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Review

Review on clinical studies with cannabis and cannabinoids 2010-2014

Mikael A. Kowal[1], Arno Hazekamp[1], Franjo Grotenhermen[2]

Bedrocan, Veendam, The Netherlands
nova-Institut, Chemiepark Knapsack, Industriestraße, D-50354 Hürth, Germany

Abstract

In 2010 a review by Hazekamp and Grotenhermen covered controlled clinical trials of the years 2006-2009 on cannabis-based medicines, which followed the example of the review by Ben Amar (2006). The current review reports on the more recent clinical data available from 2010-2014. A systematic search was performed in the scientific database of PubMed, focused on clinical studies that were randomized, (double) blinded, and placebo-controlled.

The key words used were: cannabis, marijuana, marihuana, hashish, cannabinoid(s), tetrahydrocannabinol, THC, CBD, dronabinol, Marinol, nabilone, Cannador, nabiximols and Sativex. For the final selection, only properly controlled clinical trials were retained. Open-label studies were excluded, except if they were a direct continuation of a study discussed here.

Thirty-two controlled studies evaluating the therapeutic effects of cannabinoids were identified. For each clinical trial, the country where the project was held, the number of patients assessed, the type of study and comparisons done, the products and the dosages used, their efficacy and their adverse effects are described. Based on the clinical results, cannabinoids present an interesting therapeutic potential mainly as analgesics in chronic neuropathic pain and spasticity in multiple sclerosis. But a range of other indications also seem promising. CBD (cannabidiol) emerges as another valuable cannabinoid for therapeutic purposes besides THC.

Keywords: cannabinoids, cannabis, therapeutic potential, controlled clinical trial, efficacy, safety, cannabidiol

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Author's address: Mikael A. Kowal, m.kowal@bedrocan.nl

Introduction and Method

This review presents an overview of clinical trials performed with cannabis or cannabinoids in the period 2010-2014. It is a follow-up of a previous review on clinical studies done in the period 2005-2009 (Hazekamp and Grotenhermen 2010), which itself was inspired by a review by Ben Amar (2006) covering the period 1975 to June 2005. The current review presents large studies with several hundreds of participants, but also small controlled studies on new indications, such as Crohn's disease. It also highlights the new interest in the therapeutic value of CBD (Cannabidiol), a non-psychotropic plant-derived cannabinoid.

The methodology of this review has been adopted from Ben Amar (2006) and Hazekamp and Grotenhermen (2010). In order to assess the current knowledge on the therapeutic potential of herbal Cannabis, isolated phyto-cannabinoids, and medicinal preparations directly inspired by phyto-cannabinoids, a systematic search was performed in the scientific database of *PubMed*. Hosted by the U.S. National Library of Medicine, this database contains about 20 million scientific publications from the field of life sciences and biomedical information.

The period screened was from January 1, 2010 up to December 31, 2014. The search focused on clinical studies that were randomized, (double) blinded,

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Table 1. Number of studies and patients reviewed

Pathology	Number of studies found	Total number of patients included
Chronic pain	11	1211
Multiple sclerosis	6	1515
Irritable bowel syndrome	3	133
Crohn's disease	1	21
Appetite and chemosensory perception	2	28
Chemotherapy-induced nausea and vomiting	1	16
Pulmonary disease	1	9
Cannabis dependence	2	207
Anxiety	3	94
Psychosis	1	42
Parkinson's disease	1	21
Total	**32**	**3297**

and placebo-controlled or controlled by a standard medication. The keywords used were: *cannabis, marijuana, marihuana, hashish, cannabinoid(s), tetrahydrocannabinol, THC, CBD, dronabinol, Marinol, nabilone, Cannador, nabiximols* and *Sativex*.

After initial sorting, all articles and reviews including clinical protocols or a summary of the literature evaluating the therapeutic potential of cannabinoids in humans were read. For the final selection, only properly controlled clinical trials were retained, thus open-label studies were excluded, except when they were a direct continuation of a clinical trial discussed in this paper. The research included the works and data available in English. No papers in other languages were found or excluded. Studies are presented per indication, in chronological order.

A range of different cannabis-based products are described in the studies presented in this review. For the ease of the less experienced reader, these preparations are briefly discussed below:

Inhaled cannabis refers to the dried flowers (buds) of the female plant of Cannabis. This herbal product is also commonly known as marijuana or marihuana. The main way to administer cannabis as a recreational drug is by smoking, which is also the way most medicinal users consume it. For clinical trials, most often these materials are analyzed for their content (in % of dry weight) of THC and in some studies inhalation was performed by using a vaporizer.

THC, or delta-9-tetrahydrocannabinol, or dronabinol, is the pharmacologically and toxicologically most relevant constituent found in the Cannabis plant, producing a myriad of effects in animals and humans (Hazekamp and Grotenhermen 2010). Pure THC (dronabinol) can be derived from natural sources (extraction from cannabis plants) or produced synthetically. Chemically, THC belongs to a group of closely related compounds known as cannabinoids, and they are commonly considered the main bioactive components of Cannabis. Up to date, more than 100 different cannabinoids have been described, but only a few of the major ones have been characterized for their biological activities, including cannabidiol (CBD, see below), cannabinol (CBN), and tetrahydrocannabivarin (THCV) (ElSohly and Gul 2014).

Dronabinol is the INN (international non-proprietary name) of the isomer of delta-9-tetrahydrocannabinol that is present in the cannabis plant, the (-)-trans-isomer. This is the only naturally occurring of the four possible isomers.

CBD, or cannabidiol, is the major non-psychotropic cannabinoid found in Cannabis. It has shown anti-epileptic, anti-inflammatory, anti-emetic, muscle relaxing, anxiolytic, neuroprotective and anti-psychotic activity and (when co-administered) may reduce the psychoactive effects of THC (Russo and Guy 2006; Grotenhermen et al. 2015).

Marinol® (Solvay Pharmaceuticals, Belgium) is a synthetic version of dronabinol. It is formulated as a capsule containing synthetic dronabinol in sesame oil. In the US it is indicated for the treatment of anorexia associated with weight loss in patients with AIDS, as well as nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional anti-emetic treatments. The patent on Marinol expired in 2011, which opened the way for generic preparations of dronabinol, which are now available.

Nabilone (Valeant Pharmaceuticals International, USA) is a synthetic analogue of THC which binds to the cannabinoid type 1 receptor (CB1r). In Canada, the United States, the United Kingdom and Mexico, Nabilone is marketed as Cesamet®. It is registered for treatment of chemotherapy-induced nausea and vomiting in patients that have not responded to conventional anti-emetics. It is also used for other medical conditions.

Sativex® (United States Adopted Name (USAN), nabiximols) (GW Pharmaceuticals, UK) is a cannabis-based pharmaceutical product containing delta 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in approximately a 1:1 ratio, delivered in an oromucosal (into the mouth) spray. Because of the use of whole extracts, ballast components are also present, such as minor cannabinoids and terpenes. Sativex has been approved in Canada as adjunctive treatment for

spasticity and neuropathic pain in adults with multiple sclerosis (MS) and in cancer pain. Sativex has been approved in most European countries for the treatment of spasticity in adult patients with MS. Each spray contains 2.7 mg THC and 2.5 mg CBD.

Cannador® (Society for Clinical Research, Germany, and Weleda, Switzerland) is an oral capsule containing a whole plant extract, with standardized THC content and a CBD amount controlled to lie within a fixed narrow range with a THC:CBD ratio of about 2:1. It has been used in several clinical trials. It has been clinically tested for reduction of muscle stiffness, spasms and associated pain in Multiple Sclerosis, for cachexia in cancer patients and for post-operative pain management. The development of Cannador as an approved medication has now been abandoned and no further clinical studies are planned.

Summary of clinical trials

1. Chronic pain

1.1. Oral cannabis

Compared to the years 2005-2009, a significant increase could be observed in the number of patients studied with regard to the impact of oral cannabis on chronic pain. The two extracts used were Sativex (THC/CBD oromucosal spray containing nearly equal amounts of CBD and THC) and a similar cannabis extract mainly containing THC (THC oromucosal spray). The analgesic effects were not always clearly visible in these studies. Selvarajah et al. (2010) investigated the effects of the THC/CBD oromucosal spray on 30 patients with painful diabetic peripheral neuropathy (DPN) in a placebo-controlled, double-blind, between-group study. After 12 weeks of treatment with divided doses up to four times a day no significant difference in pain scores could be observed between THC/CBD oromucosal spray and placebo, although both groups responded to treatment. Depression was suggested as a possible confounder, since depressed patients displayed higher baseline pain scores, as well as a more profound placebo effect, compared to other subjects. As a result, it was suggested that depression should be taken into account when designing future clinical studies into DPN.

In contrast, another between-group study with 177 patients (Johnson et al. 2010) found that THC/CBD oromucosal spray was effective in chronic cancer pain relief when added to standard opioid therapy. Specifically, the Intent-To-Treat (ITT; all randomized participants who received at least one dose of the medication and displayed efficacy data) responder analysis indicated that doses of THC/CBD oromucosal spray up to 48 sprays a day in a period of 2 weeks resulted in about twice as many patients displaying at least 30% reduction in pain intensity scores (generally considered to represent a clinically important difference in chronic pain trials), as compared to placebo and THC-only oromucosal spray. Treatment-related adverse events (AEs) were tolerable and mainly included somnolence, dizziness and nausea. No treatment-related serious adverse events (SAEs) were observed. In sum, it was concluded that the synergy between THC and CBD results in higher analgesic efficacy than THC alone.

Based on the promising results, an open-label follow-up study was conducted (Johnson et al. 2013) in order to evaluate the long-term safety and tolerability of THC/CBD oromucosal spray and THC oromucosal spray in patients with terminal cancer-related pain. In total 43 subjects who completed the randomized controlled trial described above (Johnson et al. 2010) took part in this multi-center experiment – 39 subjects received THC/CBD oromucosal spray for a median of 25 days and 4 received THC oromucosal spray for a median of 151.5 days. The medication doses were self-titrated by the patients, with a maximum of 48 sprays per day. Consequently, due to the variability of conditions present in this study, data regarding the comparison of the drugs' efficacy should be treated with caution. In spite of that, the results showed that up to 5 weeks of treatment with THC/CBD oromucosal spray was effective for pain reduction and sleep quality improvement. In addition, out of the patients receiving THC/CBD oromucosal spray, 10% of subjects administered the study medication for more than 6 months and 5% administered it for over a year without any need to increase the dosage. As a result, it was suggested that THC/CBD oromucosal spray remains effective and tolerable for some patients for an extended period of time. As for treatment-related AEs, the most frequently observed in the THC/CBD oromucosal spray group were dizziness, nausea, vomiting, dry mouth, somnolence, and confusion. In the four patients administered THC oromucosal spray, AEs included dizziness, headache, and an episode of memory impairment. Only three (8%) subjects from the THC/CBD oromucosal spray condition experienced a SAE that was considered to be related to study medication.

A different between-group study focusing on the impact of different doses of Sativex on chronic cancer pain only partially confirmed the analgesic effect of the THC/CBD spray as an add-on to standard opioid therapy (Portenoy et al. 2012). Specifically, none of the doses administered (low: 1-4 sprays a day; medium: 6-10 sprays a day; high: 11-16 sprays a day) was able to achieve 30% pain score reduction during the 5-week treatment phase, compared to placebo. However, the secondary responder analysis of mean daily pain from baseline to end of the trial pointed to a general analgesic effect of Sativex. Analysis of the individual treatment conditions showed that this effect was present only in the low and medium dose groups, but, surprisingly, not in the high dose group. In addition, the AEs were particularly problematic in case of the high dose condition. Out of 90 patients from this group, only 59 (66%) were able to finish the study.

However, this was partially also due to the fact that the study population was terminally ill, resulting in the death of 20.9% patients in the nabiximols condition and 17.6% in the placebo group. None of these deaths was considered to be medication-related.

Sativex produced mixed results in the treatment of neuropathic pain due to multiple sclerosis according to a between-group study with 339 patients, researchers of the Pain and Anaesthesia Research Centre of St Bartholomew's Hospital in London, UK, reported (Langford et al. 2013). Patients received the product in addition to their current medication, which failed to control their pain adequately. The trial consisted of two phases. In phase A 167 participants received the THC/CBD oromucosal spray and 172 received placebo in a double-blind manner for 14 weeks. In phase B 58 patients continued to receive either placebo or Sativex for 18 weeks to investigate maintenance of treatment effects.

In phase A 50 per cent of cannabis patients experienced pain reduction of more than 30 per cent compared to 45 per cent of placebo patients, which was not significantly different. However, during phase B Sativex was superior to placebo, with 57 per cent of patients receiving placebo failing treatment versus only 24 per cent of patients from the active treatment group. In addition, mean pain intensity and sleep quality improved in the treated group compared to placebo. Regarding AEs, during phase A 15 patients (9%) in the active condition and 12 patients (7%) in the placebo condition stopped using study medication due to, mainly, gastrointestinal and nervous system disorders. In phase B the most frequent AEs were fatigue, somnolence, vertigo, dizziness and nausea. However, in total 6 patients (10%) stopped applying their study medication due to AEs during the open-label part of phase B. Moreover, two patients from the active treatment group (10%) experienced a SAE: serious disorientation and suicidal ideation, respectively. Suicidal ideation was also observed in case of one patient (5%) from the placebo condition. Authors concluded that "the results of the current investigation were equivocal, with conflicting findings in the two phases of the study. (…) These findings suggest that further studies are required to explore the full potential of THC/CBD spray in these patients."

A between-group study by Serpell et al. (2014) was conducted to examine the efficacy of Sativex on peripheral neuropathic pain (PNP) associated with allodynia. In total 246 patients took part in the experiment, with 128 receiving THC/CBD oromucosal spray and 118 receiving placebo for 14 weeks. The dosage was self-titrated with a maximum of 24 sprays per day. The main analysis included two sets of subjects: the ITT and per protocol (PP; participants who displayed no protocol deviations from the primary parameter) analysis sets. The ITT analysis demonstrated at least 30% reduction in pain intensity scores in 34 patients (28%) in the active group, in contrast to 19 patients (16%) in the placebo group. This was further supported by the PP analysis, which showed the same effect in 27 subjects (36%) from the active group, compared to 18 subjects (20%) in the placebo condition. It was concluded that THC/CBD oromucosal spray produced a clinically significant improvement in average daily pain in a significantly greater percentage of patients, as compared to the placebo group. The treatment-related AEs were mostly mild to moderate in severity and included mostly nervous system, gastrointestinal, administration site and psychiatric effects. In total, 97 (76%) subjects in the active condition and 56 (47%) participants in the placebo group experienced at least one treatment-related AE. In total, 25 (20%) patients receiving THC/CBD oromucosal spray and 8 (7%) patients receiving placebo withdrew from the study due to AEs.

The latest (in the period covered by this review) investigation into the effect of Sativex on chronic pain was conducted by Lynch et al. (2014). It was a crossover study that included 16 patients with chemotherapy-induced neuropathic pain. Subjects self-administered their dose, with a maximum of 12 sprays per day. After establishing an optimal dose, it was fixed for the remainder of the study. The treatment lasted 4 weeks and was followed by a 2-week washout period before starting to use the other medication (placebo or Sativex). The results were not clear: there was no significant difference in pain scores between the two conditions. Nonetheless, five patients reported a borderline significant reduction in pain scores when receiving active treatment, compared to using placebo. Keeping in mind the small sample size and pilot nature of the study, this was considered a promising result for future studies into this topic. Although treatment-related AEs were reported by most subjects, they were not particularly problematic with fatigue, dizziness, dry mouth and nausea being the main ones.

1.2. Oral THC

Turning the attention of this review towards the study of isolated cannabinoids, a crossover experiment was conducted to directly compare the analgesic efficacy of oral THC (dronabinol) and diphenhydramine – an approved treatment for central neuropathic pain which may display some side-effects similar to those of THC (Rintala et al. 2010). Seven patients with traumatic spinal cord injury (SPI) received each medication for 8 weeks (which included a 12-day up-titration and 9-day down-titration phase at the start and end of this time period, respectively, a 7-day stabilization phase, and a 28-day maintenance phase), followed by a 7-day washout phase before starting to use the second drug. The doses started with 5 mg of THC or 25 mg of diphenhydramine per day, reaching a maximum daily dosage of 20 mg of THC or 75 mg of diphenhydramine, respectively. The results did not show any significant differences between the two treatments, while the AEs were similar for both medications. The most frequent AEs included dry mouth, constipation, fatigue, and drowsiness for both

drugs. All subjects reported fatigue at least once while using diphenhydramine, while fewer than three-fifth of the patients reported fatigue at least once after being administered THC. Infrequent reports of feeling high, dizziness, abdominal discomfort, confusion, lack of coordination, and nausea were found only in the THC condition. Only two treatment-related severe AEs were reported: one related to abdominal discomfort (THC) and the second one regarding drowsiness (diphenhydramine). It was concluded that THC was as effective as diphenhydramine for pain relief, while side-effects were comparable.

1.3. Inhaled cannabis

Regarding research into the analgesic potential of herbal cannabis, a crossover study was conducted (Ware et al. 2010) in order to investigate the safety and efficacy of smoked cannabis on chronic neuropathic pain. Twenty-one patients who completed the trial received a random dose of 25 mg cannabis material (obtained from Prairie Plant Systems Inc., and the United States National Institute of Drug Abuse) with varying potency (placebo, 2.5%, 6%, 9.4% THC), using a titanium pipe for smoking. Each dose was administered three times daily in single inhalations for the period of 5 days, followed by a 9-day washout phase before starting to use the subsequent dose. The results showed that only the 9.4% THC dose was effective at decreasing pain and improving sleep, compared to placebo. Treatment-related AEs were quite mild with headache, dry eyes, burning sensation in areas of neuropathic pain, numbness, cough and dizziness as the most common ones in the 9.4% THC condition. In addition, there were single reports on euphoria and feeling "high" in each of the active drug conditions (2.5%, 6%, 9.4% THC). It was concluded that the highest cannabis dose administered 3 times daily by inhalation may be a well-tolerated and effective treatment for chronic neuropathic pain.

Another study compared the subjective effects on pain management induced by smoked cannabis versus oral THC (Issa et al. 2014). Thirty chronic non-cancer pain patients received placebo, 10 mg or 20 mg of oral THC in a crossover manner. A separate comparison sample of 20 healthy individuals was administered smoked cannabis (1.99% and 3.51% THC) in a similar crossover manner. Both samples rated the subjective psychoactive effects induced by the drugs. The results demonstrated that the psychoactive effects of 10 mg and 20 mg oral THC were significantly greater than placebo and comparable to the subjective effects of smoked cannabis. However, there was a different pattern of peak effects (2 h with oral administration, compared to 30 min with smoking). Consequently, a similar "high" was induced by both oral THC in pain patients, and smoked cannabis in healthy subjects. There were no AEs reported.

A single study investigated the impact of cannabis on neuropathic pain using the Volcano vaporizer (Wilsey et al. 2013). Thirty-nine patients with central and peripheral neuropathic pain were administered a placebo, low-dose (1.29%), or medium-dose (3.53%) of cannabis by vaporizing. Subsequently, subjective side effects and neuropsychological performance were measured. The study found no significant difference between the two active dose groups. The number needed to treat (NNT) to obtain 30% pain reduction was 3.2 for placebo versus low-dose, 2.9 for placebo versus medium-dose, and 25 for medium- versus low-dose. The two active dose groups did not significantly differ in terms of analgesic efficiency. Subjective side effects were minor and easily tolerated. The results of neuropsychological testing showed that subjects in the medium-dose condition displayed lower learning and memory performance than those in the low-dose condition. However, delayed memory performance did not differ between the low-dose and placebo. Both doses produced identical effects on attentional processing, with subjects performing worse after cannabis administration. In any case, these effects were of limited duration and reversible within 1 to 2 hours. Accordingly, it was concluded that vaporized cannabis, even at low doses, may be effective in addressing treatment-resistant neuropathic pain.

2. Multiple sclerosis

2.1. Oral cannabis

Investigation into the effectiveness of oral cannabis on the treatment of multiple sclerosis (MS) included three studies with Sativex and large sample sizes and a large study with a capsulated cannabis extract (Cannador). The first one (Kavia et al. 2010) inquired into the effect of Sativex on bladder dysfunction associated with MS. Self-titrated doses (up to 48 sprays per day) of either placebo or THC/CBD oromucosal spray were randomly administered using a between-group design for the period of 8 weeks in a sample of 135 MS patients with an overactive bladder (OAB). The main variable of interest was the decrease in the daily occurrence of loss of bladder control. Although there was no significant reduction in the amount of urinary incontinence episodes, there were fewer episodes of nocturia and daytime urination in the active treatment group. As for treatment-emergent AEs, most of them were mild or moderate in severity and mostly related to CNS-type disturbances, including dizziness, disorientation, headache, dissociation, impaired balance and paraesthesia. These treatment-related AEs led to the withdrawal of ten patients from the experiment (7 from the active condition and 3 from the placebo condition). In addition, three patients reported treatment-related SAEs (2 under active treatment and 1 under placebo treatment). Moreover, a potential transient ischaemic attack was observed in case of one subject receiving Sativex 4 days after starting to use study medication. The symptoms included shaking, coordination problems and severe absence following a dose of 18 sprays in one day. The

symptoms resolved after ceasing to administer the study drug. Sativex treatment was restarted the next day but the symptoms appeared once again a day later after increasing the dose to 18 sprays.

Collin et al. (2010) examined 337 patients with MS in a between-group study regarding the effects of Sativex on symptoms of spasticity. Patients self-titrated over a period of 14 weeks (up to 24 sprays per day) and the main variable of interest was the self-reported spasticity on a 0-10 numerical rating scale (NRS) – a similar scale as the one applied in many pain studies. The PP data analysis set showed a significant decrease in spasticity NRS scores in the active condition, compared to placebo. However, the ITT data analysis set did not show any effects. The authors explained this difference with the fact that subjects who were included in the ITT set but terminated their treatment early, displayed a detrimental effect on the mean treatment response to active treatment in the ITT analysis. However, those patients who complied with the protocol showed promising beneficial effects on spasticity. In case of AEs related to the drug, the most frequent ones were urinary tract infections, nausea and vomiting. Nine (5%) participants in the Sativex group and five (3%) in the placebo condition stopped using the study medication due to AEs. In addition, 4 treatment-related SAEs were observed: one with aggression, agitation, delusions, irritability, insomnia and muscle spasms; one with depression, drug dependence and suicidal ideation; one with an acute confusional state; and one with severe urinary tract infection.

Another study also determined the impact of Sativex on spasticity in MS patients (Novotna et al. 2011). It applied a between-group study design with two phases. In the first (dose-finding) phase, 572 patients first received only THC/CBD oromucosal spray in a single-blind manner (not knowing whether they received the active drug or placebo) for the study period of 4 weeks (up to 12 sprays per day). Subsequently, 241 subjects from this phase, who displayed ≥20% improvement in spasticity, were randomized into the double-blind, placebo-controlled second phase of the investigation lasting 12 weeks (receiving the same dosage of the medication as established in the first phase). Both the ITT analysis of NRS spasticity scores and secondary endpoints (including measures of sleep disturbance, depression and overall impression of change) showed a highly significant difference in favor of Sativex treatment, compared to placebo, in the second phase of the study. The authors concluded that this clearly pointed to a beneficial effect of THC/CBD on treatment-resistant spasticity in MS patients who displayed capacity to respond to this kind of treatment. Moreover, the enriched study design allowed to identify the extent of the benefit that can be derived from the treatment with Sativex in responder subjects. The drug-induced AEs were quite mild and did not exceed 10% frequency for each type of event in both groups. The most common AEs included vertigo, fatigue, muscle spasms and urinary tract infections, which led to the exclusion of only 3% of patients in both phases of the study.

Notcutt et al. (2012) investigated the long-term maintenance of efficacy of Sativex and the effect of its withdrawal in 36 MS patients who have been using nabiximols for the treatment of spasticity for at least 12 weeks. Only subjects who were considered to tolerate and receive benefits from using the THC/CBD oromucosal spray were included in this between-group study. All eligible subjects were included in a 1-week baseline open-label phase in which they continued to use their medication at a stable dose level. Afterwards, the participants were randomized into either the nabiximols or placebo condition and asked to continue administering a stable dose of the drug (on average 7.3 sprays per day of Sativex and 9.2 of placebo). This double-blind phase of the study lasted for 4 weeks. The main variable of interest was the time to treatment failure (TTF). The results showed that 17 subjects in the placebo condition failed to complete the study (94%), compared to only 8 participants in the THC/CBD oromucosal spray group (44%). Moreover, analysis of the TTF indicated a significant difference in favor of Sativex - participants in the placebo group were three times more likely to withdraw from treatment, compared to those using THC/CBD oromucosal spray. It was concluded that Sativex remains effective in the relief of MS-related spasticity in the long-term. In case of treatment-related AEs, they were mild to moderate and included pain (experienced by 2 subjects in the active drug condition and 5 placebo patients), muscle spasticity (2 active, 3 placebo), muscle spasms (2 active, 2 placebo) and depressed mood (2 active, 2 placebo).

An investigation by Zajicek et al. (2012) examined the influence of Cannador (capsules containing 2.5 mg THC and around 1.25 mg CBD) on symptoms of muscle stiffness in 279 MS patients over the study period of 12 weeks, using a between-group design. Subjects self-titrated the total daily dosage up to 25 mg THC and the main variable of interest was muscle stiffness scored on an 11 point NRS (ranging 0-10). The results demonstrated that 29.4% of subjects treated with the cannabis extract experienced significant stiffness relief compared to 15.7% using placebo. Combining this with the beneficial effects of the active drug on body pain, spasms and sleep quality, the results were considered as an indication of the effectiveness of the cannabis extract in treating symptoms of muscle stiffness in MS patients. As for the AEs, more than 95% of these events in each condition were mild or moderate in severity and included mainly nervous system (71.3%) and gastrointestinal effects (41.3%). However, several AEs were observed at higher rates (more than 3% difference) only in the cannabis extract group: dizziness, attentional disturbance, balance disorder, somnolence, dry mouth, nausea, diarrhea, fatigue, asthenia, feeling abnormal, urinary tract infection,

disorientation, confusional state and falling. The AEs led to the exclusion of 30 participants from the active drug group (21.0%) and 9 from the placebo condition (6.7%).

2.2. Oral THC

A second between-group study by Zajicek et al. (2013) investigated the impact of oral capsulated THC on the progression of MS, instead of just symptom relief. A total of 493 progressive MS patients randomly received either oral THC (n=329; capsules containing 3.5 mg THC), or placebo (n=164) over a period of 36 months. The maximum allowed daily dosage of THC was 28 mg. There were two main variables of interest: 1) time to expanded disability status scale (EDSS) score progression of at least 1 point from a baseline EDSS score of 4.0, 4.5, or 5.0, or at least 0.5 points from a baseline EDSS score of 5.5 or more, established at the next scheduled 6 monthly visit; and 2) difference from baseline to end of trial in the physical impact subscale of the self-reported 29-item multiple sclerosis impact scale (MSIS-29-PHYS). The results did not show significant effects of oral THC on any of the scales. Consequently, it was concluded that THC has no impact on the progression of MS in a progressive phase. Treatment-related AEs were difficult to quantify, since patients also reported AEs that could have been the result of MS symptoms and the authors did not differentiate between drug- and disease-related AEs. Regarding SAEs, 114 subjects (35%) who were administered oral THC experienced at least one SAE in comparison with 46 (28%) who received placebo. The most frequent SAE were related to MS-associated events and infections. The number and type of SAEs observed did not significantly differ between conditions, suggesting that most of them were not treatment-related.

2.3. Inhaled cannabis

A single crossover study (Corey-Bloom et al. 2012) administered smoked cannabis in order to determine the efficacy of this drug on spasticity in MS patients. Thirty MS subjects completed the trial in which they received cannabis cigarettes containing 800 mg of 4% THC cannabis or placebo cigarettes with THC removed. Each treatment lasted 3 days and the two conditions were separated by a 11-day washout period. The primary measure was the change in spasticity scores on a modified 0-5 Ashworth scale. The results pointed to a significant decrease in ratings of spasticity in the cannabis group, in comparison to placebo. Additionally, pain ratings on a visual analogue scale (VAS; a 100mm scale) were significantly reduced as well (on average by 5.28 points more than placebo). The results suggested that inhaled cannabis is effective in reducing symptoms of spasticity and pain in MS patients resistant to treatment. AEs were mild and led to only 5 treatment-related withdrawals: two patients reported an intense “high”, two reported dizziness and one reported fatigue.

3. Irritable bowel syndrome

3.1. Oral THC

Research by Wong et al. (2011) focused on the impact of oral THC (dronabinol) on colonic motility in patients with irritable bowel syndrome (IBS). Seventy-five participants included in this between-group study were administered a single dose of either placebo (n=27), 2.5 mg (n=24) or 5 mg of THC (n=24) in the form of capsules. The measurements included left colonic compliance, the motility index (MI; index of colonic phasic pressure activity), tone, and colonic sensation after a meal and during fasting. Each subject had a balloon-manometry assembly placed in their colon which assessed colonic functions first during fasting, then after a standard 1000kcal liquid meal. Moreover, genetic polymorphisms of CNR1, FAAH and MGLL genotypes were analyzed to see whether genetic variants modulate the impact of THC on the assessed symptoms. The results demonstrated that a single oral THC dose of 5 mg led to improved colonic compliance and decreased fasting colonic motility in specific subgroups of IBS patients, i.e.: those with diarrhea (IBS-D) and alternating IBS (IBS-A). In contrast, the 2.5 mg THC dose had no significant effect on any of the functions measured. It was suggested that these results point to the critical role of the dosage of THC in producing clinically significant effects in IBS patients and that CNR1 and FAAH genetic variations can modulate the effects of the drug on colonic motility. AEs included fatigue (23% of all subjects) , hot flashes (19%), headache (13%), dizziness (11%), foggy thinking (11%), increased heart rate (11%), dream-like state (9%), nausea (8%), dry mouth and eyes (7%) and were evenly observed in all of the conditions, except for foggy thinking, which was more pronounced in the THC groups.

Klooker et al. (2011) examined the effect of oral THC (dronabinol) on a different aspect of IBS, i.e. visceral sensitivity to rectal distension. This crossover study included 10 IBS patients and 12 healthy volunteers. The participants were given single doses of either placebo, 5 mg, or 10 mg oral THC on three separate days. All subjects underwent a procedure in which an electronic barostat and a rectal balloon were used in order to evoke rectal pressure, combined with noxious sigmoid stimulation in order to increase visceral perception. The main variable of interest was the self-reported (using a 6-point scale) threshold for discomfort and pain during rectal distension before and after sigmoid stimulation. The results were not promising, as THC did not decrease visceral perception to rectal distension in any of the subjects groups. It was concluded that THC may not be the best treatment for reducing visceral sensitivity in IBS patients. Observed AEs were mild and occurred mostly at the highest dose (10 mg THC). Participants reported increased awareness of their surroundings (80% in the IBS group, 58% in the volunteers group), light-headedness (60% IBS, 42% volunteers) and sleepiness (50% IBS, 67%

volunteers). AEs in the 5 mg THC condition could only be observed in the healthy volunteers group: sleepiness (50%), mildly increased awareness (25%), and light-headedness (7%).

Another between-group study by Wong et al. (2012) inquired into the effect of oral THC capsules on gut transit in IBS-D patients and genetic variations which may act as modulators of this process. Thirty-six patients were administered placebo (n=13), 2.5 mg (n=10) or 5 mg of THC (n=13) twice daily, for 2 days. Gastric, small bowel, and colonic transit was examined by radioscintigraphy, and FAAH and CNR1 genetic variants were genotyped. The results did not reveal significant effects of oral THC on any of the measures. However, the CNR1 rs806378 CT/TT polymorphism was suggested to be related to a moderate delay in colonic transit, as compared to the CC genetic variant. It was suggested that neither of the THC doses had impact on gut transit in IBS-D, however, a genotype effect was suggested to be a moderating factor that might allow to identify a IBS-D patient subgroup that may respond more positively to cannabinoid therapy. Although AEs were not reported in detail, it seemed that the groups did not significantly differ from each other in terms of observed AEs.

4. Crohn's disease

4.1. Inhaled cannabis

A single study by Naftali et al. (2013) looked into the impact of smoked cannabis on induction of remission in patients with Crohn's disease. A between-group design was used in which 21 treatment-resistant patients were administered cannabis cigarettes twice daily containing herbal cannabis with a total dose of 115 mg THC (n=11) or placebo (n=10) for a period of 8 weeks. The main variable of interest was the Crohn's Disease Activity Index (CDAI) which is an indicator of remission. Although the results demonstrated that 5 subjects in the cannabis condition and 1 subject in the placebo condition entered clinical remission, the groups did not significantly differ from each other. Nevertheless, the cannabis group was still associated with a significant decrease of 100 points in CDAI scores after 8 weeks of treatment. In spite of the relatively high THC dose, there were no significant differences between the occurrences of AEs between the two groups, with sleepiness, nausea and confusion being the main ones.

5. Appetite and chemosensory perception

5.1. Oral THC

Brisbois et al. (2011) inquired into whether oral THC can enhance taste and smell (chemosensory) perception, including appetite, caloric intake, and quality of life (QOL) in cancer patients with chemosensory alterations. Twenty-one cancer patients completed this between-group study and were administered either oral THC (2.5 mg THC capsules, n=24) or placebo (n=22) two times daily for a period of 18 days. Over the course of the study, subjects were llowed to increase their dose to a total of 20 mg THC per day. All the measures included self-report forms. The results showed that THC, in comparison with placebo, enhanced chemosensory perception, macronutrient preference, appeal of foods, appetite, relaxation, and sleep quality of the patients. The AEs were minor and did not differ significantly between the groups (nausea/vomiting being the main one). However, there was one possible THC treatment-related SAE (irregular heartbeat). Consequently, it was concluded that oral THC is a well-tolerated drug that may palliate chemosensory alterations and increase food satisfaction and enjoyment.

5.2. Inhaled cannabis

A study by Riggs et al. (2012) evaluated whether smoking cannabis leads to changes in appetite-related hormones among HIV-infected male patients. Seven patients were administered cannabis joints 4 times daily for a period of 5 days, each with an individualized dose which was optimized during an initial titration session (using joints with a concentration range between 1% to 8% THC). The drugs were given in a crossover manner, with a 2-week washout period in between. The variables of interest were the concentrations of the appetite hormones ghrelin, leptin, PYY and insulin, as determined by analysis of blood samples. The results indicated that cannabis administration led to significant increases in plasma concentrations of ghrelin and leptin, and reductions in PYY, as compared to placebo. There were no effects on insulin levels. The authors concluded that the findings point to the modulation of appetite hormones through the endocannabinoid system. No AEs were reported.

6. Chemotherapy-induced nausea and vomiting

6.1. Oral cannabis

A single between-group investigation evaluated the potential of Sativex for decreasing chemotherapy-induced nausea and vomiting (CINV) in treated cancer patients (Duran et al. 2010). Sixteen patients with CINV were administered THC/CBD oromucosal spray (n=7) or placebo (n=9) for a period of 4 days (following a chemotherapy cycle) during which they self-titrated their dosage (up to maximum 48 sprays per day). Structured interviews, subject diaries, self-report questionnaires and visual analog scales were used to assess symptoms in the patients. The results pointed to a significantly higher proportion of subjects in the active condition demonstrating a complete response to treatment (defined as no vomiting and a mean nausea VAS score of ≤10mm on a 100mm scale). The AEs were rather mild, with somnolence, fatigue and dry mouth being the most common ones. Nonetheless, there were 2 AEs that were considered somewhat severe: one participant in the Sativex group and one in the placebo group experienced severe fatigue and mild somnolence and dysgeusia with vomiting. It was concluded that THC/CBD oromucosal

spray may be a safe and promising treatment for CINV that needs further confirmation in future trials.

7. Pulmonary disease

7.1. Oral cannabis

Pickering et al. (2011) inquired into the effects of Sativex on pulmonary ventilation and breathlessness. Five healthy volunteers and four chronic obstructive pulmonary disease (COPD) patients were administered a single dose of THC/CBD oromucosal spray or placebo in a crossover manner (up to 4 sprays). Breathlessness was induced by inhalation of fixed carbon dioxide loads. The measurements included self-reported breathlessness indicators, mood and activation, end-tidal carbon dioxide tension and ventilatory parameters. The results did not show any differences between the two conditions in terms of breathlessness scores or any respiratory evaluations. However, COPD patients reported fewer descriptions of the unpleasantness of the breathlessness procedure (pre-defined phrases to describe their sensation of breathlessness). The authors concluded that the addition of respiratory descriptors might be useful in the evaluation of drug effects on breathlessness. In case of AEs, one healthy subject experienced drowsiness, one COPD patient reported confusion and another COPD patient experienced transient cardiac dysrhythmia.

8. Cannabis dependence

8.1. Oral cannabis

Research by Allsop et al. (2014) investigated the efficacy of Sativex on treating cannabis dependence and withdrawal using a between-group design. Fifty-one patients with DSM-IV-TR cannabis dependence were administered increasing doses of THC/CBD oromucosal spray (up to 32 sprays per day) for a period of 6 days. The Cannabis Withdrawal Scale (CWS) was used as the measure of severity of cannabis withdrawal and cravings. Retention in the withdrawal treatment and AEs were also included as main variables of interest. The results showed that THC/CBD oromucosal spray significantly decreased CWS scores (average 66% reduction from baseline), as compared to placebo (average 52% increase from baseline) during the treatment. Subjects in the active group reported lower withdrawal-related irritability, depression, and cannabis cravings. In addition, they were more likely to stay in treatment, in comparison to participants in the placebo condition. In contrast, there were no significant differences between the two conditions in terms of number of AEs. In sum, the results were considered as a promising basis for further evaluation of the effectiveness of THC/CBD oromucosal spray for treating cannabis dependence.

8.2. Oral THC

A between-group study by Levin et al. (2011) investigated the effect of oral THC on treating cannabis addiction in 156 patients with DSM-IV-TR cannabis dependence. Subjects received either placebo or 20 mg oral THC twice daily for the period of 12 weeks. They were then required to provide urine samples, complete self-report instruments and have their vital signs and AEs evaluated twice daily. Treatment retention was significantly higher at the end of the study for the oral THC condition (77%), compared to placebo (61%). Moreover, withdrawal symptoms were significantly decreased in the oral THC group, compared to placebo. Although both conditions displayed a decrease in cannabis use over time, there were no significant differences between the groups. As for treatment-related AEs, four instances of drowsiness were observed (2 in the THC group and 2 in the placebo group), four patients reported feeling overly intoxicated (3 THC, 1 placebo), two reported heightened blood pressure (both THC), two reported nightmares and sleep disturbances (1 THC, 1 placebo), and one reported light-headedness (THC). It was concluded that oral THC is a well-tolerated, promising treatment for cannabis dependence that can enhance treatment retention and decrease withdrawal symptoms.

9. Anxiety

9.1. Oral CBD

A crossover investigation by Crippa et al. (2011) was conducted to examine the effects of oral purified CBD on generalized social anxiety disorder (SA). Ten SA patients were administered 400 mg of CBD or placebo at two separate visits, at which their regional cerebral blood flow (rCBF) was measured using 99mTc-ethylcysteinate dimer (ECD) Single Photon Emission Computed Tomography (SPECT), combined with self-assessments of subjective effects. The results displayed that CBD was related to significantly reduced subjective anxiety, decreased ECD uptake in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus, and enhanced ECD uptake in the right posterior cingulate gyrus. The authors suggested that CBD may decrease anxiety in SA and that this may be associated with its' effects on activity in limbic and paralimbic brain areas. There were no reported AEs.

A between-group study examined the impact of oral CBD on anxiety induced by a simulated public speaking test in SA patients and healthy controls (Bergamaschi et al. 2011). Twenty-four patients with SA were given either a single dose of 600 mg of oral CBD (n=12), or placebo (n=12). Twelve healthy volunteers did not receive any treatment (untreated control). All the groups participated in a simulation public speaking test (SPST) during which they completed subjective ratings on the Visual Analogue Mood Scale (VAMS) and Negative Self-Statement scales (SSPS-N). Additionally, physiological data (blood pressure, heart rate, and skin conductance) was obtained. The placebo SA condition displayed significantly increased anxiety ratings and more

Table 2. Studies on chronic pain

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Issa et al. (2014)	United States	Subjective effects in pain management	Placebo-controlled, double-blind, crossover study	Cannabis (smoked) and THC (oral) - single administration; 1.99% or 3.51% THC (smoked); 10 mg or 20 mg THC (oral)	30 chronic noncancer pain patients	Oral dronabinol had similar psychoactive effects to smoked marijuana
Lynch et al. (2014)	Canada	Neuropathic pain	Placebo-controlled, double-blind, crossover study	Sativex (sublingual) - 4 week treatment; maximum daily dosage: 12 sprays	16 patients with chemotherapy-induced neuropathic pain	Reduction in pain intensity
Serpell et al. (2014)	United Kingdom	Peripheral neuropathic pain associated with allodynia	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 14 week treatment; maximum daily dosage: 24 sprays	246 patients with peripheral neuropathic pain	Significant improvements in pain, sleep quality and subjective evaluations of patients.
Johnson et al. (2013)	United Kingdom	Chronic cancer pain	Follow-up, open-label study	Sativex and THC spray (sublingual) - long-term variable treatment; maximum daily dosage: 48 sprays	43 patients with chronic cancer pain	Long-term safety and effectiveness in pain reduction
Langford et al. (2013)	United Kingdom	Central neuropathic pain associated with MS	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 14 week treatment + 14 week open-label phase; maximum daily dosage: 12 sprays	339 patients with central neuropathic pain associated with MS	No significant difference between placebo and Sativex in Phase A; Phase B demonstrated an analgesic effect
Wilsey et al. (2013)	United States	Neuropathic pain	Placebo-controlled, double-blind, crossover study	Cannabis (vaporized) - single administration; 1.29% or 3.53% THC	39 patients with central and peripheral neuropathic pain	Reduction in pain. No difference in efficacy between the two doses
Portenoy et al. (2012)	United States	Chronic cancer pain	Placebo-controlled, double-blind, graded-dose, between-groups study	Sativex (sublingual) - 5 week treatment; maximum daily dosage: 16 sprays	263 patients with chronic cancer pain	Significant analgesic effects in secondary pain analyses when added to standard opioid therapy
Johnson et al. (2010)	United Kingdom	Chronic cancer pain	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) and THC spray (sublingual) - 2 week treatment; maximum daily dosage: 48 sprays	177 patients with chronic cancer pain	Significant reduction in pain severity when added to standard opioid therapy

Selvarajah et al. (2010)	United Kingdom	Painful diabetic peripheral neuropathy	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 12 week treatment; variable dosage	30 patients with painful DPN	No significant improvement over placebo. Depression suggested confounding factor
Rintala et al. (2010)	United States	Central neuropathic pain	Active-controlled, double-blind, crossover study	THC (oral) - 8 week treatment; maximum daily dosage: 20 mg THC	7 patients with neuropathic pain associated with spinal cord injury	Dronabinol not more effective than diphenhydramine for pain relief
Ware et al. (2010)	Canada	Chronic neuropathic pain	Placebo-controlled, double-blind, crossover study	Cannabis (smoked) - 14 day treatment; variable daily dosage: 75 mg plant material	21 patients with neuropathic pain	Significant pain reduction. Improved sleep and reduced anxiety

Table 3. Studies on multiple sclerosis

Study	**Country**	**Indication**	**Type of study**	**Study medication**	**Subjects**	**Efficacy**
Zajicek et al. (2013)	United Kingdom	Progressive MS	Placebo-controlled, double-blind, between-groups study	THC (oral) - 36 month treatment; maximum daily dosage: 28 mg THC	493 patients with progressive MS	No overall treatment effect on clinical disease progression
Corey-Bloom et al. (2012)	United States	Spasticity in MS	Placebo-controlled, double-blind, crossover study	Cannabis (smoked) - 3 day treatment; 4 % THC, 800 mg plant material	30 patients with MS and spasticity	Significant reduction in spasticity and pain
Zajicek et al. (2012)	United Kingdom	Stable MS	Placebo-controlled, double-blind, between-groups study	Cannabis extract (oral) - 12 week treatment; maximum daily dosage: 25 mg THC	279 patients with stable MS	Significant reduction in muscle stiffness
Notcutt et al. (2012)	United Kingdom	Spasticity in MS	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 1 week baseline open-label treatment + 4 week double-blind treatment; variable dosage	36 patients with MS receiving benefits from using Sativex for spasticity for at least 12 weeks	Significant difference in time to treatment withdrawal in favor of Sativex
Novotna et al. (2011)	Czech Republic	Spasticity in MS	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 4 week single-blind treatment + 12 week double-blind treatment; maximum daily dosage: 12 sprays	241 patients with MS and spasticity	Significant reduction in spasticity in patients showing adequate response to Sativex in initial study phase

Collin et al. (2010)	United Kingdom	Spasticity in MS	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 14 week treatment; maximum daily dosage: 24 sprays	337 patients with MS and spasticity	Significant reduction in treatment-resistant spasticity
Kavia et al. (2010)	United Kingdom	Bladder dysfunction in MS	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 8 week treatment; maximum daily dosage: 48 sprays	135 patients with MS and overactive bladder	No significant reduction in number of urinary incontinence episodes. Beneficial effects on other bladder symptoms

Table 4. Studies on irritable bowel syndrome

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Wong et al. (2012)	United States	Colonic transit in IBS	Placebo-controlled, double-blind, between-groups study	THC (oral) - 2 day treatment; daily dosage: 5 mg or 10 mg THC (twice daily)	36 patients with IBS	No significant effects on gut transit
Klooker et al. (2011)	The Netherlands	Rectal sensitivity in IBS	Placebo-controlled, double-blind, crossover study	THC (oral) - single administration; maximum dosage: 10 mg THC	10 patients with IBS; 12 healthy controls	No significant effects of THC on visceral hypersensitivity
Wong et al. (2011)	United States	Colonic motility and sensation in IBS	Placebo-controlled, double-blind, between-groups study	THC (oral) - single administration; 2.5 mg or 5 mg THC	75 patients with IBS	Reduction in fasting colonic motility in subgroup of patients

Table 5. Studies on Crohn's disease

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Naftali et al. (2013)	Israel	Pain in Crohn’s disease	Placebo-controlled, double-blind, between-groups study	Cannabis (smoked) - 8 week treatment; daily dosage: 115 mg THC	21 patients with Crohn's disease	Cannabis produced significant clinical benefits to 10 of 11 patients with active Crohn’s disease. Induction of remission was not achieved

Table 6. Studies on appetite and chemosensory perception

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Riggs et al. (2012)	United States	Appetite hormones in HIV-infected men	Placebo-controlled, double-blind, crossover study	Cannabis (smoked) - 10 day treatment; maximum daily dosage: four 8% THC cigarettes	7 patients with HIV infection	Significant alterations in appetite hormones
Brisbois et al. (2011)	Canada	Reduced appetite and chemosensory alterations in cancer	Placebo-controlled, double-blind, between-groups study	THC (oral) - 18 day treatment; maximum daily dosage: 20 mg THC	21 cancer patients with chemosensory alterations	Significant improvement of chemosensory perception and appetite

Table 7. Studies on chemotherapy-induced nausea and vomiting

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Duran et al. (2010)	Spain	Chemotherapy-induced nausea and vomiting	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 4 day treatment; maximum daily dosage: 48 sprays	16 cancer patients with CINV	Significantly improved protection against delayed CINV when added to standard antiemetic therapy

Table 8. Studies on pulmonary disease

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Pickering et al. (2011)	United Kingdom	Breathlessness	Placebo-controlled, double-blind, crossover study	Sativex (sublingual) - single administration; maximum dosage: 4 sprays	4 patients with COPD; 5 healthy controls	No reduction in breathlessness, but reduction in unpleasantness of symptoms

Table 9. Studies on cannabis dependence

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Allsop et al. (2014)	Australia	Cannabis withdrawal symptoms	Placebo-controlled, double-blind, between-groups study	Sativex (sublingual) - 6 day treatment; maximum daily dosage: 86.4 mg THC, 80 mg CBD	51 patients with DSM-IV-TR cannabis dependence	Significant reduction in severity and time course of cannabis withdrawal symptoms

Levin et al. (2011)	United States	Cannabis withdrawal symptoms	Placebo-controlled, double-blind, between-groups study	THC (oral) - 12 week treatment; maximum daily dosage: 40 mg THC	156 patients with DSM-IV-TR cannabis dependence	Significant improvement in treatment retention and withdrawal symptoms

Table 10. Studies on anxiety

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Das et al. (2013)	United Kingdom	Fear extinction and consolidation	Placebo-controlled, double-blind, between-groups study	CBD (vaporized) - single administration; 32 mg CBD	48 healthy subjects	CBD administered post-extinction enhanced consolidation of extinction. No acute effects of CBD were found on extinction
Bergamaschi et al. (2011)	Brazil	Anxiety associated with public speaking	Placebo-controlled, double-blind, between-groups study	CBD (oral) - single administration; 600 mg CBD	24 patients with SAD; 12 healthy controls	Significant reduction in anxiety, discomfort and cognitive impairment
Crippa et al. (2011)	Brazil	rCBF in social anxiety	Placebo-controlled, double-blind, crossover study	CBD (oral) - single administration; 400 mg CBD	10 patients with SAD	Reduction in anxiety associated with altered activity in limbic and paralimbic brain areas

Table 11. Studies on psychosis

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Leweke et al. (2012)	Germany	Psychotic symptoms	Active-controlled, double-blind, between-groups study	CBD (oral) vs. amisulpride - 4 week treatment; maximum daily dosage: 800 mg CBD	42 patients with DSM-IV-TR schizophrenia	Significant antipsychotic effects of CBD

Table 12. Studies on Parkinson's disease

Study	Country	Indication	Type of study	Study medication	Subjects	Efficacy
Chagas et al. (2014)	Brazil	Parkinson's disease: motor functioning, neuroprotection and well-being	Placebo-controlled, double-blind, between-groups study	CBD (oral) - 6 week treatment; daily dosage: 75 mg or 300 mg CBD	21 patients with idiopathic PD	Significant improvement in well-being. No effects on motor functioning or neuroprotection

pronounced cognitive impairment, discomfort, and alertness, in comparison with the untreated control group. In contrast, CBD significantly decreased anxiety, cognitive impairment, and discomfort during speech performance in SA patients. Moreover, CBD led to a significant reduction in anticipatory speech alert. In general, similar effects were observed both in the CBD-SA group, as well as in the healthy volunteer condition. It was concluded that a single dose of CBD can decrease the anxiety induced by SPST in SA patients, suggesting a beneficial effect of the drug on fear of speaking in public. No AEs were observed, which is in line with other studies using higher doses of CBD.

9.2. Inhaled CBD

In an experiment with 48 healthy participants who underwent a fear-conditioning test CBD enhanced consolidation of subsequent fear extinction learning and thus may be helpful in anxiety disorders (Das et al. 2013). Participants received a single dose of 32 mg vaporized CBD either before or after extinction in a between-group design. Successful fear conditioning and extinction were found in both treatment groups. CBD given post-extinction enhanced memory consolidation of extinction learning. No acute effects of CBD were found on extinction. There were no adverse events reported.

10. Psychosis

10.1. Oral CBD

Leweke et al. (2012) conducted an active-controlled between-group study into the effects of oral CBD on symptoms of psychosis in DSM-IV-TR schizophrenia patients. A total of 42 subjects were administered daily doses of either 800 mg oral CBD or amisulpride (a dopamine receptor antagonist) for the period of 4 weeks (starting with a dose of 200 mg and titrating up in the first week). The main measures included the scores of the Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Symptoms Scale (PANSS), which were administered at baseline, and at day 14 and day 28 of treatment. Both groups were found to display significant enhancements in clinical symptoms, while CBD was found not to produce side-effects typical of amisulpride. Moreover, the decrease in psychotic symptoms following CBD administration was associated with an increase in serum anandamide levels. In sum, the authors suggested that the inhibition of anandamide deactivation might play a role in the antipsychotic impact of CBD, potentially highlighting a new mechanism for treating schizophrenia.

11. Parkinson's disease

11.1. Oral CBD

One between-group investigation into the effectiveness of CBD for treating Parkinson's disease (PD) included 21 patients with PD without dementia or comorbid psychiatric disorders (Chagas et al. 2014). Three groups of 7 subjects each received either placebo, 75 mg, or 300 mg of oral CBD per day for a period of 6 weeks. Evaluations were done at baseline and in the last week of the dosage regimen. The main variables of interest were scores regarding motor and general symptoms (UPDRS), well-being and quality of life (PDQ-39), and potential neuroprotective effects (BDNF and H1-MRS). The 300 mg CBD group was found to differ significantly from placebo only in case of the PDQ-39. It was concluded that CBD has the potential to enhance the quality of life of PD patients without psychiatric comorbidities, however, no neuroprotective or motor effects of CBD were found. There were no observed AEs.

Discussion on the state of cannabis research in medicine

In recent years, the medical use of herbal cannabis has gained unprecedented attention worldwide. Despite the fact that limited clinical data is available for most medical indications, multiple countries have introduced legislation, and sometimes entire government supported programs, to provide patients access to cannabis-based medicine. The Netherlands, Canada and Israel have had such programs already for many years, while Australia, Uruguay, Chile, Jamaica, Czech Republic, Croatia, Italy and Germany are just a few of the more recent examples. In other countries such as Spain and Portugal patients may use the national laws, which allow possession of cannabis for personal use to enable self-medication.

Given the limited clinical research on cannabis and cannabinoids in many indications, patients, physicians, scientists and policy-makers in many countries alike struggle with the task to make responsible choices regarding administration forms, dosing regimen, cannabis botanical variety, and long-term effects. Further properly designed clinical trials are needed to provide more information on these questions.

What makes cannabinoids particularly fascinating is the wide range of possible therapeutic effects they are claimed to have. Currently, cannabis and cannabinoids are being used by patients for treatment of anything ranging from pain, cancer and epilepsy, to sleep, depression and anxiety, from attention deficit/hyperactivity disorder (ADHD), autism, cluster headaches and Crohn's disease to irritable bowel syndrome, restless legs syndrome and Tourette‘s syndrome, (Grotenhermen et al. 2015; Hazekamp et al. 2013). But despite the major promise these compounds seem to hold, in the period 2010-2014 (see Table 1) significant clinical data has only been added for multiple sclerosis (1515 patients in total) and chronic pain (1211 patients). Compared to

our previous review of the period 2005-2009 (Hazekamp and Grotenhermen 2010) an increase can be observed mainly in the number of patients included in pain trials. Consequently, it seems that the investigation of the effects of cannabinoids on different types of chronic pain (central and peripheral neuropathic pain, cancer pain, etc.) is currently of major interest to the cannabinoid research field. Indeed, all cannabinoid-based drugs covered in this review have been studied in at least one trial addressing some type of pain. Interestingly, surveys performed among medicinal cannabis users usually indicate pain as the main indication for which cannabis is used (Hazekamp and Pappas 2014).

It has recently been suggested that THC may target the affective quality of pain, instead of simply reducing pain intensity and hyperalgesia (de Vries et al. 2014). If such is the case, it would seem interesting to also explore the analgesic potential of CBD - a cannabinoid not commonly associated with pain reduction. After all, aside of the anxiolytic effects discussed in this review (Bergamaschi et al. 2011; Crippa et al. 2011; Das et al. 2013), CBD has been suggested to affect emotional processing through modulation of the activity of the anterior cingulate cortex (Kowal et al. 2013), and enhance emotional facial recognition (Hindocha et al. 2015). As a result, such emotion-regulating properties of CBD allow us to speculate whether this cannabinoid may also be beneficial in targeting the affective qualities of pain. Possibly, it may prove to modulate the effects of THC in this regard.

Potential interactions between THC and CBD is only one example to show the complexity of performing studies on cannabinoid-based drugs - especially those containing whole-plant cannabis extracts. Evidence indicates that the synergy of different compounds present in cannabis defines the final effect of the drug in various aspects (Russo 2011). Consequently, researchers, patients and physicians should keep in mind the complete composition of the cannabinoid-based drug that they are interested in - not only the amounts of specific cannabinoids such as THC or CBD. Possibly, subtle differences in composition may significantly affect the usefulness of the drug in treating specific medical conditions.

Conclusion

By providing a clear overview of the design, outcomes and side effects of clinical trials performed with cannabis and cannabinoids, this review hopes to inspire the development of more and better trials in the future. Currently, the clinical researchers' toolbox contains a wide range of cannabinoid-based drugs, including single cannabinoids (Marinol, Dronabinol, CBD), plant-based extracts (Sativex, Cannador), herbal cannabis (NIDA, Bedrocan), and synthetic analogues (Nabilone, various others not covered in this review). Taken together, clinical experiences with these compounds may provide us further knowledge on the indications for cannabinoid based medicines.

References

1. Allsop DJ, Copeland J, Lintzeris N, Dunlop AJ, Montebello M, Sadler C et al. Nabiximols as an agonist replacement therapy during cannabis withdrawal. JAMA Psychiatry. 2014;71(3):281.
2. Ben Amar M. Cannabinoids in medicine: A review of their therapeutic potential. Journal of Ethnopharmacology. 2006;105(1-2):1-25.
3. Bergamaschi MM, Queiroz RHC, Chagas MHN, de Oliveira DCG, De Martinis BS, Kapczinski F et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. Neuropsychopharmacology. 2011;36(6):1219-1226.
4. Brisbois TD, de Kock IH, Watanabe SM, Mirhosseini M, Lamoureux DC, Chasen M et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. Annals of Oncology. 2011;22(9):2086-2093.
5. Chagas MHN, Zuardi AW, Tumas V, Pena-Pereira MA, Sobreira ET, Bergamaschi MM et al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial. Journal of Psychopharmacology. 2014;28(11):1088-1098.
6. Collin C, Ehler E, Waberzinek G, Alsindi Z, Davies P, Powell K et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. Neurological Research. 2010;32(5):451-459.
7. Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. Canadian Medical Association Journal. 2012;184(10):1143-1150.
8. Crippa JA, Derenusson GN, Ferrari TB, Wichert-Ana L, Duran FL, Martin-Santos R et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. Journal of Psychopharmacology. 2011;25(1):121-130.
9. Das RK, Kamboj SK, Ramadas M, Yogan K, Gupta V, Redman E et al. Cannabidiol enhances consolidation of explicit fear extinction in humans. Psychopharmacology. 2013;226(4):781-792.
10. de Vries M, van Rijckevorsel DC, Wilder-Smith OH, van Goor H. Dronabinol and chronic pain: importance of mechanistic considerations. Expert Opinion on Pharmacotherapy. 2014;15(11):1525-1534.
11. Duran M, Pérez E, Abanades S, Vidal X, Saura C, Majem M et al. Preliminary efficacy and

safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. British Journal of Clinical Pharmacology. 2010;70(5):656-663.
12. ElSohly M, Gul W. Constituents of Cannabis sativa. In: Pertwee R. (ed.) Handbook of Cannabis. 1st ed. Oxford: Oxford University Press; 2014.
13. Grotenhermen F, Berger M, Gebhardt K. Cannabidiol. Solothurn: Nachtschatten; 2015.
14. Hazekamp A, Grotenhermen F. Review on clinical studies with cannabis and cannabinoids 2005-2009. Cannabinoids. 2010;5:1-21.
15. Hazekamp A, Pappas G. Self-medication with cannabis. In: Pertwee R. (ed.) Handbook of Cannabis. 1st ed. Oxford: Oxford University Press; 2014.
16. Hazekamp A, Ware MA, Muller-Vahl KR, Abrams D, Grotenhermen F. The medicinal use of cannabis and cannabinoids—an international cross-sectional survey on administration forms. Journal of Psychoactive Drugs. 2013;45(3):199-210.
17. Hindocha C, Freeman TP, Schafer G, Gardener C, Das RK, Morgan CJ et al. Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: A randomized, double-blind, placebo-controlled study in cannabis users. European Neuropsychopharmacology. 2015;25(3):325-334.
18. Issa MA, Narang S, Jamison RN, Michna E, Edwards RR, Penetar DM et al. The subjective psychoactive effects of oral dronabinol studied in a randomized, controlled crossover clinical trial for pain. The Clinical Journal of Pain. 2014;30(6):472-478.
19. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. Journal of Pain and Symptom Management. 2010;39(2):167-179.
20. Johnson JR, Lossignol D, Burnell-Nugent M, Fallon MT. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. Journal of Pain and Symptom Management. 2013;46(2):207-218.
21. Kavia R, De Ridder D, Constantinescu C, Stott C, Fowler C. Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. Multiple Sclerosis. 2010;16(11):1349-1359.
22. Klooker TK, Leliefeld KEM, Van Den Wijngaard RM, Boeckxstaens GE. The cannabinoid receptor agonist delta-9-tetrahydrocannabinol does not affect visceral sensitivity to rectal distension in healthy volunteers and IBS patients. Neurogastroenterology & Motility. 2011;23(1):30-e2.
23. Kowal MA, Hazekamp A, Colzato LS, van Steenbergen H, Hommel B. Modulation of cognitive and emotional processing by cannabidiol: the role of the anterior cingulate cortex. Frontiers in Human Neuroscience. 2013;7.
24. Langford RM, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. Journal of Neurology. 2013;260(4):984-997.
25. Levin FR, Mariani JJ, Brooks DJ, Pavlicova M, Cheng W, Nunes EV. Dronabinol for the treatment of cannabis dependence: a randomized, double-blind, placebo-controlled trial. Drug and Alcohol Dependence. 2011;116(1-3):142-150.
26. Leweke FM, Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Translational Psychiatry. 2012;2(3):e94.
27. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. Journal of Pain and Symptom Management. 2014;47(1):166-173.
28. Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM. Cannabis induces a c1inical response in patients with Crohn's disease: a prospective placebo-controlled study. Clinical Gastroenterology and Hepatology. 2013;11(10):1276-1280.e1.
29. Notcutt W, Langford R, Davies P, Ratcliffe S, Potts R. A placebo-controlled, parallel-group, randomized withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex® (nabiximols). Multiple Sclerosis Journal. 2012;18(2):219-228.
30. Novotna A, Mares J, Ratcliffe S, Novakova I, Vachova M, Zapletalova O et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. European Journal of Neurology. 2011;18(9):1122-1131.
31. Pickering EE, Semple SJ, Nazir MS, Murphy K, Snow TM, Cummin AR et al. Cannabinoid effects on ventilation and breathlessness: a pilot study of efficacy and safety. Chronic Respiratory Disease. 2011;8(2):109-118.
32. Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S et al.

Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. The Journal of Pain. 2012;13(5):438-449.
33. Riggs PK, Vaida F, Rossi SS, Sorkin LS, Gouaux B, Grant I et al. A pilot study of the effects of cannabis on appetite hormones in HIV-infected adult men. Brain Research. 2012;1431:46-52.
34. Rintala DH, Fiess RN, Tan G, Holmes SA, Bruel BM. Effect of dronabinol on central neuropathic pain after spinal cord injury. American Journal of Physical Medicine & Rehabilitation. 2010; 89(10):840-848.
35. Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Medical Hypotheses. 2006;66(2):234-246.
36. Russo E. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. British Journal of Pharmacology. 2011;163(7):1344-1364.
37. Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care. 2010;33(1):128-130.
38. Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. EJP. 2014;18(7):999-1012.
39. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. Canadian Medical Association Journal. 2010;182(14):E694-E701.
40. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. The Journal of Pain. 2013;14(2):136-148.
41. Wong BS, Camilleri M, Busciglio I, Carlson P, Szarka LA, Burton D et al. Pharmacogenetic trial of a cannabinoid agonist shows reduced fasting colonic motility in patients with nonconstipated irritable bowel syndrome. Gastroenterology. 2011;141(5):1638-1647.e7.
42. Wong BS, Camilleri M, Eckert D, Carlson P, Ryks M, Burton D et al. Randomized pharmacodynamic and pharmacogenetic trial of dronabinol effects on colon transit in irritable bowel syndrome-diarrhea. Neurogastroenterology & Motility. 2012;24(4):358-e169.
43. Zajicek JP, Ball S, Wright D, Vickery J, Nunn A, Miller D et al. Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial. The Lancet Neurology. 2013;12(9):857-865.
44. Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG. MUltiple Sclerosis and Extract of Cannabis: results of the MUSEC trial. Journal of Neurology, Neurosurgery & Psychiatry. 2012; 83(11):1125-1132.