[120]

In two trials, the patients were treated with oral nabilone 1 mg per day[125] or every other day,[116] for a period of 4 weeks. Both reported significant reduction of spasticity or pain with moderate adverse effects. However, since those reports are based on just 14 patients in total, their significance is limited. Three trials[114,115,121] treated patients with Δ^9-THC dosages between 2.5 and 20 mg/day. Two of these[114,115] found a reduction of spasticity compared with placebo, and in one of these trials this effect was associated with doses of at least 7.5 mg Δ^9-THC per day; however, adverse effects were also common at these doses.[115] In addition, only the patients, not the examiners, were able to detect the reduction of spasticity in this study. The third noted significant pain reduction and elevated pressure pain thresholds compared with placebo, an improvement in bodily pain and mental health, but also notably more adverse events than with placebo.[121]

The remaining ten RCTs used either an oral cannabis extract with a defined mixture of Δ^9-THC and CBD with a ratio of mostly 2 : 1[117,118,122,123] or a CBM of Δ^9-THC/CBD with a ratio of 1 : 1 administered as an oromucosal spray,[119,120,124,126-128] supplemented by two open-label extension studies.[129,130] While three of those RCTs showed significant effects of the active interventions compared with placebo,[119,123,124] in five RCTs either the primary outcome parameters (Ashworth score and 'primary symptom score', respectively) did not change significantly,[118,120] or the primary outcome parameter (Ashworth score) was reordered into a secondary outcome parameter and was not changed significantly,[126] or no significant effects were observed in the intention-to-treat set,[122,128] or only pain thresholds increased, while perception of pain and spasticity remained unchanged.[127] In one trial, the results were completely negative (Ashworth score not significantly changed, global

Table III. Clinical trials of cannabinoids (CBs) for chronic neuropathic pain and spasticity in multiple sclerosis (MS)

Study (year)	Study design	Quality score	Patients, indication	CB/dosage	Route of administration	Efficacy	Adverse effects and events
Petro and Ellenberger[114] (1981)	RCT, co	2 (no randomization, blinding procedure not described)	9, MS	Δ^9-THC 5 mg vs 10 mg vs placebo, one single dose	PO	Significant reduction of spasticity in four pts (both dosages)	Minimal
Ungerleider et al.[115] (1987)	RCT, co	3 (blinding and randomization procedures not described)	13, MS	Δ^9-THC 2.5–10 mg/d bid vs placebo, three paired trials for 5 d each	PO	Significant reduction of spasticity at 7.5 mg rated by the pts, not by the physicians	Tolerable adverse effects at 7.5 mg, two pts withdrew due to limb weakness and two pts due to anxiety regarding possible adverse effects at higher doses
Martyn et al.[116] (1995)	RCT, co	4 (randomization procedure not described)	1, MS	Nabilone 1 mg every other day vs placebo for 2 × 4-wk periods	PO	Significant reduction of spasticity, pain and frequency of nocturia	Moderate sedation
Killestein et al.[117] (2002)	RCT, co	2 (randomization and blinding procedures and dropouts not reported)	16, MS	Δ^9-THC 2.5 mg bid for first 2 wk and 5 mg bid for second 2 wk vs Δ^9-THC 2.5 and 5 mg in cannabis extract containing 20–30% CBD vs placebo for 4 wk each	PO	No reduction of spasticity (Ashworth score); pt's global impression worsened	Mild (e.g. dizziness, dry mouth, increased spasticity), one acute psychosis lasting for 5 h under cannabis extract
Zajicek et al.[118] (2003)	RCT	5	630, MS	Δ^9-THC vs Δ^9-THC/CBD (2.5 mg/1.25 mg), maximum possible dose Δ^9-THC 25 mg/d vs placebo for 14 wk each	PO	In both active treatments no significant changes in overall spasticity score (Ashworth score), but significant treatment effects on pt-reported spasticity and pain	Mild (most commonly dizziness and dry mouth)
Wade et al.[119] (2003)	RCT, co	5	24, MS, spinal cord injury, brachial plexus damage, limb amputation due to neurofibromatosis	CBM (Δ^9-THC/CBD 1 : 1; one pump action [metered dose] = 2.5 mg/2.5 mg) vs Δ^9-THC alone vs CBD alone vs placebo for 2 wk each; maximum possible dose 120 mg/24 h	OM	Compared with placebo, significant reduction of pain with Δ^9-THC or CBD alone; significant reduction of spasm and spasticity with Δ^9-THC alone; significant reduction of spasm with CBM	Four withdrawals due to AEs

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Table III. Contd

Study (year)	Study design	Quality score	Patients, indication	CB/dosage	Route of administration	Efficacy	Adverse effects and events
Wade et al.[120] (2004)	RCT	5	160, MS	CBM (Δ^9-THC/CBD 1 : 1; one pump action = 2.5 mg/ 2.5 mg) vs placebo for 6 wk each; maximum possible dose 120 mg/24 h	OM	Primary Symptom Score with no statistically significant difference between the groups. Significant reduction of spasticity and improvement of quality of sleep, no difference between groups according to pain	Dizziness in 26 pts, local discomfort at the application site in 21 pts and fatigue in 12 pts; three withdrawals due to AEs
Svendsen et al.[121] (2004)	RCT, co	5	24, MS	Δ^9-THC up to 5 mg bid vs placebo for 18–21 d each	PO	Significant pain reduction (20.5% different to placebo; NNT 3.45); significant elevation of the PPT; in the SF-36 physical functioning, bodily pain and mental health significantly improved	Significantly more AEs (mainly dizziness, tiredness and myalgia), dose reduction in four pts due to AEs, no withdrawals
Vaney et al.[122] (2004)	RCT, co	5	57, MS	Δ^9-THC/CBD (2.5 mg/0.9 mg): 2.5–10 mg Δ^9-THC tid vs placebo for 2 wk each	PO	Significant improvement of spasm frequency and mobility in the PP set, no significant effects in the ITT set	Mild (most commonly dizziness, euphoria, difficulty concentrating). Three withdrawals due to persistent adverse effects
Zajicek et al.[123] (2005)	RCT	5	502, MS (approximately 80% of the study population of Zajjicek et al.[118])	Δ^9-THC vs Δ^9-THC/CBD (2.5 mg/1.25 mg), maximum possible dose 25 mg Δ^9-THC/d, vs placebo for 12 mo each	PO	Compared with placebo, significant improvement in Ashworth score and RMI, and significant reduction of pain, spasticity, spasm and improvement of sleep	No major safety concerns
Rog et al.[124] (2005)	RCT	5	66, MS, in the CBM group 50% with prior cannabis experience	CBM (Δ^9-THC/CBD 1 : 1; one pump action = 2.5 mg/ 2.5 mg) vs placebo for 5 wk each; maximum possible dose 129.6 mg/24 h; mean dose 25.9 mg	OM	In comparison with placebo, significant reduction of pain (NNT 3.7 for 50% pain reduction) and improvement of sleep, especially in pts with spasm	88.2% of the CBM group vs 68.8% of the placebo group developed at least one AE; 53% of the CBM group vs 16% of the placebo group developed dizziness; two withdrawals due to AEs; NNH 5.13 for at least one AE and 2.68 for dizziness

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Table III. Contd

Study (year)	Study design	Quality score	Patients, indication	CB/dosage	Route of administration	Efficacy	Adverse effects and events
Wade et al.[129] (2006)	ol (extension study of Wade et al.[120] 2004)	NA	137, MS	CBM (Δ^9-THC/CBD 1 : 1; one pump action = 2.5 mg/2.5 mg) for 434 d (mean); maximum possible dose 120 mg/24 h	OM	In 72 pts pain reduction maintained over 1 y	Sore mouth in 20.4%, altered attention in six, serious AEs in three (seizures in two, ankle injury after loss of balance in one); in 11 of 25 pts some withdrawal symptoms in the 2-wk interruption period
Wissel et al.[125] (2006)	RCT, co	3 (randomization and blinding scheme not described)	13, MS	Nabilone 1 mg/d vs placebo for 4 wk each	PO	Significant reduction of painful spasticity	Moderate dizziness (n = 2), weakness in the legs (n = 2)
Rog et al.[130] (2007)	ol (extension study of Rog et al.[124] 2005)	NA	63, MS	CBM (Δ^9-THC/CBD 1 : 1; one pump action = 2.5 mg/2.5 mg) for a mean duration of 463 d dose 129.6 mg/24 h	OM	NRS-pain score in the final wk 2.9	>1 AE in 92%, severe in 51%; most common dizziness, nausea, feeling intoxicated, oral discomfort (in 15% buccal mucosal patches), 25% AE-related withdrawals
Collin et al.[126] (2007)	RCT	4 (blinding procedure not described)	189, MS	CBM (Δ^9-THC/CBD 1 : 1; one pump action = 2.5 mg/2.5 mg) vs placebo, maximum of 48 doses per day, mean dose of 23.5 mg for 6 wk	OM	Significant reduction of spasticity (NRS), no group differences regarding Ashworth score and Motricity Index	More dizziness, impaired balance, disturbance in attention, blurred vision in CBM group. Six AE-related withdrawals on CBM vs 2 AE-related withdrawals on placebo
Conte et al.[127] (2009)	RCT, co	5	18, MS	CBM (Δ^9-THC/CBD 1 : 1; one pump action = 2.7 mg/2.5 mg) vs placebo for 3 wk each; maximum possible dose 129.6 mg/24 h, maximum daily dose of 33.75 mg	OM	Significant increase of neurophysiologically determined pain threshold, no change in pain perception and spasticity	Minor adverse effects, mainly drowsiness and dizziness

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Table III. Contd

Study (year)	Study design	Quality score	Patients, indication	CB/dosage	Route of administration	Efficacy	Adverse effects and events
Centonze et al.[131] (2009)	ol	NA	20, MS	CBM (Δ^9-THC/CBD 1 : 1; one pump action = 2.7 mg/ 2.5 mg), maximum of 40 doses per day, period of 6 wk	OM	No effects on pain (VAS) and spasticity (NRS, Ashworth score); no change in activity of FAAH, NAPE-PLD, expression of cannabinoid CB1 and CB2 receptors on peripheral lymphocytes	Sedation, dizziness, and nausea most frequently reported AEs, one AE-related withdrawal (hallucinations)
Collin et al.[128] 2010	RCT	5	337, MS	CBM (Δ^9-THC/CBD 1 : 1; one pump-action = 2.7 mg/ 2.5 mg) vs placebo for 15 wk	OM	Significant improvement of spasticity (NRS, responder) in PP set, no significant effects in ITT set	CBM well tolerated, adverse effects mild-to-moderate

Δ^9-THC = Δ^9-tetrahydrocannabinol; **AE** = adverse event; **bid** = twice daily; **CBD** = cannabidiol; **CBM** = cannabis-based medicine; **co** = crossover; **FAAH** = fatty acid amide hydrolase; **ITT** = intention to treat; **NA** = not applicable; **NAPE-PLD** = *N*-acyl-phosphatidylethanolamines; **NNH** = number needed to harm; **NNT** = number needed to treat; **NRS** = numeric rating scale; **ol** = open-label; **OM** = oromucosal, **PO** = oral; **PP** = per protocol; **PPT** = pressure pain threshold; **pt(s)** = patient(s); **RCT** = randomized, double-blind, placebo-controlled trial; **RMI** = Rivermead mobility index; **SF-36** = Short Form 36; **tid** = three times daily; **VAS** = visual analogue scale.

impression worsened).[117] However, the CAMS (Cannabinoids Against Multiple Sclerosis) study, which alone comprised 630 patients, showed a significant effect on patient-reported spasticity and pain and a significant improvement on the Ashworth score after a 12-month period with no additional safety concerns.[118,123] Interestingly, neither this nor any of the other studies comparing Δ^9-THC to cannabis extract or CBM found significant differences in efficacy between these different cannabinoid preparations. While Svendsen et al.[121] and Rog et al.[124] reported a number needed to treat (NNT) of 3.45 and 3.7, respectively, Rog et al.[124] showed a number needed to harm (NNH) for dizziness of 2.68, and for at least one adverse event an NNH of 5.13. However, in general, all studies rated the adverse effects within the narrow dose limit of up to approximately 34 mg Δ^9-THC per day as mild to moderate.

The two open-label extension studies were associated with withdrawal rates of up to 25%.[130] Furthermore, a mild and inconsistent withdrawal syndrome was observed after interruption of study medication,[129] although this was seen only in half of the studied patients. A sore mouth was observed in 20.4% of the 137 patients using the oromucosal CBM preparation,[129] an adverse effect that may be related to the high alcohol concentration in the CBM spray.[132] On the other hand, these trials confirmed the effectiveness of CBM over periods longer than 1 year. In contrast, in a third open-label study on 20 patients with MS no significant changes in the intensity of pain and spasticity and in the modulation of the ECS were observed during a 6-week treatment period with CBM.[131] However, a mean pain relief of 20–25% was reported.

In summary, recognizing subjective measurements in pain and spasticity, the vast majority of the RCTs demonstrate a significant treatment effect of the tested cannabinoid preparations versus placebo. The fact that 9 of the 13 RCTs showed significant treatment effects on subjective spasticity, but only 1[123] confirmed this result with objective assessments, raises questions about the sensitivity and validity of current objective outcome instruments in spasticity.

4.4 Cannabinoids for Chronic Neuropathic Pain and Spasticity of Differing Origins

Out of 11 RCTs (mean quality score 4.5) investigating the effects of cannabinoids on chronic neuropathic pain[133-144] that included 473 patients with differing diagnoses, all but three[138,142,143] showed significant reduction of pain, and some studies reported NNTs for 30% pain reduction of 2.14,[135] 3.6,[141] 5.29,[135] 7.7[136] and 9.0[136] (table IV). Three of the studies investigated a CBM (Δ^9-THC/CBD 1 : 1 oromucosally, 2.5 mg/2.5 mg for one pump action) for a period of 2, 5 and 12 weeks, respectively, against peripherally induced neuropathic pain.[136,137,142] In addition to an analgesic effect, the studies by Berman et al.[136] and Nurmikko et al.[137] also noted improvements in sleep, but only the study by Nurmikko et al. also showed a reduction of allodynia. However, again, superiority of CBM over Δ^9-THC could not be shown.[136] No pain reduction was observed in painful diabetic neuropathy;[142] however, in this study the dose was restricted to a maximum of 10 mg Δ^9-THC as a CBM per day. Δ^9-THC 5 mg up to four times per day was no more effective than diphenhydramine for relieving chronic neuropathic pain in persons with spinal cord injury;[143] however, in this crossover pilot RCT only five patients completed all phases, which is less than half of the anticipated sample size. Furthermore, the study design forced to wean off gabapentin in three patients who then felt more spasticity. Generally, there were noticeably more adverse effects in the treatment groups than with placebo but most patients tolerated these well.

Four studies evaluated cannabis cigarettes, two of them[139,141] for 5 days, for the treatment of HIV-associated chronic neuropathic pain, one[139] also noting some reduction of experimentally induced hyperalgesia. Wilsey et al.[140] studied 7% or 3.5% cannabis cigarettes for central or peripheral neuropathic pain, and found a similar analgesic response with both doses but no effect on experimentally evoked pain. Compared with 0% Δ^9-THC Ware et al.[144] found a single inhalation of 25 mg of 9.4% Δ^9-THC herbal cannabis three times daily for 5 days to be significantly superior in reducing the intensity of pain and improving sleep in 23 patients with chronic posttraumatic or postsurgical neuropathic pain. All studies with cannabis cigarettes reported more adverse effects, which were mostly mild or well tolerated, in the treatment groups. However, only patients who had previous experience with cannabis were included.

One study compared Δ^9-THC 5 mg with codeine 50 mg and placebo administered as a single daily dose in one patient over a period of 18 days each.[133] While both active treatments resulted in significant pain reduction compared with placebo, only Δ^9-THC significantly reduced spasticity as well.

One study tested nabilone versus dihydrocodeine (DHC) in a crossover design for 6 weeks each, showing significantly more pain reduction and fewer adverse effects for DHC than nabilone, but more DHC-related withdrawals.[138]

One study evaluated AJA for a period of 1 week.[134,135] While significant pain reduction was observed, a significant effect on mechanical hypersensitivity was closely missed. Similarly to the other trials, adverse effects were mild to moderate and no particular effects on psychotropic measurements were found, probably because of the pronounced peripheral action of this compound.

Overall, adverse effects were mostly mild (dizziness, concentration difficulties, sedation, tiredness, dry mouth, slight increase in heart rate), with few withdrawals, although one study had 18% withdrawals in the treatment group versus 3% in the placebo group.[137]

One retrospective multicentre study reported that a mean oral daily dose of 7.5 mg Δ^9-THC led to significant pain reduction with tolerable adverse effects.[147] In contrast, one prospective open-label study administering a mean daily dose of 17 mg Δ^9-THC in eight patients with chronic refractory peripheral or central neuropathic pain found a significant pain reduction only in one patient who was unable to continue the drug after 6 weeks because of adverse effects.[145] Another prospective open-label study focused mainly on spasticity in 25 para- or tetraplegics after spinal cord injury. In this study, oral daily doses of up to 60 mg Δ^9-THC were administered, resulting in a significant reduction of spasticity compared with

Table IV. Clinical trials of cannabinoids for chronic neuropathic pain and spasticity of differing origins

Study (year)	Study design	Quality score	Patients, indication	Cannabinoid/dosage	Route of administration	Efficacy	Adverse effects and events
Maurer et al.[133] (1990)	RCT, compared with placebo and codeine, co	3 (randomization and blinding procedures not reported)	1, chronic pain and spasticity due to spinal cord injury	Δ^9-THC 5 mg vs codeine 50 mg vs placebo, one daily dose for 18 d	PO	Significant pain reduction caused by Δ^9-THC 5 mg and codeine 50 mg compared with placebo, but only with Δ^9-THC significant reduction of spasticity	No altered consciousness
Karst et al.[134] (2003); Salim et al.[135] (2005)	RCT, co	5	21, neuropathic pain due to trauma	Ajulemic acid 20–40 mg bid vs placebo for 1 wk each	PO	Significant pain reduction, NNT for 30% pain reduction between 2.14 and 5.29, no effect on mechanical hypersensitivity	Mainly tiredness and dry mouth, one AE-related withdrawal, no effects on psychotropic measurements
Berman et al.[136] (2004)	RCT, co	4 (blinding procedure not described)	48, brachial plexus avulsion	CBM (Δ^9-THC/CBD 1 : 1; one pump action = 2.5 mg/2.5 mg) vs Δ^9-THC alone for 2 wk, respectively; maximum possible dose 129.6 mg/24 h; maximum dose of 30 mg/d	OM	Compared with placebo significant pain reduction and improvement of sleep with CBM or Δ^9-THC alone. NNT for 30% pain reduction 9.0 and 7.7 for CBM and Δ^9-THC, respectively	Dizziness most frequently experienced, one withdrawal due to AE with CBM
Attal et al.[145] (2004)	ol	NA	8, chronic refractory peripheral or central neuropathic pain	Δ^9-THC, maximum dose 25 mg/d, mean dosage 17 mg, for 6 wk	PO	Only one pt with significant decrease in the intensity of spontaneous pain	AE-related withdrawals in six pts
Hagenbach et al.[146] (2007)	ol (phase I + II) RCT (phase III)	NA	25, spinal cord injury, discontinuation of antispastic medication before inclusion	Δ^9-THC (mean daily dose 31 mg), Δ^9-THC-hemisuccinate (mean daily dose 43 mg), Δ^9-THC vs placebo for 6 wk each	PO, PR	Significant reduction of spasticity (modified Ashworth Scale) in phase I + II compared with placebo in phase III, no comparative results for phase III due to different baseline scores regarding spasticity. Pain relief in four pts, pain augmentation in five	Dry mouth, sleepiness, anxiety; pain augmentation in five pts with four of them withdrawing; reaction time significantly reduced

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Table IV. Contd

Study (year)	Study design	Quality score	Patients, indication	Cannabinoid/dosage	Route of administration	Efficacy	Adverse effects and events
Nurmikko et al.[137] (2007)	RCT	5	125, neuropathic pain of peripheral origin	CBM (Δ^9-THC/CBD 1 : 1; one pump action = 2.5 mg/2.5 mg) with on average 15 mg/d vs placebo for 5 wk each	OM	Significant reduction of pain and allodynia and improvement of sleep and functionality, NNT for 30% and 50% pain reduction 8.6 and 8.5, respectively	91% of the CBM group vs 77% of the placebo group developed at least one AE. 18% AE-related withdrawal in CBM group vs 3% in the placebo group
Frank et al.[138] (2008)	RCT, compared with DHC, co	5	96, neuropathic pain	Nabilone 250 μg to 2 mg vs DHC 30 mg to 240 mg/d for 6 wk each	PO	Significantly more pain reduction with DHC	Slightly fewer adverse effects with DHC; however, eight DHC-related withdrawals vs four nabilone-related withdrawals
Abrams et al.[139] (2007)	RCT	4 (blinding scheme not described)	50 (prior experience smoking cannabis), painful HIV-associated sensory neuropathy	Cannabis cigarettes (3.56% Δ^9-THC) tid vs placebo for 5 d	inh	Significant pain reduction, reduction of experimentally induced hyperalgesia but not of painfulness of noxious heat stimulation	Mild (anxiety, sedation, disorientation, confusion, dizziness), one severe dizziness, one severe transient anxiety
Wilsey et al.[140] (2008)	RCT, co	5	38 (previous cannabis exposure required), central and peripheral neuropathic pain	Cannabis cigarettes (3.5% Δ^9-THC) vs cannabis cigarettes (7% Δ^9-THC) vs placebo, standardized cued-smoking procedure with nine cumulative puffs for 6 h each	inh	Significant pain reduction (intensity and unpleasantness) in both active groups compared with placebo. No differences between the two cannabis doses, no effect on evoked pain	Minimal psychoactive effects, some acute cognitive effects (memory) particularly at higher doses
Ellis et al.[141] (2009)	RCT, co	5	34 HIV pts, distal sensory predominant neuropathy	Cannabis cigarettes containing 1–8% Δ^9-THC (target dose) vs placebo qid standardized cued-smoking procedure for 5 consecutive d each	inh	Significant pain reduction, NNT 3.6 for 30% pain relief	Concentration difficulties, sedation, reduced salivation, increase in heart rate, two AE-related withdrawals

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Table IV. Contd

Study (year)	Study design	Quality score	Patients, indication	Cannabinoid/dosage	Route of administration	Efficacy	Adverse effects and events
Weber et al.[147] (2009)	Retrospective mc telephone survey	NA	172 (–48 dropouts), chronic central neuropathic pain, fibromyalgia	Mean dose of Δ^9-THC 7.5 mg/d for 7 mo	PO	Significant pain reduction and improvement of psychometric parameters	34 withdrawals due to dizziness, tiredness, enhanced appetite or insufficient therapy effect (29 due to expenses)
Selvarajah et al.[142] (2010)	RCT	3 (randomization and blinding procedure not described)	30, painful diabetic peripheral neuropathy	CBM (Δ^9-THC/CBD 1 : 1; one pump action = 2.5 mg/2.5 mg) vs placebo up to qid for 12 wk	OM	No differences in different pain scores, neuropathic pain scale and functionality between groups; pain reduction in depressed pts in both groups more pronounced	Six AE-related withdrawals
Rintala et al.[143] (2010)	RCT, compared with diphenhydramine, co	5	7, chronic neuropathic pain due to spinal cord injury	Δ^9-THC, maximum dose 20 mg/d, for 28 d maintenance phase each after run-in and washout periods	PO	No group differences	One AE-related withdrawal; one pt denied to be switched to second medication due to good pain relief by the first medication (dronabinol); common adverse effects dry mouth, constipation, fatigue, and drowsiness for both medications
Ware et al.[144] (2010)	RCT, co	5	23, post-traumatic or postsurgical chronic neuropathic pain	25 mg dose of 9.4% Δ^9-THC herbal cannabis in a single inh from a pipe tid vs 6.0%, 2.5% and 0% for 5 consecutive d followed by 9 d washout period each	inh	Compared with 0% significant pain reduction and improvement of sleep	One AE-related withdrawal (increased pain), one exclusion since pt was screened positive for cannabis at baseline; common adverse effects headache, dry eyes, burning sensations in areas of neuropathic pain, dizziness, numbness, cough

Δ^9-THC = Δ^9-tetrahydrocannabinol; **AE** = adverse event; **bid** = twice daily; **CBD** = cannabidiol; **CBM** = cannabis-based medicine; **co** = crossover; **DHC** = dihydrocodeine; **inh** = inhalation; **mc** = multicentre; **NA** = not applicable; **NNT** = number needed to treat; **ol** = open-label; **OM** = oromucosal; **PO** = oral; **PR** = rectal; **pt(s)** = patients(s); **qid** = four times daily; **RCT** = randomized, double-blind, placebo-controlled trial; **tid** = three times daily.

placebo.[146] However, pain relief was only observed in four patients and five patients withdrew because of pain augmentation.

In summary, 8 of 11 high-quality RCTs on cannabinoids for neuropathic pain seem to indicate that cannabinoids have a noticeable effect on peripheral and central neuropathic pain and, in some cases, can improve spasticity and quality of sleep and reduce hyperalgesia. Although adverse effects occurred regularly and no clearly defined dose limit could be concluded from the results of the studies included in this review, the available evidence suggests that the disadvantages were outweighed by the positive effects in most cases.

5. Discussion

While in animal studies – using either acute or chronic pain models – significant analgesic and antihyperalgesic effects, which were independent of motor impairment or hypothermia, could clearly be demonstrated, the role of cannabinoids in humans is less obvious.

The discrepancy between absent or mild analgesic effects of Δ^9-THC in human trials (see below) and data from animal models may be the result of species-related differences. This is supported by the fact that endocannabinoid levels are higher in humans, possibly rendering them less sensitive to endogenous and exogenous cannabinoids. Even data generated from different animal species may not be easily translated to other species. For example, oxcarbazepine and carbamazepine did not affect mechanical hyperalgesia or tactile allodynia induced by partial sciatic nerve ligation in the rat. However, using the same model in the guinea pig, both drugs produced up to 90% reversal of mechanical hyperalgesia.[148] Furthermore, motor impairments may be misinterpreted as pain relief in some animal models (see section 3.1). Dysphoria and fear associated with higher doses may reduce the analgesic effects,[75,79] and hyperalgesic effects may be triggered by the activation of receptors not primarily associated with cannabinoids (e.g. TRPV1 receptor).

In fact, the reviewed studies in this article lead to the conclusion that cannabinoids do not seem to reliably reduce acute pain, either in experimental or in clinical settings. Any (weak) analgesic effects that have been observed were found in a medium dose range, suggesting a bell-shaped dose-effect response. Furthermore, even hyperalgesic effects have been found, for which a specific model has been described.[90]

In contrast, in chronic pain states, 20 of 25 RCTs showed a significant pain reduction (15 in neuropathic pain, 5 in nociceptive pain), 3 showed mixed results (2 in nociceptive pain, 1 in neuropathic pain) and 2 no analgesic effects (in neuropathic pain) [table V].

In chronic spasticity, 10 of 14 RCTs showed significant improvements at least at the subjective level, 2 showed mixed results and 2 no statistically meaningful effects.

From five active RCTs, none showed superiority of Δ^9-THC compared with diphenhydramine, codeine or amitriptyline regarding pain reduction, but in one study[112] nabilone performed better regarding improvement of sleep, and in a second study[133] Δ^9-THC performed better regarding spasticity.

Thus, while 70–80% of the placebo-controlled trials exerted beneficial effects on pain or spasticity, none of the five head-to-head comparisons showed superiority of cannabinoids over 'weak' opioids or other compounds regarding pain.

Patients with long-lasting chronic neuropathic pain or (painful) spasticity or central pain disorders, such as FMS, particularly benefited from cannabinoids. These conditions share the dysfunction and the disturbance of the normal homeostasis by stress and consist of pain symptoms, impaired physical functioning and psychological distress, which all together form a complex 'network malfunctioning'. Therefore, it is difficult to define whether the lack of resilience to stress-related disease exists *a priori* or is the consequence of ongoing symptoms. As the ECS has emerged as one of the most important facilitators of stress adaptation in the body,[23] these conditions may be associated with specific changes in the ECS (e.g. upregulation of cannabinoid receptors), which make it more likely that exogenous cannabinoids exert a corrective 'relaxing' effect, in addition to the protective activity of the ECS in

Table V. Efficacy outcomes in randomized controlled trials

Pain type	Favours treatment	Mixed results	No significant effects
Chronic nociceptive pain	Noyes et al.[101] (1975), Notcutt et al.[105] (2004), Blake et al.[108] (2006), Narang et al.[109] (2008), Skrabek et al.[111] (2008)	Pinsger et al.[107] (2006), Johnson et al.[113] (2010)	
Chronic neuropathic pain	Maurer et al.[133] (1990),[a] Karst et al.[134] (2003), Berman et al.[136] (2004), Nurmikko et al.[137] (2007), Abrams et al.[139] (2007), Wilsey et al.[140] (2008), Ellis et al.[141] (2009), Ware et al.[144] (2010)		Selvarajah et al.[142] (2010)
Chronic (mainly central) neuropathic pain in MS	Martyn et al.[116] (1995), Wade et al.[119] (2003),[a] Svendsen et al.[121] (2004), Zajicek et al.[118] (2003),[a] Zajicek et al.[123] (2005),[a] Rog et al.[124] (2005), Wissel et al.[125] (2006)[a]	Conte et al.[127] (2009)[a]	Wade et al.[120] (2004)[a]
Chronic spasticity in MS	Petro and Ellenberger[114] (1981), Ungerleider et al.[115] (1987), Maurer et al.[133] (1990),[a,b] Martyn et al.[116] (1995), Zajicek et al.[118] (2003), Wade et al.[119] (2003),[a] Wade et al.[120] (2004),[a] Zajicek et al.[123] (2005),[a] Wissel et al.[125] (2006),[a] Collin et al.[126] (2007)	Vaney et al.[122] (2004), Collin et al.[128] (2010)	Killestein et al.[117] (2002), Conte et al.[127] (2009)[a]
Head-to-head studies	Maurer et al.[133] (1990)[a,c,d] [codeine]	Noyes et al.[100] (1975) [codeine], Ware et al.[112] (2010) [amitriptyline]	Frank et al.[138] (2008) [DHC], Rintala et al.[143] (2010) [diphenhydramine]

a Studies focused on both pain and spasticity and are therefore repeatedly cited.

b Spasticity due to spinal cord injury.

c Pain reduction comparable, but significant reduction of spasticity only with Δ^9-tetrahydrocannabinol.

d Three-arm study.

DHC = dihydrocodeine; **MS** = multiple sclerosis.

the modulation of neuropathic pain and pain memory.[91,149]

Although the formal quality score of the evaluated RCTs reached a fair score of 4.0, several factors may limit the conclusions that can be drawn from their results.

1. Prior to randomization, a number of the studies had an open phase in which all subjects received the active agent.[105,124,137] Furthermore, some studies had a high proportion of prior cannabis users among their participants.[77,124,139,140,144] This approach may screen out individuals with a low tolerance to cannabinoids and reduce the occurrence of adverse events, consequently overestimating the efficacy of the intervention and underestimating its adverse effects.
2. Adequacy of blinding was usually not tested in the trials and the characteristic adverse effects caused by these substances render perfect masking extremely difficult, especially when participants were 'experienced' due to previous cannabis use and when a crossover design was used. In fact, in the CAMS study, patients and treating physicians correctly guessed treatment allocation in the active treatment arms more often than in the placebo group and only the assessors remained blinded to treatment allocation. Together, this may result in an overestimation of efficacy.
3. In a substantial number of the studies, there were losses and withdrawals of subjects. However, most studies did not specify whether the intention-to-treat analysis was used and how this was defined.
4. In real-world situations, the patient's expectations regarding the benefits derived from an intervention generally contribute to more pronounced treatment effects, which may result in some underestimation of efficacy in RCTs.
5. Studies varied considerably in participant population and how outcomes were assessed and reported. In one study, a primary outcome parameter was even reordered into a secondary outcome during patient recruitment.[126]
6. The Jadad score does not take into account the number of patients participating in each study and the total number of withdrawals, which may challenge the internal validity of the study and

result in overestimation of the meaning of the results.

Adverse effects such as sedation, dizziness, cognitive impairment, anxiety and dry mouth are common and increase with increasing dosage, which also has been reported in a recent review.[150] Although they are usually mild in nature, serious adverse events, such as acute psychosis and vasovagal syncope, may occur and result in withdrawal events in up to 25% of subjects. Only one open-label study conducted over a mean period of 434 days reported information about the potential addictive effect of CBM.[129] In this study, a 2-week interruption period was included in which 44% of subjects reported at least one withdrawal symptom; however, intensities were mild and no consistent withdrawal syndrome was observed. Other adverse effects are associated with the specific route of administration, such as sore mouth due to the alcohol content in the oromucosal spray[132] and lung impairment caused by inhalation of cannabis smoke.[151] Data showed that usually a daily dose of more than 10 mg Δ^9-THC is necessary for relevant reduction of pain and spasticity. On the other hand, considerable adverse effects were usually observed at doses of 15 mg Δ^9-THC per day. This points to a very narrow therapeutic window of Δ^9-THC itself.

Although it could be demonstrated that the addition of the non-psychoactive CBD as well as the oromucosal administration of small doses of Δ^9-THC usually allow for much higher daily doses, interestingly, except for one study,[113] no clinically relevant advantage was found as a result of the added CBD, when comparisons were not only performed against placebo but also against CBD-free spray.[105,119,136] Such a difference could also not be shown for the oral preparations.[117,118,123] However, recent data from a cross-sectional study conducted in the UK suggest that the significant decrease in the CBD portion along with the simultaneous increase in the Δ^9-THC concentration of street cannabis (higher-potency cannabis) to 12–18% is associated with an approximately 7-fold increase for the risk of a first manifestation of psychotic illness,[152] an observation that clearly argues for the addition of CBD to Δ^9-THC. However, the use of cannabis with the 'well balanced' mixture of about 70 naturally occurring cannabinoids beyond the CBD proportion does not seem to result in a principal change regarding efficacy and adverse effects, and correspondingly in the therapeutic index of the clinically available cannabinoids.

To overcome this problem, one approach is to address primarily peripheral neurons, while CNS penetration is restricted, which could be shown for AJA (CT-3 or IP-751). Based on the rationale that the terminal carboxy metabolite of Δ^9-THC (Δ^9-THC-11-oic acid) has shown no psychotropic effects in studies in humans[153] and mice,[154] AJA was synthesized from the dimethyl heptyl analogue of Δ^9-THC-11-oic acid by modification of the pentyl side chain, which can be used to change the analgesic and anti-inflammatory potency of Δ^9-THC.[155] In fact, statistically significant pain reduction compared with placebo and a strong trend towards anti-allodynic properties was demonstrated for daily doses of AJA 40 and 80 mg without complex psychotropic effects characteristic of Δ^9-THC.[134,135] However, transient vertigo, tiredness and dry mouth in some patients indicate the presence of some central activity. In fact, Dyson et al.[68] revealed that about 30–40% of AJA penetrates into the central compartment, but apparently the analgesic effect is mainly mediated by the activity on peripheral CB1 receptors, since the antihyperalgesic effects of AJA in rats were inhibited by a CB1 receptor antagonist. Similarly, naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl) methanone[156] and AZD1940 are peripherally selective cannabinoid receptor agonists that are currently undergoing preclinical and clinical validation.[157]

Animal models have compellingly shown that cannabinoids, in combination with opioids, can increase the degree of pain reduction and reduce tolerance development typically associated with opioid therapy.[158,159] That these effects may be present in humans as well is indicated by data from the study of Naef et al.[79] and Roberts et al.[83] showing that an analgesic effect was only achieved in the electrical stimulation test and heat stimulation, respectively, when cannabinoids were given in combination with morphine, and by the observation in one patient with familial Medi-

terranean fever that morphine use in the treatment of breakthrough pain could be significantly reduced.[104] However, again, in RCTs on acute postoperative pain such an effect could not be confirmed.[81,84]

A recent review and meta-analysis investigating 18 RCTs on cannabinoids for the treatment of chronic pain suggests that cannabis treatment is moderately efficacious against chronic pain, but that beneficial effects may be partially or completely offset by potentially serious harms.[160] NNHs were calculated between 5 (for events affecting motor function) and 8 (for events that altered cognitive function). In this meta-analysis, NNTs could not be calculated because only one of the 18 studies included the intensity of pain as a dichotomous variable defining response as a reduction of 50% or more. However, there is an ongoing debate as to whether a 50% pain reduction is mandatory to approve a clinically meaningful improvement. Other reports cite a 30% change in pain scores as meaningful improvement,[161] which is what is also included in the guideline on clinical medicinal products intended for the treatment of neuropathic pain of the European Medicines Agency,[162] and in that case the NNTs found are comparable with those described for other agents such as opioids[163] or NSAIDS.[92] Moreover, in opioids, comparable NNHs were found for nausea at 4.2 and dizziness at 7.1 and adverse event-related withdrawals were as high as 56%.[164,165]

Approaches to increase the therapeutic range include (i) change in route of application; (ii) combination with cannabinoids exhibiting antipsychotic effects such as CBD; (iii) combination therapy, especially with opioids; (iv) use of CB1 receptor agonists with predominantly peripheral action; (v) use of CB2 receptor agonists; (vi) change in the overall activity of the ECS via FAAH- and MGL-modulating compounds; and (vii) topical or perineural (e.g. epidural or spinal) application.

While the first three approaches are already in use, the latter are still in preclinical assessment or not beyond clinical phase II trials. It seems that a breakthrough by significantly increasing the therapeutic index could not be brought about by a change in route of application, combination with CBD, use of whole plant extracts or combination with opioids. Therefore, efforts supporting the alternative approaches are warranted. Further insights on these topics may be found in two recent review articles.[166,167]

6. Conclusion

Together, the data from the reviewed studies allow the conclusion that cannabinoids are efficacious in the treatment of chronic pain, especially in neuropathic pain and (painful) spasticity and in a patient group whose therapy success is otherwise unsatisfactory and who are characterized by failed stress adaptation. The Canadian regulatory authority, Health Canada, has approved the CBM spray under the trade name Sativex®, and the product has been available on prescription in Canadian pharmacies since 20 June 2005. The regulatory approval was explicitly issued for the symptomatic relief of central neuropathic pain associated with MS, although the approval was extended to treatment of intractable cancer pain unresponsive to optimized opioid therapy in 2007.[98] The UK and Spain approved Sativex® for treatment of spasticity in MS in June and July 2010, respectively. While RCTs established efficacy of cannabinoids in chronic (neuropathic) pain and an increasing number of different drugs has been approved for this condition, more three-arm studies (study drug vs comparator vs placebo) should be provided in order to allow the assessment of comparative efficacy and safety of cannabinoids. In addition, in future clinical trials the systematic assessment of behavioural responses to stress and the activity of the HPA axis are encouraged. Since with the available cannabinoid preparations the relationship of benefit to harm seems not to be optimally balanced, efforts are warranted to investigate the ideal method of administration and to develop cannabinoids with a more favourable therapeutic index.

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