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ORIGINAL ARTICLE

The Role of Cannabis, Cannabidiol and Other Cannabinoids in Chronic Pain. The Perspective of Physicians

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Abstract

Currently, there is a renewed interest in treatments with medical cannabis and cannabinoids. Based on an increasing number of publications over the last decades that permitted new insights into mechanisms, efficacy and safety of cannabinoids, the use of cannabinergic medications is authorised in an increasing number of European and non-European countries. The alleviation of chronic, painful conditions is, since thousands of years, one of the primary reasons for the use of cannabis. Depending on the country, a wide range of medicinal cannabis preparations are available:ranging from defined cultivars of medical cannabis, mainly varying in their THC:CBD ratio, that are inhaled or taken as whole plant extracts,to highly purified single cannabinoids, such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD),or mixtures of two enriched extracts, standardised to a 1:1 ratio of THC:CBD (nabiximols). Although conflicting opinions continue to exist, the majority of reviews in the past concluded that medical cannabis and cannabinoids play a significant role in the management of pain. Surprisingly, systematic studies to date do not support an "entourage effect" of the other plant constituents of cannabis (mainly terpenoids) in treatment of chronic pain. An emerging cannabinoid is CBD which is the only cannabinergic medication available at present that does not cause the typical "cannabis high"; it is not a "controlled substance". However, despite years of research, there is either no study or no well-conducted, head-to-head, comparison available between different cannabis cultivars, between pure cannabinoids, and between pure cannabinoids and extracts. It remains unanswered which is the optimal treatment approach.

Keywords Cannabis · Cannabinoids · Cannabidiol · Delta-9-tetrahydrocannabinol · Opioids

Abbreviations

CND	Commission on Narcotic Drugs (the UN's central drug policy-making body)
ECDD	Expert Committee on Drug Dependence (WHO)
EMA	European Medicines Agency
EO	Essential oil
FDA	Food and Drug Administration (US)
MS	Multiple sclerosis
NRS	Numerical rating scale
VAS	Visual analogue scale

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Introduction

Chronic pain is a very frequent condition, affecting approximately 20% of the worldwide population. Pain is regarded as chronic when it lasts or recurs for more than 3 to 6 months; it persists beyond normal healing time. The most important diseases or clinical conditions associated with chronic pain are primary pain, cancer pain, postsurgical or posttraumatic pain, neuropathic pain, headache, orofacial pain, musculoskeletal pain and visceral pain. Particularly in the case of chronic pain, a multifactorial therapeutic approach is necessary to achieve the desired goals.

Pain relief (analgesia) or decreased pain sensitivity (antinociception) since ancient times is one of the most commonly-cited therapeutic effects of smoking cannabis, the use of which can be traced back thousands of years. It is often the last option patients seek who are suffering. As chronic pain increasingly occurs in elderly subjects, it is even more important to deliver analgesia with minimal risk of adverse drug reactions. Unfortunately, almost 50% of all

patients experience inadequate pain relief and serious side effects with nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, both being the mainstay of pain treatment.

The use of cannabis (as the whole plant or extract of the plant) should be clearly separated from the use of pure cannabinoids. Cannabis is not a defined "substance". It is estimated that over 1,200 cultivars may exist that differ not only in their content of the two main cannabinoids, cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) but also in their profile of other cannabinoids and phytosubstances, namely terpenes and polyphenols known to be pharmacologically active (de la Fuente et al. 2019; Nahler 2019). Cannabis may contain more than 750 different phytosubstances (Upton 2014). Articles referring to or describing the effects of "cannabis" very often lack details about the profile of phytocompounds so that the results of different publications cannot easily be compared. Cannabis can be divided into three main categories, cannabis dominant in THC/low in CBD (slang name "marijuana", correct term: drug-type- or Type I cannabis), cannabis with a "mixed" ratio of CBD to THC (mixed or hybrid type/type II cannabis) and cannabis high in CBD/low in THC ("hemp-" or "fibre-type"/ type III) (Nahler 2019). In contrast to "street cannabis", medical (pharmaceutical grade) cannabis has a relatively standardised and controlled composition; most often it is used as dried flowers (flos) which are smoked or vaporised. Nonetheless, batch to batch variations can still be observed (Hueber 2004; Maida 2017; Namdar 2018). Differences in temperatures during the production process, individual inhalation techniques and a high inter-subject variability of oral bioavailability add further to the variability of blood levels and effects. In addition to inhalation, flowers of medical cannabis, rarely also leaves, are extracted and dispensed as "magisterial" / "specials" preparations.

In contrast, "CBD-oils" ("Hemp-oils"), "full-spectrum oils" or THC-dominant "Rick Simpson oils" are usually not derived from pharmaceutical grade cannabis; they are ill-defined but popular over-the-counter products often of poor,non reproducible, quality varying widely in their manufacturing and composition (Vandrey et al. 2015; Ruth et al. 2016; Bonn-Miller et al. 2017; Pavlovic et al. 2018). In addition, numerous studies have demonstrated that their active ingredient content is often not correctly declared in more than a third of such commercial extracts (The CBD content is usually overstated and the THC-content understated); Such products may contain impurities such as pesticides, mold or bacterial toxins, solvent residues and heavy metals (Corey-Bloom et al. 2012; Bernhrd 2016; Liebling 2020; McGregor et al. 2020). In fact cannabis plants can extract heavy metals from the soil and have even be used to clean contaminated soils (Linger et al. 2002). In contrast to pharmaceutical products, their manufacture and quality is not routinely controlled by Regulatory authorities. For some products, If the recommended daily intake is exceeded, this can trigger psychotomimetic and other toxic effects.

Pure pharmaceutical cannabinergic products such as CBD, dronabinol, nabilone or nabiximols clearly differ from the abovementioned medical cannabis or "street products". Synthetic THC (dronabinol) received marketing authorisation in 1985 by the US FDA; pure phyto-CBD in June 2018 (FDA) and September 2019 (European Community). Nabilone which is a synthetic cannabinoid with similar properties to THC was authorised in 1985. Nabiximols which is also a cannabis product, is not a pure substance but a mixture of two extracts standardised to a 1:1 ratio of THC:CBD and containing up to 35% of other phytosubstances. It received marketing authorisation first in Canada in 2005. Although all being cannabinoids, since the above mentioned products differ in their composition and hence pharmacological properties, they should not be substituted. CBD is the only substance currently available for treatment which is not a "controlled substance", and not inducing the typical "high" of cannabis and positive drug tests, even in high doses.

There are many published reviews of the treatment of pain with cannabinergic medicines, e.g.,(Iskedjian et al. 2007; Rahn and Hohmann 2009; Aggarwal 2013; Andreae et al. 2015; Lynch and Ware 2015; Petzke et al. 2016; (NASEM) 2017; Aviram and Samuelly-Leichtag 2017; Blake et al. 2017; Häuser et al. 2017; Lötsch et al. 2018; Mücke et al. 2018; Stockings et al. 2018; Vučković et al. 2018; Fitzcharles et al. 2020; Haleem and Wright 2020; Johal et al. 2020; Rabgay et al. 2020; Wong et al. 2020; Chang et al. 2021) (Table 1). The majority conclude that cannabinoids had modest but empirically demonstrable and statistically significant pain-relieving effects, more for neuropathic than for non-neuropathic pain, in addition to improvements in sleep, and without serious adverse effects. However, the main problem with these reviews is that they pooled data from very different studies, with different cannabinergic preparations and heterogeneous populations. In fact, most reviews have assessed results across a broad range of treatments with THC, nabilone, CBD, THC + CBD or medical cannabis, in many cases assuming that these are camparable.

In the present article we summarise the available results of the above mentioned cannabinergic treatments, separately for each of them, focussing on CBD and head-to-head comparisons of cannabinergic medications where available.

Methods

Literature Search

This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses

Table 1 Important Systematic reviews and comments

Title (Reference)	Method	Intervention	Objectives/Primary endpoint	Results	Conclusion	Comment
Efficacy of cannabis-based medicines for pain management: a systematic review and meta-analysis of randomized controlled trials (Namdar 2018)	Systematic review and Meta analysis	Electronical search in Medline/ Pubmed and Google Scholar until July 2015. RCT´s which compared the analgesic effects of CBMs to Placebo	To update clinicaians and researchers knowledge in efficacy and adverse events of CBMs for chronic and postoperative pain treatment	43 RCT (2437 patients) included, 24 RCTs (1334 patients) eligible for meta analysis	Limited evidence in showing more pain reduction in chronic pain -0,61 (-0,78 to -0,43, p < 0,0001) especially by inhalation -0,93 (-1,51 to -0,35, p = 0,001) compared to placebo. Some RCTs showed a clinically significant improvement of pain scores of 2 points or more. Majority of studies did not show an effect. Most prominent AEs are related to the central nervous and the gastrointestinal system	Limited evidence. CBMs might be effective for chronic pain treatment
A selective review of medical cannabis in cancer pain management (Blake et al. 2017)	Systematic Review	Review on Medline between 1975 and 2017. RCT s that evaluate the effect of THC or CBD	To evaluate the efficiacy of cannabinoid based therapies containing THC and CBD for reducing cancer-associated pain	5 RCT (dosage between 2.7 and 43.2 mg/d THC and 0-40 mg/d CBD) Reported side effects are drowsiness, hypotension, mental clouding and nausea and vomiting	Evidence that medical cannabis reduces chronic or neuropathic pain in advanced cancer patients	Lack of statistical power
Cannabinoids in pain management and palliative medicine—an overview of systematic reviews and prospective observational studies (Häuser et al. 2017)	Systematic Review	Review in Cochrane Database, Database of Abstracs of Reviews of Effects and Medline between January 2009 and January 2017	Studies of the use of cannabinoids in pain management and palliative medicine	11 SR met the inclusion criteria; 3 with high and 8 of moderate methodological quality. Limited evidence for a benefit of THC/ CBD spray in the treatment of neuropathic pain. Inadequate evidence for any benefit of cannabinoids to treat cancer pain Central nervous and psychiatric side effects are reported		Public perception of the efficacy, tolerability and safety of cannabis based medicines in pain management and palliative care medicine conflicts with the findings of systematic reviews and prospective observational studies
Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials (Lynch and Ware 2015)	Systematic review	Literature search in PubMed, Embase, CINAHL, PsycInfo, Cochrane Library, ISI Web of Science, ABI Inform, Dissertation Abstracts, Academic Search Premier, Clinical Trials.gov, Trials Center.orgindividual pharmaceutical company trial sites, OAIster and Google Scholar between 2003 and 2010	RCTs comparing a cannabinoid with a placebo or active control group with primary outcome pain in subjects with chronic non-cancer pain	18 RCT s (total 766 patients). 15 trials demonstrated a significant analgesic effect. Four trials examined smoked cannabis	The studies demonstrates that cannabinoids are a modestly effective and safe treatment option for chronic non-cancer pain	More large scale trials of longer duration reporting on pain and level of function are required

Table 1 (continued)

Title (Reference)	Method	Intervention	Objectives/Primary endpoint	Results	Conclusion	Comment
Cannabis-based medicines for chronic neuropathic pain in adults (Mücke et al. 2018)	Systematic Review	Review in CENTRAL, Medline, Embase and two trial registries	To assess the efficacy, tolerability and safety of cannabis based medicines compared to placebo or conventional drugs for conditions with chronic neuropathic pain in adults	16 studies (1750 patients). Cannabis based medicines may increase number of people achieving 50% or greater pain relief (21% vs 17%). More patients withdrew from the studies due to adverse events with cannabis based medicines (10% vs 5%)	The potential benefits of cannabis based medicine in chronic neuropathic pain might be outwighted by their potential harms	Low evidence for most outcomes because of indirectness and inconsistent results
Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies (Stockings et al. 2018)	Systematic Review	Review in Medline, Embase, PsycInfo, CENTRAL and clinicaltrials.gov	Examines evidence for the effectiveness of cannabinoids in chronic noncancer pain	91 publications with 104 studies (9958 patients) were eligible. 30% pain reduction was achieved in 29% of cannabinoids vs 25,9% in placebo patients. Significant effect for cannabinoids (95% CI 15–61); 50% pain reduction 18,2%vs 14,4%, no significant difference	Evidence for effectiveness of cannabinoids in CNCP is limited	Effects suggest that number needed to treat to benefit is high and number needed to treat to harm is low. It seems unlikely that cannabinoids are highly effective medicines for CNCP
Efficacy and adverse effects of medical marijuana for chronic noncancer pain: systematic review of randomized controlled trials (Deshpande et al. 2015)	Systematic Review	Review in April 2014 in Medline and EMBASE	To determine if medical marijuana provides pain relief for patients with chronic noncancer pain and to determine the therapeutic dose, AE and specific indications	6 RCT (226 patients) were included. All studies had challenges with masking. Data could not be pooled. Experimental Sessions with short duration, reported statistically significant pain relief with nonserious side effects	Evidence for the use of low-dose medical marijuana in refractory neuropathic pain in conjunction with traditional analgesics	Trials are limitated by short duration, variability in dosing and strength of THC and lack of functional outcomes
Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review (Campbell et al. 2001)	Systematic Review	Search in October 1999 in Medline, Embase, Oxford Pain Database, Cochrane Database references from identified papers and hand searches	To establish whether cannabis is an effective and safe treatment option in the management of pain	9 trials included (222 patients). 5 trials related to cancer pain, 2 to chronic non malignant pain and 2 to acute postoperative pain. No randomised controlled trials evaluated cannabis	Cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the central nervous system	Further valid randomised controlled studies are needed before cannabinoids can be considered for treating spasticity and neuropathic pain
Benefits and Harms of Cannabis in Chronic Pain or Post-traumatic Stress Disorder: A Systematic Review (Kansagara et al. 2018)	Systematic review	Review in Medline, Embase, PsycInfo, EMB Reviews PILOTS and from grey literature sources	To show what are the effects of cannabis on health outcomes and healthcare utilization for adults with chronic pain	12 systematic reviews and 48 primary studies were included. No pooled data	A limited evidence on the potential benefits and harms of cannabis use in chronic pain populations was found. Low strength evidence was found for precisely defined THC:CBD content to improve neuropathic pain	Most studies are small, many have methodologic flaws, brief follow up duration

Table 1 (continued)

Title (Reference)	Method	Intervention	Objectives/Primary endpoint	Results	Conclusion	Comment
Cannabinoids for medical use: a systematic review and meta-analysis (Whiting et al. 2015)	Systematic review	28 databases from inception to April 2015	To conduct a review of the benefits and adverse events of cannabinoids	79 trials (6462 patients) were included. Cannabinoids were associated with a complete nausea and vomiting response (47% vs 20%, OR 3.82, 95% CI 1.55–9.42); reduction in pain (37% vs 31%, OR 1.41, 95% CI 0.99–2.0), reduction in NRS (-0.46, 95% CI -0.8 to -0.11). Increased risk of short term AEs like dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance and halluzination	There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity	Future studies should assess patient-relevant outcomes (including disease-specific end points, quality of life, and AEs) using standardized outcome measures at similar time points to ensure inclusion in future meta-analyses Pooled analysis of AEs was done
Medical cannabis for non-cancer pain: a systematic review (Butler 2015)	Systematic Review	Review in Medline, EMBASE, amed, and Cochrane Central Register of from inception to July, 2015	To show what are the benefits and harms of medical cannabis use	19 studies were included. Low-strength evidence suggested: No difference between nabiximols and placebo for pain improvement among patients with MS and central neuropathic pain. Improvement in neuropathic pain scale favors nabiximols over placebo among adults with peripheral neuropathic pain	When separated by specific treatments or patient populations, the evidence is generally insufficient to address whether a particular treatment works for a particular population. When the literature is examined as a whole, some patterns appear to signal that the hypothesis that medical cannabis could be beneficial to some patients is worth exploring. This position is consistent with the growing basic science around the pain mechanisms and treatment pathways. Cannabinoids are associated with greater risk of any Adverse Event (AE), serious AE, withdrawals due to AE, and other specified AEs, as compared to placebo. There was essentially no empirical literature, beyond one small study comparing nabilone to dihydrocodeine, comparing AEs between cannabinoids and opioids or other analgesics	Treatment durations examined in the literature are too short to speak to long-term use for both benefits and harms

Table 1 (continued)

Title (Reference)	Method	Intervention	Objectives/Primary endpoint	Results	Conclusion	Comment
Medical Cannabis for Chronic Noncancer Pain: A Systematic Review of Health Care Recommendations (Chang et al. 2021)	Systematic Revie	Review in Medline, Embase, PsycINFO, Cochrane database, website for clinical guidelines and recommendations	To identify and summarize the currently available evidence- based recommendations	12 studies were eligible. In the studies, medical cannabis for CNCP in general and for the specific conditions of neuropathic pain, chronic pain in people living with HIV and chronic abdominal pain is recommended	Clinicans can attend to the guidance currently offered, being aware that only weak recommendations are available for medical cannabis	Detailed discussions with patients regarding the benefits and potential adverse effects
A scoping Review on Clinical Trials of Pain Reduction With Cannabis Administration in Adults (Haleem and Wright 2020)	Scoping Review	Review in PubMed and Cochrane database between 2000 and 2020	To investigate the effect of herbal cannabis and cannabis-based medicine on neuropathic, non-neuropathic pain, acute pain and experimentally induced pain	34 studies (30 RCT´s) were eligible. Cannabis-based medications were found most effective as an adjuvant therapy in multiple sclerosis. Weak evidence was found in the support of cancer pain. Also chronic rheumatic pain showed promising results	In summary cannabis is effective for neuropathic pain in MS patients. Also promising effects could be found at neuropathic pain associated with HIV, diabetic pain, post trauma, post surgical pain and peripheral neuropathic pain	Adverse events of cannabis-based treatment were found to be more frequent with THC
Cannabinoids in Chronic Non-Cancer Pain: A systematic review and Meta-analysis (Johal et al. 2020)	Systematic Review	Review in Medline, Embase, Cinahl, Scopus, Google Scholar and Cochrane Database	To analyse the evidence between benefits and harms of medical and harms of medical cannabinoids in treatment of chronic, non-cancer related pain	36 trials were included. Cannabinoids showed a significant reduction in pain compared with placebo (VAS -0.68, 95% CI -0.96 to -0.4). Oral cannabinoids had a higher pain reduction compared to oromucosal and smoked formulations. SAEs were rare, the risk of AEs was higher at cannabinoids compared with placebo	There is moderate evidence to support cannabinoids in treating chronic, non- cancer pain at 2 weeks	After 2 weeks the confidence in effects becomes lower
The effects of cannabis, cannabinoids, and their administration routes on pain control efficacy and safety: A systematic review and network metaanalysis (Rabgay et al. 2020)	Systematic Review	Review in PubMed, Science Direct, ClinicalTrials.gov, Scopus, Cochrane Library and Embase	To determine the effects of cannabis, cannabinoids, and their administration routes on pain and adverse euphoria events	25 studies were included. It was found, that THC/CBD, THC and standardized dried cannabis could reduce neuropathic pain score (SMD -0.41, 95% CI -0.7 to -0.1). For nociceptive pain only standardized cannabis extract, in cancer pain THC/CBD and THC could reduce pain score	The use of cannabis and cannabinoids could reduce different types of pain	A optimal product design for more effective routes should be choosen

Table 1 (continued)

Title (Reference)	Method	Intervention	Objectives/Primary endpoint	Results	Conclusion	Comment
Analgesic Effects of Cannabinoids for Chronic. Non-cancer Pain: a systematic Review and Meta-Analysis with Meta-Regression (Wong et al. 2020)	Systematic Review and Meta-Analysis	Review in PubMed, EMBASE, web of Science, Cochrane CENTRAL and Clinical Trial.gov	To determine the analgesic efficacy and adverse effects of cannabinoids for chronic non-cancer pain	43 RCT´s were included. 33 studies showed a mean pain score reduction (scale 0–10, reduction -0.7). The analgesic efficacy was similar for neuropathic and non-neuropathic pain. All administration routes showed a small, but statistically significant pain reduction. SAE´s were rare, AEs were mild to moderate	The pain intensity of chronic non-cancer patients was reduced by cannabinoids	The effect sizes of pain reduction are small

(PRISMA) statement. Comprehensive searches of MEDLINE (Ovid), Google Scholar the Cochrane Library (Wiley) and "citation chasing" were performed to identify clinical trials and case reports that evaluated CBD on adults (age ≥ 18 for the treatment of chronic pain from database inception through January 28, 2019. An updated search was performed (from January 29, 2019, through April 1, 2021) to identify new publications. To maximise the search for relevant articles, we reviewed reference lists of identified trials and systematic reviews. We did not apply language restrictions.

Quantity of Search Available

A total of 493 citations were identified in the literature search. Following screening of titles and abstracts, 422 citations were excluded and 71 potentially relevant reports from the electronic search were retrieved for full-text review.

Overview on Pain Studies with Cannabinergic Products

Cannabis Flos (Herbal Cannabis)

Smoking the dried flowers of cannabis (cannabis flos) is the most widely observed use of cannabis whereby THC-rich cultivars are generally preferred. A large amount of literature suggests that cannabis high in THC (marijuana, correct term: drug-type cannabis) may provide pain relief. A recent epidemiologic study on 2,032 patients shows that among 21 illnesses, pain syndromes are the main reason (> 40%) for taking medical cannabis, usually rich in THC (Baron et al. 2018).

Only few, small, controlled trials on cannabis flos for chronic pain exist. A study on 55 patients with HIV-associated neuropathic pain (smoking three times daily for five days active or placebo cigarettes in which THC had been removed) found that smoking cannabis (standardized to an amount of 3.56% THC) reduced pain by at least 30% (commonly considered as clinically relevant effect size), in 52% of patients of the cannabis group compared to 24% in the placebo group (Abrams 2010).

A double-blind, placebo-controlled, crossover study on 38 patients with central and peripheral neuropathic pain, compared the effect of smoked cannabis with 7% THC versus cannabis with 3.5% THC and placebo. The results showed that both active preparations were effective at reducing pain, with no apparent correlation between dose levels and pain relief (Wilsey et al. 2008). In another double-blind, placebo-controlled, four-fold crossover trial with 34 subjects (28 completers) the proportions of subjects achieving at least 30% pain relief were clearly

in favour for cannabis (46%, versus 18% with placebo); mood and daily functioning improved to a similar extent during treatment periods. Although most side effects were mild and self-limited, two subjects experienced treatment-limiting toxicities (Ellis et al. 2009). A further randomized, double-blind, placebo-controlled, crossover study with 23 participants (21 completers) assessed neuropathic pain of at least three months duration caused by trauma or surgery. Each participant smoked/inhaled four different potencies of a cannabis preparation (0%, 2.5%, 6.0%, 9.4% THC) three times per day for the first five days of each two weeks period. The average daily pain intensity (visual analogue scale, VAS) was significantly lower with 9.4% THC-cannabis (5.4) than with 0% THC (6.1) (Ware et al. 2015). There was a trend to a higher efficacy but also more adverse reactions with higher doses of THC. Finally, a placebo-controlled, crossover trial investigated patients with multiple sclerosis (MS) and spasticity; perception of pain was a secondary outcome (Corey-Bloom et al. 2012) Patients smoked cannabis or identical placebo cigarettes, once daily for three days, with a washout interval of 11 days; 30 of 37 patients completed this two weeks study. Cannabis reduced pain scores (VAS) significantly more than placebo (by an average of 5.28 points).

Only two publications were found on vaporised cannabis including 39 and 42 subjects respectively. Inhaling vaporized cannabis with 3.53% THC in subjects with neuropathic pain was similar effective as 1.29% THC but significantly superior to placebo in the first study (Wilsey et al. 2013). In the second, vaporized cannabis (with 2.9% or 6.7% THC) or placebo, inhaled on three separate occasions, provided a significant reduction in pain intensity (numerical rating scale, NRS) in patients with neuropathic pain related to injury or disease of the spinal cord (Wilsey et al. 2016).

In addition to these controlled clinical trials, numerous observational studies and case reports exist. For example, a patient with an oral squamous cell cancer was able to discontinue pregabalin and dexamethasone while reducing hydromorphone to approximately 25% of his pre-cannabis-dosage by inhaling 0.5 to 1.0 g medical cannabis (ARGYLE™) per day; a temporary regression of tumour size was also observed (Maida 2017). In a prospective-cohort study including 431 patients, cannabis users experienced a small reduction on average pain intensity (VAS -0.92 compared to an increase of + 0.18 in the control group); this reduction of pain was maintained over a one-year observational period (Ware et al. 2015). One of the latest studies found that of 1,211 cancer patients, 95.9% reported an improvement in their condition (with pain and sleep problems being the most common complaints), whereas only 45 patients (3.7%) reported no change and four patients (0.3%) reported deterioration in their medical condition (Bar-Lev Schleider et al. 2018).

Physicians should, however, be aware of possible bias related to these studies. A complete blinding with THC-containing cannabinergic treatments is virtually impossible due to the characteristic euphoric effect ("high") of THC, whether smoked, inhaled or orally applied. In cross-over designs without a sufficiently long wash-out period, the long half life of THC (terminal half life 25–36 h) is likely causing carry-over effects. Duration of cannabis use also plays a role, as with continued use analgesic tolerance develops. Over time, the dose of cannabis to manage pain increased significantly (Cuttler et al. 2018). Furthermore, inhalation is a short acting form of cannabis administration with high serum peaks triggering the typical pleasure reward pathway; such rewarding effects are missing after oral administration. The most important draw back of inhaled cannabis, however, is the use of largely varying potencies and the lack of standardization of other phytocomponents, in addition to the potential for lung damage by combustion products and contaminants such as pesticides (Russo 2008). Vaporisation avoids risks from combustion products but not others.

Recently a number of standardised, pharmaceutical grade, medical cannabis flos products with a relative specific THC:CBD ratio have become available on prescription in some European countries for. Examples are *FM1* (13–20% THC, < 1% CBD) and *FM2* (8% THC, 6.5% CBD) both from Italy, and *Bediol* (6.3% THC, 8% CBD), *Bedrocan* (19–22% THC, < 1.0% CBD), *Bedrobinol* (13.5% THC, < 1.0% CBD, from C. sativa), *Bedica* (14% THC, < 1.0% CBD, from C. indica) or *Bedrolite* (< 1% THC, 9% CBD) which are all cultivars from The Netherlands. Interestingly, a recent comparative, four-way crossover study investigating *Bediol, Bedrocan* and *Bedrolite* could not demonstrate significant differences to placebo after electric stimulation of an acute pain response in 20 chronic pain patients with fibromyalgia (van de Donk et al. 2019). Of further interest is an observation made with *Bedrocan*. Patients who were insufficiently responding to a previous therapy with nabiximols for MS-related spasticity still responded to *Bedrocan (*Saccà et al. 2016*).*

The use of medical cannabis with varying THC:CBD ratios is increasingly accepted in a number of European and non-European countries such as in the Czech Republic, Denmark, Finland, Germany, Greece, Italy, Irland, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Slovenia, UK, Switzerland, Australia, Canada, Israel, Mexico, Turkey and in the majority of US States. Although (usually small) controlled clinical trials suggest a reduction of (neuropathic) pain by cannabis, insufficient characterisation of the products used is common, and leaves physicians and patients to a large uncertainty about substances and doses actually administered. Systematic head to head comparisons of (including inhaled versus oral) medical cannabis with pure THC, different THC:CBD-ratios or nabiximols are almost

missing. Therefore, the question whether unmodified dried plant material or whole plant cannabis extracts which are the formulations most patients are using, is superior to the pure active ingredients, THC, CBD or standardised formulations such as nabiximols, remains unanswered.

The controlled use of cannabis is relatively safe. Although adverse neurological or psychiatric events (e.g., headaches, sedation, dysphoria, poor concentration, poor memory, disorientation, confusion, dizziness) increased with cannabis use and with higher THC-concentrations, surveys confirmed that no serious adverse events had occurred in any of the clinical studies (Deshpande et al. 2015), despite that more adverse events occurred (81.2% among people receiving cannabinoids compared to 66.2% receiving placebo) (Stockings et al. 2018). As a clear dose-proportional effect on pain in relation to the THC concentration is not apparent; responses to cannabis preparations likely depend on other phytocompounds as well.

Cannabis Extracts

Instead of using the pulmonary route of administration, medicinal cannabis can also de delivered orally and by the transdermal route. Medicinal cannabis can also be extracted using various techniques from Dried herbal cannabis (usually flos, rarely leaves or other parts). Commonly used solvents are ethanol, various herbal oils, aliphatic compounds (e.g., butane, heptane, naphtha, petroleum ether) or supercritical CO_2. The type of solvent as well as other manufacturing aspects such as the temperature and duration of extraction and purification has a major impact on the profile of phytocompounds, notably on the content of the decarboxylated cannabinoids THC and CBD (Romano and Hazekamp 2013). In nature, cannabinoids exist mainly as their precursors which are acids, namely delta-9-tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA). They are decarboxylated by a time- and temperature-depending process. Temperature influences also the content of volatile byproducts in extracts, such as terpenes and polyphenols.

Unsurprisingly, published investigations of extracts demonstrated a significant variability in THC and CBD concentrations which may have an impact on efficacy and safety (Bettiol et al. 2018; Corli et al. 2019). The high variability, even from the same producer, may necessitate a titration to the optimal dose with each new supply/supplier.

Nabiximols (*Sativex*®)

The only standardised, pharma-grade extract which is currently authorised is nabiximols. Unlike dronabinol, nabilone and cannabidiol, nabiximols (*Sativex*®) is not a pure substance but a mixture of two extracts, each containing approximately 65–70% of THC or CBD respectively, with a standardised 1:1THC:CBD ratio and up to 35% of other phytocompounds. It is administered as an oral, ethanolic spray. It was first approved in Canada in 2005 for treatment of central neuropathic pain in multiple sclerosis (MS), and in 2007 as an adjunctive analgesic for moderate to severe pain in patients with cancer insufficiently controlled with strong opioid therapy. The combination of THC with CBD in nabiximols may improve the tolerability and safety of THC by reducing some unwanted side effects (e.g., cognitive impairment, anxiety, paranoia, tachycardia). Numerous randomized clinical trials have demonstrated safety and efficacy for nabiximols in central and peripheral neuropathic pain, rheumatoid arthritis and cancer pain (Russo 2008). A few selected studies are summarised below.

In a two-week double-blind, randomized, placebo-controlled study on 177 patients with intractable cancer-related pain, twice as many patients taking nabiximols showed a reduction of more than 30% from baseline pain (numerical rating score, NRS) when compared with placebo (43% vs. 21%), whereas the rate of responders in the "THC extract only" group was similar to placebo (23%), at a median dose of 8.75 sprays per day ($\geq$ 25 mg THC/day) (Johnson et al. 2010).

A five-week, randomised, double-blind, placebo-controlled, clinical trial examining the effects of nabiximols as an adjunct to existing stable analgesia in 125 patients suffering from peripheral neuropathic pain showed that 26% of participants reported more than 30% reductions in pain intensity, compared to 15% in those on placebo. Similarly, Patient's Global Impression of Change, Pain Disability Index and sleep improved more in patients receiving nabiximols than in the placebo group (Nurmikko et al. 2007).

In another study where patients were randomized to nabiximols (n = 199) or placebo (n = 198) median percent improvements in average pain (NRS) from baseline to end of treatment in the nabiximols and placebo groups were significantly higher (15.5% vs. 6.3%) in the per-protocol population. Patients in this trial had advanced cancer and chronic pain (Numerical Rating Scale scores $\geq$ 4 and $\leq$ 8) despite optimized opioid therapy. They were asked to self-titrate study medications over a two-week period, and then maintain the titrated dose over the next three-weeks. Nabiximols was also statistically superior to placebo on all three quality-of-life instruments at week 5. Surprisingly, in exploratory post hoc analyses, U.S. patients, but not patients from the rest of the world, experienced significant benefits from nabiximols on multiple secondary endpoints ! It was concluded that nabiximols might be suitable for patients with advanced cancer who receive a lower opioid dose (Lichtman et al. 2018).Two other studies with

nabiximols which included a separate group receiving CBD are referenced in the section on cannabidiol.

A meta-analysis (involving 298 patients) of cannabis based treatments concludes that they are all significantly effective in treating neuropathic pain in MS (VAS or 11-point NRS): CBD decreased pain by 1.5 ± 0.7, THC by 1.5 ± 0.6, and CBD/THC (buccal spray) by 1.7 ± 0.7, compared to placebo (0.8 ± 0.4) (Iskedjian et al. 2007).

A recent critical review including 60 publications found low-strength evidence that combinations of THC with CBD improve neuropathic pain but insufficient evidence in other pain related conditions such as cancer, rheumatoid arthritis and musculoskeletal pain (Kansagara et al. 2018). This confirms two previous reviews, examining the use of medical cannabis for pain related to other conditions such as cancer, rheumatoid arthritis, and musculoskeletal pain (Butler 2015; Whiting et al. 2015); both found insufficient evidence**.** To note, the overwhelming number of studies which have been included in these reviews assessed studies with nabiximols as active pain treatment whereas the number of studies on smoked or vaporised cannabis was very limited.

Delta-9-tetrahydrocannabinol (THC, dronabinol), Nabilone

Dronabinol (*Marinol*®, in short THC) is a synthetic form of delta-9-tetrahydrocannabinol, the primary psychoactive ingredient of cannabis. Nabilone (*Cesamet*®) is also a synthetic cannabinoid. It is very similar to THC and psychotropic but does not occur naturally. It appears to be roughly 5 to 10 times more potent. Furthermore, a THC-predominant extract with a 2:1 ratio of THC to CBD (*Cannador*®) or other synthetic "THC-like" cannabinoids such as levonantradol have been investigated in the past but are not commercialised.

Studies show that THC fails in *acute* pain. A randomized double-blind, placebo-controlled trial on post-operative acute pain (elective abdominal hysterectomy) on 40 women treated with 5 mg THC did not find evidence of an analgesic effect (Buggy et al. 2003). Lack of efficacy in acute pain was confirmed in a randomized, placebo-controlled, double-blinded, crossover study on 12 healthy volunteers (Naef et al. 2003). No analgesic effect resulted in the pressure and heat test, neither with THC alone (20 mg) nor in combination with 30 mg morphine. A recent review also concludes that THC or synthetic THC analogues have no role in the management of acute pain (Stevens and Higgins 2017).

Concerning *chronic* pain, results of treatment with THC remain mixed. As tumour hyperalgesia is mediated by CB1 receptors which are primary targets of THC, two small, double-blind, controlled studies investigated oral THC (*Marinol*®) in cancer pain. The first was a dose ranging study of 5, 10, 15 and 20 mg THC, given on successive days, to ten cancer patients; significant pain relief was found with 15 and 20 mg. A second, placebo-controlled, study compared THC with codeine in 34 patients with cancer pain; it found that 10 and 20 mg THC were equivalent in analgesic potency to 60 and 120 mg codeine respectively (Noyes et al. 1975). However, at higher THC doses most of the patients were heavily sedated with mental clouding common.

A small, open label study on eight consecutive patients with chronic refractory neuropathic pain treated with oral THC (mean dosage: 16.6 ± 6.5 mg/day up to 4 months) did not demonstrate any significant benefits on ongoing and paroxysmal pain (Attal et al. 2004). At four weeks there was a tendency to a reduction in number of painful attacks from 9.8 daily before the treatment to 3.2 daily, but this effect disappeared after 2 months. Whether this should be interpreted as some sign of tolerance development or not is unclear. Despite side effects necessitating premature discontinuation of treatment in 5 patients, treatment duration was much longer in this study than in most others investigating THC in chronic pain.

In a within-subject, placebo-controlled, blinded comparison of dronabinol (10 or 20 mg) with drug-type cannabis (0, 1.98, or 3.56% THC) drug-type cannabis produced greater decreases in subjective pain ratings relative to the respective dronabinol doses ($p < 0.01$)(Cooper et al. 2013). Unfortunately, the content of CBD was not stated in this report.

A two-week, multicentre, double-blind, randomized, placebo-controlled, parallel-group trial with THC, nabiximols and placebo including a total of 177 patients did not observe a significant reduction of cancer pain with THC compared to placebo, in contrast to nabiximols (Johnson et al. 2010).Further, withdrawal for adverse events was twice (THC) and three-times (nabiximols) more frequent than with placebo. Adverse effects, most often psychotropic such as "feeling stoned", were common with THC and increased with the dose (weakness, dry mouth, dizziness, relaxation, mental clouding, short term memory impairment, spatial time distortions). As mentioned above, maintenance of blinding is hardly possible with THC, nabilone or nabiximols due to the typical psychotomimetic effects, particularly when daily doses exceed 10 mg THC.

A review that included 9 of 20 randomised placebo-controlled trials comprising 222 patients, almost exclusively treated with THC (5 trials related to cancer pain, 2 to chronic non-malignant pain, and 2 to acute postoperative pain) concluded that cannabinoids (5–20 mg THC p.o. and 4 mg of a nitrogen analogue of THC, 1 publication) are no more effective than codeine in controlling pain and have depressant effects on the central nervous system that limit their use (Campbell et al. 2001). Nonetheless, it seems that subgroups

of patients may benefit from oral THC (Rudich et al. 2003; Svendsen et al. 2004; Likar 2008).

Cannabidiol (CBD)

Although chemically very similar, CBD effects differ from those of THC, and even counteract some of its negative reactions. Pure CBD is not interchangeable with CBD-rich cultivars (hemp-type cannabis) and is also not the same as so called "CBD-oils" or "hemp-oils". The latter are extracts with more or less CBD, usually with a THC-concentration below the legally permitted concentration of 0.2% to 0.3% and containing numerous other plant ingredients and excipients. As CBD has no psychotomimetic effects and is not a "controlled substance", a majority of consumers of CBD-rich cultivars or "CBD-oils" try them for the relief of symptoms inadequately controlled by other medications. According to a cross-sectional study which included 2,409 individuals, almost 62% of users of CBD-rich cannabis cultivars (hemp-type cannabis) reported taking "CBD" (type of product not defined) to treat a medical condition, with the top three being pain, anxiety, and depression (Corroon and Phillips 2018).

The popularity of CBD-oils contrasts to the relatively limited research on pure CBD in other indications than pediatric epilepsy, particularly in chronic pain. Pure CBD (extracted from plant) holds a marketing authorisation for the treatment of two forms of pediatric epilepsy as speciality (Epidiolex), but is also available for "magisterial"/"specials" prescription/preparation of pharmacy formulations (formula magistralis) in Austria, Germany and Switzerland (phyto-CBD purified to > 99.8%, with < 0.01% THC, Trigal Pharma GmbH, Wien). CBD exists also as synthetic molecule. Pure CBD is described as substance in the "Deutscher Arzneimittel-Codex / Neues Rezeptur-Formularium" (DAC/NRF).

Despite of promising results in a number of animal pain models (Nahler 2018), clinical experiences with CBD in chronic pain are almost missing. Human experiences with pure CBD and enriched extracts are summarised in Table 2 and demonstrate improvement of chronic pain including neuropathic and MS-related pain.

As can be seen, only a limited number of publications, and with small numbers of subjects, are available. In two small cross-over studies it was demonstrated that a subtherapeutic dose of CBD improves the analgesic effect of THC. In the first, which included 24 patients, improvement of pain with CBD was significantly superior to placebo (order: CBD ≃ THC > THC + CBD > placebo) (Wade et al. 2003). Each patient entered an eight-week double-blind study phase with four, randomised two-week treatment periods using THC + CBD, or CBD alone, or THC alone, or placebo. As there were no "wash-out" periods between each treatment period, results are likely distorted by carry-over effects. The second study, a series of 34 N-of-one/single case studies comparing a CBD-rich extract (> 95% of CBD) with THC, THC + CBD and placebo, demonstrated in the first series of four treatment sequences pain improvements in the order: THC + CBD > THC > CBD > placebo; in the second sequence the order was: THC + CBD > THC > placebo > CBD and differences between treatment periods were distinctly smaller. Each treatment lasted for only one week, without wash-out periods between. As CBD is eliminated from the body with a half-life of about two to three days (~ 60 h) with large inter-individual variations, it is likely that carry-over effects have distorted differences between treatments in this study (Notcutt et al. 2004). Furthermore, in both studies, the CBD dose per application (spray) was the same as in the combination for methodological reasons. Usual therapeutic doses for CBD are, however, in the order of 400 mg/day compared to about 10 to 20 mg for THC. CBD was therefore heavily underdosed and treatment periods much too short for demonstrating reliable effects.

A small case study with pure phyto-CBD at a dose of 200 mg twice daily as add-on treatment to analgesics (mainly opioids) in five patients with chronic pain of various origin found a remarkable reduction of pain as well as of the dose of concomitant analgesics. One patient could stop all analgesics after one month, the others were able to cut dosages by one third to two thirds (Likar 2016). Similar benefits of a comedication with CBD have been observed in a patient with rheumatoid arthritis who suffered from intractable pain for more than 10 years (Stromer 2021). Another recent case study that included four glioma patients confirmed this preliminary observation (Likar 2016). Interestingly, pain relief has also been reported in patients who received topical CBD for knee osteoarthritis and for chemotherapy-induced peripheral neuropathy (Halbritter 2018; Hunter et al. 2018).

Intriguingly, despite that medical cannabis contains large amounts of terpenes in addition to cannabinoids, and despite that terpenoid-rich essential oils (EOs) are known to exert anti-inflammatory and antinociceptive activities, none of the EOs was as effective as purified CBD (Gallily et al. 2018). Similar observations were made with THC in a study in rats. Animals received various doses either of a cannabis extract without terpenes, isolated terpenes, the full THC-rich extract, THC, morphine or vehicle. Thermal nociception was tested on hotplate and tail-flick tests and inflammatory nociception in the abdominal writhing test. Tests were performed on the same animals one week apart. Whereas cannabinoid-containing preparations demonstrated dose-depending analgesic effects, pure terpenes did not produce analgesia (Harris et al. 2019). In binding- respectively displacement studies with CBD and THC, a series of terpenoids commonly found in cannabis did also not mediate an entourage effect when studying their action at cannabinoid

Table 2 Original publications on painful conditions treated with cannabidiol

Painful condition	Treatment	Results	Ref
Fibromyalgia (self medication with CBD due to inadequate relief from other medications)	CBD not specified, probably "CBD-oils" Survey including 2,701 participants with fibromyalgia	60% of participants had tried CBD in the past or currently used CBD; 32% currently used CBD, mostly for pain, anxiety, sleep; ~ 30–40% reported much or very much relief across symptom domains	(Boehnke et al. 2019)
Self medication of various conditions mainly pain, anxiety, and depression	CBD not specified, probably "CBD-oils" Survey including 2,409 participants	Almost **36%** of respondents reported that CBD treats their medical condition(s) "**very well** by itself"; only 4.3% reported "not very well."	(Corroon and Phillips 2018)
CBD prescription in primary care for various symptoms	CBD-oil, 5.0 mg THC & 20.0 mg CBD/ml (~ 40—300 mg/day); outcomes after 3 weeks; survey	Non-cancer pain (n = 53) but also cancer pain (n = 24) decreased significantly; significant improvements were also reported for anxiety, depression and other health-related symptoms	(Gulbransen et al. 2020)
Chemotherapy-induced neuropathy	Topical CBD ointments (4% CBD), 8 patients, case series	Subjective improvement in all patients after 2 weeks,	(Halbritter 2018)
adults with knee pain due to OA	Transdermal synthetic CBD gel administered twice daily for 12 weeks; 320 patients randomised in 3 groups: 0 vs 250 vs 500 mg/day; Phase IIa, randomized, double-blind, placebo-controlled, multiple-dose study;	mean reduction from baseline in average worst knee pain at week 12 was − 2.64 for 250 mg/day (n = 106), − 2.83 for 500 mg/day (n = 105) and − 2.37 for placebo (n = 103); 250 mg/d (n = 93) significantly outperformed placebo (n = 88) for the responder analysis; gender differences: men treated with 250 mg/d (n = 43) had significantly greater reductions from baseline in average worst knee pain scores	(Hunter et al. 2018)
Mixed treatment-resistant chronic pain (carcinoma, myeloma, fibromyalgia, cervicocephalgia)	5 patients received 2 × 200 mg pure CBD/day in addition to their standard medication (mostly hydromorphone, pregabalin or opioids such as oxycodone hydrochloride), case series	After ~ 6 to 8 weeks, all patients showed marked improvement of their pain, allowing a reduction of their concomitant medication by about 30% to 50%. One patient could stop all other medications	(Likar 2016)
Chronic, stable pain, poorly responsive to other modalities (MS patients)	CBD:THC (~ 1:1) vs THC vs CBD vs placebo; 34 patients, 4-way cross –over; each patient received each treatment for two separate 1-week periods with no wash-out between	THC-Extracts proved most effective in symptom control (efficacy, 1st period: placebo < CBD < THC < THC + CBD); improved quality of sleep was seen in all, with a similar order of effects; in combination, CBD improved the effect of THC despite of being underdosed	(Notcutt et al. 2004)
Rheumatoid arthritis, treatment-resistant chronic pain since 10 years;	Single case, 2 × 200 mg pure CBD/day, add-on to other analgesics, > 1 year,	marked improvement (-50%) of pain scores, allowing a reduction of the concomitant medication by about 30% to 50%	(Stromer 2021)
patients with neurogenic symptoms	Nabiximols (CBD:THC ~ 1:1) vs THC vs CBD vs placebo; 2.5–120 mg (= max. permitted dose)/24 h; 20 patients	Pain relief associated with both THC and CBD (score over last seven days of each two-week period) was comparable and significantly superior to placebo; in combination, CBD improved the effect of THC despite of being highly underdosed	(Wade et al. 2003)

receptors (Finlay et al. 2020). However, this does not preclude that terpenes could contribute to other effects.

CBD has a good safety profile as has been confirmed recently by the WHO. In contrast to THC-containing cannabis preparations, pure CBD does not cause adverse neurological or psychiatric effects such as "high", poor concentration, poor memory, disorientation or confusion, and possibly counteracts drug abuse and dependence. Currently it is also the only available cannabinergic medication not causing a positive drug test. The WHO Expert Committee on Drug Dependence (ECDD) concluded: *"Preparations containing predominantly cannabidiol and not more than 0.2% of delta-9-tetrahydrocannabinol are not under international control"* [WHO Expert Committee on Drug Dependence (ECDD), 41st meeting, 12–16 Nov. 2018].

Opioid-Sparing Effects, Potentiation with Opiates and Analgesics

Whereas pre-clinical studies suggest that cannabis may play a role in ameliorating the impact of opioid use disorder (Katsidoni et al. 2013; Markos et al. 2018), evidence in man is still limited and mixed. Ecological studies in states that allow medical cannabis have reported a lower use of opioids and a slower rate of increase in opioid overdose deaths compared to states without such laws (Shah et al. 2019), supporting isolated observations on a reduced opioid consumption for severe chronic pain (Meng et al. 2016). Furthermore, some epidemiological studies provide evidence that cannabis availability may reduce opioid administration. However, interpretation is limited by the lack of characterisation of the cannabinergic products, selection bias, cross-sectional designs, and self-reported assessments of the opioid-sparing effects (Campbell et al. 2018a). According to a retrospective cross-sectional survey of patients with chronic pain, medical cannabis use was associated with a 64% decrease in opioid use (Boehnke et al. 2016); according to another survey, about 80% reported substituting cannabis for traditional pain medications (53% for opioids, 22% for benzodiazepines), citing fewer side effects and better symptom management (Boehnke et al. 2019). Other recent studies support prior research that individuals use cannabis as a substitute for prescription drugs, particularly, narcotics/opioids (Corroon et al. 2017; Lucas and Walsh 2017).

In contrast, a prospective, open, 4-year cohort study provided no evidence that cannabis use improved patient outcomes or that cannabis use reduced prescribed opioids (Campbell et al. 2018b). Similarly, a review that included nine clinical studies and one small case series also found only low evidence for a reduced need in opioids when cannabinoids were co-administered (Nielsen et al. 2017). An experimental, cross-over study with normal volunteers demonstrated only weak evidence for a synergistic interaction between morphine and THC. This effect was limited to the affective component, making pain less unpleasant, but not to the sensory component (Roberts et al. 2006).

No randomised, controlled clinical trial could be identified that studied opioid-sparing effects of CBD or THC as primary end-point. A recent open, prospective study which followed patients with chronic pain and stable opioid use over 8 weeks found that 50 of 94 (53%) were able to reduce or stop their opioids with concomitant CBD-rich extract (Capano et al. 2020) 94% reported also improved quality of life. Of these 94 patients, 91 took twice daily CBD-soft gels each containing 15.7 mg CBD, 0.5 mg THC, 0.3 mg cannabidivarin (CBDV), 0.9 mg cannabidiolic acid (CBDA), 0.8 mg cannabichrome (CBC), and > 1% botanical terpene blend (Capano et al. 2020).

Overall, a review of the recent literature suggests that implementation of medical cannabis policies using well defined products could reduce prescription opioid medications—associated mortality, improve pain management, and significantly reduce health care costs (Vyas et al. 2018). Cannabinoids when used in conjunction with opiates may lead to a greater cumulative relief of pain, resulting in a reduction in their use (and associated side-effects). Additionally, cannabinoids can prevent the development of tolerance to and support withdrawal from opiates, and can even rekindle opiate analgesia after a prior dosage has become ineffective (Lucas 2012). Unfortunately, the reviews included studies regardless of route of administration, dosage or type of cannabinoids. As long as no well controlled clinical trials have been conducted with pure cannabinoids or at least with cannabinergic products of defined composition, results will remain mixed and conflicting.

Discussion and Conclusion

A large number of articles suggest that THC is able to reduce chronic pain, although dosages above 10 mg per day are needed and the effect size seems to be small. Surprisingly, experimental studies showed that terpenes do not contribute to the analgesia of drug-type cannabis. The potential contribution of other cannabinoids to analgesic effects of THC is, at present, restricted to observations with CBD. In a fixed, 1:1 combination with THC, even sub-therapeutic dosages of CBD improved the effect of THC. This suggests that CBD has, per se, a role in analgesia. Cannabis cultivars demonstrate an enormous variability in terms of chemical composition and perceptual profiles (de la Fuente et al. 2019).

In THC-dominant, drug-type cannabis, the content of CBD is variable, although usually below 0.3%. This variability may explain conflicting results in some studies but also differences in the perception of the analgesic potential

of THC as monosubstance compared to drug-type cannabis. An "optimal" ratio of CBD:THC, possibly higher than 1:1, is currently unknown as systematic investigations are missing. Similar, any contribution of other natural cannabinoids in alleviating pain is, at present, also unknown. Claims that inhaled cannabis or "full spectrum cannabis extracts" are more powerful pain medications than individual, purified cannabinoids remain therefore unconfirmed. It should also be noted that medical cannabis and extracts containing levels of THC above 0.2 -0.3% including nabiximols are regulated substances, causing positive drug tests (driving!) and are therefore not freely available in many countries.

As with drug-type cannabis, systematic head-to head comparison between pure CBD and CBD-rich extracts (hemp-type cannabis) are lacking. Pharmacological models do not support a modulation of the analgesic effects of pure CBD by terpenoids ("entourage effect") thus the influence of other plant constituents is unknown and remains to be elucidated by systematic investigations. At present, most of the convincing results concerning the analgesic effects of CBD come from animal studies. Clinical experiences, let alone clinical trials are still very limited and mainly restricted to "add-on" treatments with CBD where an "analgesic-sparing effect" has been observed. Although these observations are promising, they need confirmation by statistically powered,controlled clinical trials.

Health /Therapeutic claims for "CBD-oils" or "hemp-oils" which are widely available "over-the-counter" (OTC) products are not allowed. In general, native CBD-oils contain only low amounts of CBD. And,hence, large doses would be necessary to achieve effects. As such products may contain contaminants such as heavy metals, pesticides, microbes or mycotoxins and may be adulterated by the addition of (synthetic) cannabinoids, the intake of high amounts can expose consumers to considerable and unforeseen risks. In contrast to pure, pharma-grade cannabinoids, the production and quality is not routinely controlled by health regulatory authorities.

Products vary in their profile of components making extrapolation of results and comparisons difficult. In a strict sense, results are valid only for the product (cultivar or extract) used and should not be generalised as often done in a majority of review articles in the past. Characterisation of the components beyond the content of CBD and THC is also not only insufficient but often inaccurate.

With all these limitations, studies with pure substances are likely producing more reliable and reproducible results unless extracts are better characterised.

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Declarations

Conflict of Interests The authors declare that there is no overlap with previous publications and they don´t have any conflicts of interests.

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