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POSITION PAPER

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European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management

Winfried Häuser[1,2] | David P. Finn[3] | Eija Kalso[4] | Nevenka Krcevski-Skvarc[5] | Hans-Georg Kress[6] | Bart Morlion[7] | Serge Perrot[8] | Michael Schäfer[9] | Chris Wells[10] | Silviu Brill[11]

[1]Department Internal Medicine 1, Klinikum Saarbrücken gGmbH, Saarbrücken, Germany

[2]Department Psychosomatic Medicine and Psychotherapy, Technische Universität München, Munich, Germany

[3]Pharmacology and Therapeutics, School of Medicine, Galway Neuroscience Centre and Centre for Pain Research, NCBES, National University of Ireland Galway, Galway, Ireland

[4]Department of Perioperative Medicine, Intensive Care and Pain Medicine, Pain Clinic, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

[5]Department of Anesthesiology, Intensive Care and Pain Treatment, Faculty of Medicine of University Maribor, University Medical Center Maribor and Institute for Palliative Medicine and Care, Maribor, Slovenia

[6]Department of Special Anaesthesia and Pain Therapy, Medical University of Vienne/AKH, Vienna, Austria

[7]Leuven Centre for Algology and Pain Management, University Hospital Leuven, Leuven, Belgium

[8]Department of Pain Center and INSERM U987, Cochin Hospital, AP-HP, Paris Descartes University, Paris, France

[9]Department of Anaesthesiology and Intensive Care Medicine, Charité University Berlin, Berlin, Germany

[10]Pain Matters Ltd, Liverpool, UK

[11]Pain Center, Sourasky Medical Center, Tel Aviv, Israel

Correspondence
Winfried Häuser, Klinikum Saarbrücken gGmbH, Winterberg 1, D-66119 Saarbrücken, Germany.
Email: whaeuser@klinikum-saarbruecken.de

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Abstract

Cannabis-based medicines are being approved for pain management in an increasing number of European countries. There are uncertainties and controversies on the role and appropriate use of cannabis-based medicines for the management of chronic pain. EFIC convened a European group of experts, drawn from a diverse range of basic science and relevant clinical disciplines, to prepare a position paper to empower and inform specialist and nonspecialist prescribers on appropriate use of cannabis-based medicines for chronic pain. The expert panel reviewed the available literature and harnessed the clinical experience to produce these series of recommendations. Therapy with cannabis-based medicines should only be considered by experienced clinicians as part of a multidisciplinary treatment and preferably as adjunctive medication if guideline-recommended first- and second-line therapies have not provided sufficient efficacy or tolerability. The quantity and quality of evidence are such that cannabis-based medicines may be reasonably considered for chronic neuropathic pain. For all other chronic pain conditions (cancer, non-neuropathic noncancer pain), the use of cannabis-based medicines should be regarded as an individual therapeutic trial. Realistic goals of therapy

have to be defined. All patients must be kept under close clinical surveillance. As with any other medical therapy, if the treatment fails to reach the predefined goals and/or the patient is additionally burdened by an unacceptable level of adverse effects and/or there are signs of abuse and misuse of the drug by the patient, therapy with cannabis-based medicines should be terminated.

Significance: This position paper provides expert recommendations for nonspecialist and specialist healthcare professionals in Europe, on the importance and the appropriate use of cannabis-based medicines as part of a multidisciplinary approach to pain management, in properly selected and supervised patients.

1 | BACKGROUND

Public interest in the use of cannabis products for medical purposes in Europe has been accelerated by advocacy and by the legalization of marijuana for recreational and medical use by lay organizations and political parties (Health Products Regulatory Authority, 2017). Some European governments have sanctioned and legalized herbal cannabis for medicinal use for a wide range of potential indications, including chronic pain management, and in so doing have abandoned the due diligence process required to ensure efficacy and safety (Häuser, Petzke, & Fitzcharles, 2018). A recent survey conducted by the European Pain Federation EFIC found striking differences between European countries in (a) the availability of plant-derived and synthetic cannabinoids, (b) the use of medical cannabis for pain management and for symptom control in palliative care and (c) the covering of costs by health insurance companies or state social security systems (Krcevski-Skvarc, Wells, & Häuser, 2018). Systematic reviews have come to partially divergent conclusions on the efficacy and safety of cannabis-based medicines for chronic pain. Some national guidelines and expert groups have given different recommendations on the role of cannabis-based medicines for some pain syndromes such as neuropathic pain and fibromyalgia (Häuser et al., 2018).

Therefore, the pain community has the responsibility to examine the currently available evidence so as to competently advise and inform other jurisdictions, healthcare workers, patients and their relatives about the role and the responsible use of cannabis-based medicines for chronic pain management. Our recommendations are intended for primary care physicians who are confronted with the desire of patients for a prescription of cannabis-based medicines, and for specialist prescribers.

2 | METHODS

This position paper was produced by a task force (TF) of the European Pain Federation (EFIC) in order to provide a fair, balanced and evidence-based summary of the role of cannabis-based medicines for use in pain management. The recommendations summarize the relevant data where such exist. Where data are lacking, the recommendations presented reflect the clinical experience of the TF.

The development of the position paper followed recent recommendations of a clinical consensus statement development manual (Rosenfeld, Nnacheta, & Corrigan, 2015) and followed an nine-step process:

1. The board of directors of European Pain Federation EFIC decided in November 2016 to constitute a task force (TF) to develop a position paper on appropriate use of cannabis-based medicines for chronic pain management.
2. The board of directors of EFIC identified two chairs and members of a TF based on their clinical and scientific experience with the topic in Spring and Summer 2017.
3. A face-to-face meeting of the TF took place at the EFIC congress at 8 September 2017 in Copenhagen. The key questions, goals and remit of the TF were identified during the meeting.
4. The chairs of the TF performed a selective search of literature in the databases MEDLINE and CENTRAL from 2005 to October 2017. The search strategy for MELINE was as follows: : (‘guideline’[All Fields] AND ‘systematic review’[All Fields]) AND ‘chronic pain’)[All Fields] AND ‘cannabis’[All Fields] OR ‘marijuana’[All Fields] OR ‘hashish’[All Fields] OR ‘cannabinoids’[All Fields] OR ‘dronabinol’[All Fields] OR ‘marinol’’[All Fields] OR ‘nabilone’[All Fields] OR ‘cesamet’[All Fields] OR ‘tetrahydrocannabinol’[All Fields] OR ‘cannabidiol’[All Fields] OR (‘nabiximols’[Supplementary Concept] OR ‘nabiximols’[All Fields] OR ‘sativex’[All Fields]) AND ‘OR’[All Fields] AND (‘nabiximols’[Supplementary Concept] OR ‘nabiximols’[All Fields]) In addition, systematic reviews and guidelines, which were not found by the search but were provided by members of the TF, were considered.

5. The systematic reviews and guidelines identified by the search were made available to the members of the TF on a password-protected electronic platform.
6. A first draft of the sections of the position paper was developed by subgroups of two to three members of the TF from December 2017 to January 2018.
7. All drafts were reviewed by all members of the TF. Based on the reviews, the chair of the TF developed a second draft and identified controversies at the start of February 2018.
8. During a telephone conference on 21 February 2018, a consensus on all controversial issues was reached.
9. Based on the results of the consensus conference, the chair of the TF developed a third draft which was finally approved by all members of the TF after two Delphi procedures.
10. The final draft of the manuscript was internally reviewed by the head of EFIC's scientific committee, Dr. Chris Eccleston. and approved by the executive board of EFIC on 14 April 2018.
11. The manuscript was submitted to European Journal of Pain for peer review on 18 April 2018.
12. The manuscript was revised based on the extensive and helpful comments of three reviewers by the two chairs of the TF and finally approved by all members of the TF by one Delphi procedure.

3 | RESULTS

We identified 15 systematic reviews (Andreae et al., 2015; Asbridge, Hayden, & Cartwright, 2012; Aviram & Samuelly-Leichtag, 2017; Finnerup et al., 2015; Fitzcharles, Baerwald, Ablin, & Häuser, 2016; Häuser et al., 2017; Häuser et al., 2018; Martın-Sanchez, Furukawa, Taylor, & Martin, 2009; Mücke et al., 2016; Mücke, Philipps, Radburch, Petzke, & Häuser, 2018; National Institute of Health, 2018; National Academies of Sciences, Engineering, and Medicine, 2017; Nugent et al., 2017; Petzke, Enax-Krumova, & Häuser, 2016; Whiting et al., 2015) and five recommendations or guidelines of scientific societies and national agencies (Committee on Obstetric Practice, 2017; Kahan, Srivastava, Spithoff, & Bromley, 2014; National Board of California, 2017; The College of Family Physicians in Canada, 2018; Health Products Regulatory Agency, 2017). The reviews cover the same limited evidence. The first review on efficacy of cannabis-based medicines for chronic pain was published in 2009 and the most recent in 2018. All systematic reviews found limited evidence on which to base any recommendations. Of the five guidelines / recommendations of scientific societies, the first was produced in year 2014 and the most recent in year 2018. Of the 37 countries in the European Pain Federation, none have produced a national guideline on the use of cannabis-based medicines for chronic pain (Krcevski-Skvarc et al., 2018).

We identified 55 recommendations from the review of both the existing other guidelines/recommendations and evidence summaries of systematic reviews. The topics of the position paper were selected based on the scientific and clinical experience of the authors (which issues are important for clinical practice?) and on the literature reviewed. For each recommendation of the EFIC position paper, we summarize the 'key point(s)' and provide a comment to capture the view of the panel.

We start with terminology and then move to evidence-based recommendations across clinical presentations.

4 | TERMINOLOGY AND DEFINITIONS

4.1 | Medical cannabis

> Key point: The term 'medical cannabis' (or 'medical marijuana') should only be used for cannabis plants and plant material, for example flowers, marijuana, hashish, buds, leaves or full plant extracts used for medical reasons.

4.2 | Cannabis-based medicines

> Key point: Registered medicinal cannabis extracts with defined and standardized THC and THC/CBD content should be classified as 'cannabis-derived' or 'cannabis-based' medicines.

Because of potential for abuse and the widespread political stigmatization of cannabis as a 'street' drug, a rational public debate on the use medical cannabis and cannabis-based medicines is strongly hampered by erroneous beliefs, and by inaccurate and inconsistent terminology. For example, by not distinguishing 'cannabis' from 'cannabis-derived' (or 'cannabis-based') medicines or pharmacological modulators of the endogenous cannabinoid (endocannabinoid) system, public discussions are dominated by the generalizing term 'cannabis', confusing illicit 'street' trading and abuse with the therapeutic use of medical cannabis and cannabis-based medicines. The discussion is further confused by the fact that cannabidiol (CBD)-containing oils and extracts of low or even unclear CBD content are freely sold as nutritional supplements (so-called cannabis-oils).

Cannabis refers to the whole plant, as well as its parts. The term medical cannabis (or medical marijuana) refers to using the whole, unprocessed marijuana plant or its extracts for medical reasons (National Institute of Health, 2018). Herbal cannabis contains more than 100 distinct cannabinoid constituents in addition to a large number of different terpenes, flavonoids and other compounds. Cannabinoids are biologically active constituents of cannabis, or synthetic compounds, usually having affinity for and activity at cannabinoid receptors. The best-characterized cannabinoids found in the cannabis plant or purified/extracted from plant material (phytocannabinoid) are THC and CBD. Medical cannabis with a THC and CBD content is produced by licensed manufacturers in countries which have legalized cannabis for medical reasons (e.g. Italy). Medical cannabis must be clearly distinguished from cannabinoid agents (cannabinoids) that are either synthetic, semisynthetic or plant-derived, but always chemically defined, single compounds, for example Δ^9-tetrahydrocannabinol (THC) or cannabidiol (CBD; Fine & Rosenfeld, 2013; Grotenhermen & Muller-Vahl, 2012; Pertwee, 2015). Dronabinol is a plant-derived semi-synthetic cannabinoid (THC). It is produced by different methods: a) It's precursor tetrahydrocannabinolic acid is extracted from medicinal hemp plants and is chemically converted in the extract by decarboxylation to THC. b) In the semi-synthetic production, CBD is converted by chemical reaction steps to THC. In the full synthesis, the entire molecule is generated by chemical reaction steps.

Namisol® is an oral tablet which contains pure (>98%) plant-derived Δ^9-tetrahydrocannabinol or dronabinol (de Vries, van Rijckevorsel, Vissers, Wilder-Smith, & van Goor, 2017).

Nabilone is a completely synthetic THC analogue.

Thus, cannabis and single pharmaceutical cannabinoid compounds or modulators of the endocannabinoid system are not the same and should never be referred to synonymously.

Registered medicinal cannabis extracts with defined and standardized THC and THC/CBD content, such as nabiximols, show only minor contaminations of other phytocannabinoids and should be classified as 'cannabis-derived' or 'cannabis-based' medicines rather than 'cannabis extract'.

In addition to individual phytocannabinoids, cannabis-derived or cannabis-based medicines, and cannabis extracts, other pharmacological approaches under development for manipulation of the endocannabinoid system include selective synthetic cannabinoid receptor agonists or antagonists, and inhibitors of the catabolism (e.g. fatty acid amide hydrolase [FAAH] inhibitors) or reuptake of endogenous cannabinoid ligands (endocannabinoids; see Table 1).

4.3 | Availability as prescription medicine

Key point: There are differences in the approval and availability of medical cannabis and cannabis-based medicines (plant-derived THC/CBD = Nabiximols [Sativex™], synthetic THC (Nabilone [Cesamet™ or Canemes™]) or plant-derived/semi-synthetic THC (Dronabinol [Marinol™, Dronabinol™, Namisol™]) in European countries.

International drug control treaties like the 1961 UN Single Convention and national legislation restrict the use of cannabinoids, cannabis and cannabis-based or cannabis-derived products. Plant-derived as well as semi-synthetic THC (e.g., dronabinol), and the synthetic THC analogue nabilone, are available on special prescription in some European countries (Krcevski-Skvarc et al., 2018). In the USA and several European countries, oral capsules of semi-synthetic THC have been registered as medicine for more than three decades under the brand Marinol™. In Germany, Austria and some other European countries, pure dronabinol is provided to pharmacies for the production of drops or capsules on prescription.

The phytocannabinoid CBD, which does not have the same psychoactivity profile as THC, has also received considerable attention as a potential pharmaceutical agent (Devinsky et al., 2014; Fasinu, Phillips, ElSohly, & Walker, 2016) and is available in many formulations, as a

TABLE 1 Terminology and definitions

Term	Definition	Examples
(Herbal) Cannabis	The whole plant or parts or material from the plant (e.g. buds, resin, leaves)	Cannabis sativa, hashish
Cannabinoid	Biologically active constituents of cannabis, or synthetic compounds, usually having affinity for and activity at cannabinoid receptors	THC, CBD, CP55,940, WIN55,212-2, HU210
Phytocannabinoid	A cannabinoid found in the cannabis plant or purified/extracted from plant material	THC, CBD
Endocannabinoid	An endogenous ligand found in the body of humans and other animals and which has affinity for, and activity at, cannabinoid receptors	Anandamide, 2-AG

Notes. CBD,: cannabidiol; THC,: tetrahydrocannabinol; 2-AG,: 2-arachidonoyl glycerol.

synthetic or plant-derived pure substance (e.g., the oral solution Epidiolex™ currently has orphan drug designation in the United States and Europe for treatment of childhood epilepsy disorders) or as freely sold preparations or 'nutritional supplements' of varying purity, content and quality, often under the banner of 'cannabis-oils'.

The sublingual spray nabiximols (trade name Sativex™), containing a combination of cannabis-derived 2.7 mg THC and 2.5 mg CBD per spray), has been approved for the treatment of spasticity associated with multiple sclerosis (MS) in a number of European countries (Krcevski-Skvarc et al., 2018).

With regard to medicinal cannabis, there is great variety in the number and type of cannabis strains which can be prescribed in different European countries, with the THC content ranging from 1% to 22% and the CBD content from 0.05% to 9% (Häuser et al., 2017).

4.4 | The Endocannabinoid System

Key point: The endocannabinoid system plays an important role in the regulation of a wide array of physiological processes including appetite, metabolism, mood, motor function, gastrointestinal tract function, cardiovascular control, stress response, developmental biology, cell fate, immune and inflammatory response, endocrine function, neurotransmission and pain.

In the 1960s, (-)-trans-Δ^9-tetrahydrocannabinol (THC) was identified as the primary active constituent of *Cannabis sativa* (Gaoni & Mechoulam, 1964; Mechoulam & Gaoni, 1967). This discovery prompted research which led to the identification of cannabinoid receptors that mediate the pharmacological effects of THC and other cannabinoids, and subsequently the identification of endogenous ligands for these cannabinoid receptors. Cannabinoid receptors belong to the important superfamily of G protein-coupled, seven-transmembrane domain receptors. The endogenous cannabinoid (endocannabinoid) system consists of cannabinoid type 1 (CB_1; Devane, Dysarz, Johnson, Melvin, & Howlett, 1988; Matsuda, Lolait, Brownstein, Young, & Bonner, 1990) and cannabinoid type 2 (CB_2; Munro, Thomas, & Abu-Shaar, 1993) receptors, their endogenous ligands (or endocannabinoids) *N*-arachidonoyl ethanolamide (anandamide, AEA) and 2-arachidonoyl glycerol (2-AG; Devane et al., 1992; Mechoulam et al., 1995; Sugiura et al., 1995), and the enzymes responsible for the synthesis and degradation of the endocannabinoids. While AEA and 2-AG are the best-characterized endocannabinoids, there are a number of other endogenous ligands with affinity and activity at CB_1 and CB_2 receptors, including 2-AG ether (noladin ether), virodhamine, *N*-arachidonoyl dopamine (NADA) and others (Battista, Di Tommaso, Bari, & Maccarrone, 2012; Di Marzo, 2008; Di Marzo, Stella, & Zimmer, 2015).

The CB_1 receptor is the most abundant G protein-coupled receptor subtype in the central nervous system (CNS), with particularly high density in the basal ganglia, as well as in brain regions that are key components of the descending pain pathway and the stress/fear/anxiety circuitry (Glass, Dragunow, & Faull, 1997; Herkenham et al., 1991). CB_1 receptors are also expressed in most other tissues and organs of the body. CB_2 receptors, although expressed in the CNS (Baek, Zheng, Darlington, & Smith, 2008; Concannon, Okine, Finn, & Dowd, 2015; Onaivi et al., 2006; Van Sickle et al., 2005; Zhang et al., 2014), are mainly distributed in the periphery, with particularly high density on cells and tissues of the immune system (Berdyshev, 2000; Munro et al., 1993). Both subtypes of cannabinoid receptor are $G_{i/o}$ protein-coupled receptors, negatively coupled to adenylate cyclase (Howlett, Mukhopadhyay, Shim, & Welsh, 1999) and positively coupled to mitogen-activated protein kinase (MAPK; Bouaboula et al., 1995). Upon binding to CB_1 receptors, cannabinoids also inhibit N- and P/Q-type voltage-activated Ca^{2+} channels and induce inwardly rectifying K^+ currents, resulting in inhibition of neurotransmitter release (Demuth & Molleman, 2006). In addition to CB_1 and CB_2, several lines of evidence suggest that endocannabinoids, as well some synthetic and phytocannabinoids, act at numerous other non-CB_1/non-CB_2 receptors including the transient receptor potential cation channel subfamily V member 1 (TRPV1; also known as the capsaicin or vanilloid receptor VR1), members of the nuclear receptor family of peroxisome proliferator-activated receptors (PPARs*), and* G protein-coupled receptors such as *GPR55 and GPR119* (Alexander & Kendall, 2007; Brown, 2007; O'Sullivan, 2007).

In keeping with the ubiquitous expression of all components of the endocannabinoid system throughout the body, this lipid signalling system plays a very important role in the regulation of a wide array of physiological processes including appetite, metabolism, mood, motor function, gastrointestinal tract function, cardiovascular control, stress response, developmental biology, cell fate, immune and inflammatory response, endocrine function, neurotransmission and pain. With respect to pain, the components of the endocannabinoid system are expressed throughout nociceptive pathways, and thus, targeting the system via enhancement of endogenous signalling or exogenous cannabinoid ligands can regulate nociceptive signalling at the levels of the periphery, the dorsal horn of the spinal cord and in supraspinal pain-associated regions of the brain (Guindon & Beaulieu, 2009; Hohmann, 2002; Lötsch, Weyer-Menkhoff, & Tegeder, 2018; Sagar et al., 2010; Starowicz &

Finn, 2017). Endocannabinoids are generated on-demand in response to pain or stress and produce short-term antinociceptive effects via their actions as retrograde transmitters at presynaptic inhibitory CB_1 receptors. Endocannabinoids play a key role in the resolution of acute pain states and in mediating stress-induced analgesia (Butler & Finn, 2009; Finn et al., 2004; Hohmann et al., 2005), and they are elevated at various sites in nociceptive pathways in chronic pain states (Guindon, Lai, Takacs, Bradshaw, & Hohmann, 2013; Sagar, Burston, Woodhams, & Chapman, 2012; Woodhams, Chapman, Finn, Hohmann, & Neugebauer, 2017; Woodhams, Sagar, Burston, & Chapman, 2015), highlighting their role as endogenous analgesics.

4.5 | Potential indications for cannabis-based medicines for chronic pain management

4.5.1 | Uncertainties

Key point: There is insufficient evidence as to whether medical cannabis and cannabis-based medicines differ in their efficacy, tolerability and safety. There is no evidence available that the different formulations of medical cannabis, such as cannabis oil, are more effective or safer than dried medical cannabis.

Some divergent conclusions of systematic reviews (SRs) on the efficacy of cannabis-based medicines in chronic pain might be due to the analyses of different studies based on different inclusion criteria for study duration, the inclusion of 'grey' literature, and in the methods chosen for balancing benefits and risks (Häuser et al., 2018).

There are no head-to-head comparisons of different cannabis-based medicines for pain management available. We are only aware of one head-to-head randomized controlled trial (RCT) which compared medical cannabis with pharmaceutical cannabinoids in the context of pain medicine and palliative care (Häuser, Fitzcharles, Radbruch, & Petzke, 2017). Dronabinol was compared with smoked cannabis for weight loss in AIDS in 45 patients. The study was conducted before the availability of highly active Anti-Retroviral Therapy. Both cannabis-based medicines were superior to placebo for weight gain, but were not significantly different to one another (Abrams, Hilton, & Leiser, 2003).

The studies with medical cannabis in chronic pain available used only THC-containing strains of cannabis flowers. The THC content of medical cannabis ranged from 2.5% to 9% in the RCTs included into the overview of SR on cannabis-based medicines for chronic pain. No RCTs with cannabis strains containing THC and CBD are available until now (Häuser et al., 2018). Only one RCT with CBD alone (in Crohn's disease) is available until to date.

The evidence of differential effects (benefit or harm) with varying concentrations of CBD and THC or its individual components is inconclusive: A RCT with 177 patients found that THC/CBD was more effective at achieving a 30% cancer pain reduction compared to THC alone (43% vs. 23%). Adverse effects were similar between the two agents (Johnson, Burnell-Nugent, & Lossignol, 2010). One RCT found THC/CBD versus THC to be equally as effective for treating pain in 48 patients with brachial nerve injury. There were no statistically significant differences in the frequency of adverse events (Berman, Symonds, & Birch, 2004). A four arm 'n-of-1' trial studied THC, CBD, the combination of THC/CBD and placebo in 24 patients with stable chronic pain and unresponsive to pain management. Most patients found more effective symptom control with THC/CBD and THC alone (38% and 33%) and less response to CBD alone (17%) when compared to the run-in treatment of THC/CBD. Euphoria/dysphoria less often reported when patients used CBD only (Notcutt et al., 2004).

Most systematic reviews (SRs) have pooled the results of medical cannabis and pharmaceutical cannabinoids. Subgroup analyses have rarely been conducted (Häuser et al., 2018). Therefore, we present the data of pooled analysis and, if available, for medical cannabis and single pharmaceutical cannabinoids separately.

4.5.2 | Cancer pain

Key point: Nabiximols oromucosal spray can be considered as part of an add-on individual therapeutic trial * for cancer pain without sufficient relief from opioids or other established analgesics.1*

Studies conducted in the 1980s suggested a therapeutic benefit of THC (Noyes, Brunk, Avery, & Canter, 1975; Noyes, Brunk, Baram, & Canter, 1975; Staquet, Gantt, & Machin, 1978). The methods of these studies do not meet current standards of RCTs. Four studies which meet the current standards of RCTs have been conducted in the last 10 years (Fallon et al., 2017; Johnson et al., 2010; Portenoy, Ganae-Motan, & Allende, 2012). They compared nabiximols oromucosal spray as add-on therapy to conventional drug therapy versus placebo add-on. The studies included 1,130 patients and lasted between two and nine weeks. All studies failed to reach the primary endpoint (statistically significant superiority over placebo in pain relief of 30% or greater or mean pain intensity reduction) with p-values >0.05 to <0.10. For some secondary

endpoints, (e.g., sleep problems, health-related quality of life, continuous responder analysis of average daily pain), nabiximols oromucosal spray was statistically significantly superior to placebo (Mücke et al., 2016).

4.5.3 | Chronic neuropathic pain

Key point: Cannabis-based medicines can be considered as third-line therapy for chronic neuropathic pain.

A systematic overview of SRs concluded that there were inconsistent findings of four SR on the efficacy of cannabinoids compared to placebo in chronic neuropathic pain (Häuser et al., 2018).

In a systematic review of five RCTs including 178 patients with HIV-neuropathy (two studies), post-traumatic (one study) and mixed peripheral neuropathic pain (two studies), the number needed to treat for an additional benefit (NNTB) of a pain relief of 30% or greater was 6 [95% CI: 3–13] for medical cannabis. The authors stated that inhaled cannabis appeared to provide short-term relief from chronic neuropathic pain. However, study duration was one day in two studies, five days in one study and two weeks in two studies (Andreae et al., 2015). No data on intermediate-term (13–26 weeks) efficacy of medical cannabis are available. In addition, up to 90% of the patients in the studies included had previous experience with cannabis for recreational use (Petzke et al., 2016).

The systematic review of Finnerup et al. (2015) included nine RCTs with a study duration of three weeks or longer and 1,110 participants (eight studies with nabiximols oromucosal spray, one RCT with oral dronabinol). Patients suffered from diabetic peripheral polyneuropathy (two studies), central pain in multiple sclerosis (three studies), peripheral polyneuropathies of different origins (three studies) and spine injury (one study). The risk difference (RD) of 30% and more pain relief 0.03 (−0.03 to 0.09) was not statistically significant. The NNH (dropout due to adverse events) was 12 (95% CI: 9–20). The authors gave a weak recommendation against the use of cannabis-based medicines for chronic neuropathic pain.

The systematic review of Petzke et al. (2016) included 15 RCTs with a study duration of 2 weeks and longer (up to 15 weeks) with 1,519 participants. Ten studies used nabiximols oromucosal spray, two studies used oral nabilone, two studies used inhaled medical cannabis and one study used oral dronabinol. Patients suffered from diabetic peripheral polyneuropathy (three studies), central pain in multiple sclerosis (three studies), peripheral and central pain of different aetiologies (three studies), peripheral polyneuropathies of different origins (two studies), spine injury (one study), plexus injury (one study), chemotherapy-induced polyneuropathy (one study), and HIV-neuropathy (one study). Thirteen placebo-controlled studies were available for meta-analysis. NNTB for pain relief of 30% or greater was 10 (95% CI: 6–33). RD dropout due to adverse events was 0.04 (0.01, 0.07); Needed to Treat for an additional Harm NNTH was 19 (13–37); A subgroup analysis, if a single cannabis-based medicine was superior to placebo for a defined neuropathic pain condition, was not possible due to the lack of sufficient data. Subgroup analysis demonstrated that in pooled analysis of all neuropathic pain syndromes, nabiximols was superior to placebo for pain relief of 30% or greater with a NNTB of 12 (95% CI: 7–50). This outcome was available for only one study with medical cannabis. In one study with an Enriched Enrolment Randomised Withdrawal (EERW) design, nabilone was not superior to placebo for pain reduction. In one study, nabilone was not superior to dihydrocodeine for pain reduction (Petzke et al., 2016). The authors concluded that a short-term and intermediate-term therapy with cannabis-based medicines can be considered in selected patients with chronic neuropathic pain after failure of first-line and second-line therapies.

Nugent et al. (2017) included 13 RCTs with 735 patients with central or peripheral neuropathic pain related to various health conditions. Studies tested smoked or vaporized cannabis or nabiximols or THC oromucosal spray. Study duration ranged between one day and 13 weeks. Nine RCTs were meta-analysed: Risk ratio for 30% or more pain relief was 1.43 (95% CI: 1.16–1.88). The authors concluded that there is evidence, albeit of low strength, that cannabis may alleviate neuropathic pain in some patients (Nugent et al., 2017).

A recent Cochrane review included the same studies as Petzke et al., 2016 and a recently published RCT of 16-week duration with 234 patients with central neuropathic pain due to multiple sclerosis with oral dronabinol (Schimrigk et al., 2017). Sixteen studies with 1750 participants were included. The studies were 2 to 26 weeks long and compared nabiximols oromucosal spray (10 studies), nabilone (two studies), inhaled herbal cannabis (two studies) and dronabinol (two studies) against placebo (15 studies) and an analgesic (dihydrocodeine; one study). Study quality was low in two studies, moderate in 12 studies and high in two studies. Nine studies were at high risk of bias for study size. Cannabis-based medicines (26% of participants) were superior to placebo (21% of participants) in Patient Global Impression of Change (PGIC) was much or very much improved (RD 0.09 (95% CI: 0.01–0.17); NNTB 11 (95% CI: 6–100); 1,092 participants, six studies, very low-quality evidence). Cannabis-based medicines (39%) were superior to placebo (33%) in pain relief of 30% or greater (RD 0.09 (95% CI: 0.03–0.15); NNTB 11 (95% CI: 7–33); 1,586 participants, 10 studies, moderate-quality evidence). More participants withdrew from the studies due to adverse events

TABLE 2 Main findings of systematic reviews of randomized controlled trials of medical cannabis and cannabis-based medicines for chronic neuropathic pain

Author	Study duration for inclusion	Substances	Number of trials	Number of patients	Pain relief of 30% or more (95% CI)	NNTH for dropout due to side effects (95% CI)
Andreae et al. (2015)	None	Inhaled medical cannabis	5	178	NNTB 6 (3–13)	Not reported
Finnerup et al. (2015)	≥3 weeks	Inhaled medical cannabis; dronabinol; nabiximols; nabilone	9	1,110	RD 0.03 (−0.03 to 0.09)	12 (9–20)
Petzke et al. (2016)	≥2 weeks	Inhaled medical cannabis; dronabinol; nabiximols; nabilone	15	1,519	NNTB 10 (6–33)	19 (13–37)
Nugent et al. (2017)	None	Inhaled medical cannabis; dronabinol; nabiximols; nabilone	9	1,034	RD 1.43 (1.16–1.88)	Not reported
Mücke et al. (2018)	≥2 weeks	Inhaled medical cannabis; dronabinol; nabiximols; nabilone	16	1,750	NNTB 11 (7–33)	25 (16–30)

Notes. CI,: confidence interval; NNTB,: number needed to treat for an additional benefit; NNTH,: number needed to harm for an additional harm; RD,: risk difference.

with cannabis-based medicines (10% of participants) than with placebo (5% of participants; RD 0.04 (95% CI: 0.02–0.07); NNTH 25 (95% CI: 16–50); 1848 participants, 13 studies, moderate-quality evidence). There was no statistically significant difference between cannabis-based medicines (7% of participants) and placebo (5% of participants) in the frequency of serious adverse events (RD 0.01 (95% CI: −0.01 to 0.03); 1876 participants, 13 studies, low-quality evidence). Nervous system adverse events occurred in 61% of participants using cannabis-based medicines and in 29% using placebo (RD 0.38 (95% CI: 0.18–0.58); NNTH 3 (95% CI: 2–6); 1,304 participants, nine studies, low-quality evidence). Psychiatric disorders occurred in 17% of participants using cannabis-based medicines and in 5% using placebo (RD 0.10 (95% CI: 0.06–0.15); NNTH 10 (95% CI: 7–16); 1,314 participants, nine studies, low-quality evidence). The authors concluded that there was no high-quality evidence suggesting that any cannabis-based medicine (herbal cannabis, plant-derived or synthetic THC (dronabinol, nabilone), nabiximols oromucosal spray) was of value in treating people with chronic neuropathic pain. The potential benefits of cannabis-based medicines might be outweighed by their potential harms (Mücke et al., 2018).

The main results of the SRs are summarized in Table 2.

The Special Interest Group on Neuropathic Pain (NeuPSIG) revised recommendations for the pharmacotherapy of neuropathic pain gave a strong recommendation for use and proposal as first-line treatment in neuropathic pain for tricyclic antidepressants, serotonin–noradrenaline reuptake inhibitors, pregabalin and gabapentin; a weak recommendation for use and proposal as second line for lidocaine patches, capsaicin high-concentration patches and tramadol based on balancing NNTB and NNTH (Finnerup et al., 2015). It is the panel expert opinion that medical cannabis and cannabis-based medicines can be considered as third-line therapies in view of the NNTB for pain relief of 30% or more and the NNTH for dropout rates due to adverse events reported in the most comprehensive systematic reviews on neuropathic pain.

4.6 | Chronic non-neuropathic noncancer pain

> Key point: In exceptional cases, cannabis-based medicines can be considered as an individual therapeutic trial, if all established treatments have failed and after careful analyses and multidisciplinary assessment.

One recent systematic review demonstrated the superiority of all cannabis-based medicines pooled together for pain relief for all types of noncancer pain (CNCP) pooled together. Twenty-four RCTs with 1. 334 patients were eligible for meta-analysis. This analysis showed more pain reduction of chronic pain with a Hedges's g −0.61 (−0.78 to −0.43), compared to placebo. The majority of studies analysed included patients with neuropathic pain. A separate analysis of studies with non-neuropathic and noncancer pain was not performed. (Aviram & Samuelly-Leichtag, 2017). The review included experimental studies (1 day) and did not search for unpublished studies. Therefore, the review overestimated the efficacy of cannabis-based medicines for CNCP (Häuser & Fitzcharles, 2018). In addition, there are

many CNCP syndromes for which no RCT with cannabis-based medicines has been conducted to date, for example irritable bowel syndrome, painful bladder syndrome or chronic pelvic pain syndrome. It cannot be concluded, therefore, that cannabis-based medicines are effective for every CNCP. This conclusion is supported by a recent systematic review which concluded from 27 chronic pain trials that there is insufficient evidence in pain populations other than chronic neuropathic pain (Nugent et al., 2017).

Below, we list the evidence based on RCTs for cannabis-based medicines in single types of non-neuropathic CNCP. In sum, there is insufficient evidence for cannabis-based medicines for any type of non-neuropathic CNCP.

4.6.1 | Chronic abdominal pain

In a study of 8-week duration with 56 patients with chronic abdominal pain (postsurgery, chronic pancreatitis) oral THC (Namisol®) was not statistically superior to placebo in pain reduction at the end of treatment (de Vries et al., 2017). No RCTs with other cannabis-based medicines are available.

4.6.2 | Chronic low back pain

In a study of 8-week duration with 30 patients, current spine pain intensity was significantly lower with nabilone than with placebo. There was no significant difference between the two study groups in the 4 weeks average pain intensity reduction (Pinsger et al., 2006). No RCTs with other cannabis-based medicines are available.

4.6.3 | Crohn's disease

In a study of 8-week duration with 21 patients with Crohn's Disease Activity Index (CDAI) scores greater than 200 who did not respond to therapy with steroids, immunomodulators, or anti-tumour necrosis factor-alpha agents, smoked cannabis was statistically superior to placebo for pain relief, but not in the induction of remission (Naftali et al., 2013).

In a study of 8-week duration with 20 patients with Crohn's Disease Activity Index (CDAI) scores greater than 200 who did not respond to therapy with steroids, immunomodulators, or anti-tumour necrosis factor-alpha agents, cannabidiol was not statistically superior to placebo for pain relief (Naftali et al., 2017). No RCTs with other cannabis-based medicines are available.

4.6.4 | Fibromyalgia

One study with 40 patients compared nabilone with placebo over 4 weeks. The authors reported that nabilone but not placebo was statistically significant to placebo for pain relief in pre-post comparison. (Skrabek, Galimova, Ethans, & Perry, 2008). However, a re-analysis of the data, based on the means and SDs provided in the publication, found no statistically significant difference between nabilone and placebo in pain reduction at the end of treatment. (Fitzcharles et al., 2016). One study with 32 patients found no statistically significant difference between nabilone and amitriptyline for pain reduction after two weeks study duration (Ware, Fitzcharles, Joseph, & Shir, 2010). No RCTs with other cannabis-based medicines are available.

4.6.5 | Headache

A crossover RCT compared nabilone to ibuprofen for the reduction in pain and frequency of headache in 30 adults with long-standing, intractable medication overuse headache (MOH). After eight weeks of treatment with each, nabilone was found to be statistically significantly more effective than ibuprofen in reducing pain intensity on visual analogue scale and the number of concurrent daily analgesic therapies. However, 30% of the patients enrolled had MOH secondary to NSAID use (Pini et al., 2012).

4.6.6 | Rheumatoid arthritis

In a 5-week study with 58 patients, nabiximols oromucosal spray was statistically significantly superior to placebo in reducing morning pain on movement and at rest (NRS) and pain at present (a subcomponent of the Short Form MCGill Pain Questionnaire), but not for reducing total intensity of pain (single visual analogue scale score and intensity of pain at present (verbal rating scale; Blake, Robson, Ho, Jubb, & McCabe, 2006). No RCTs with other cannabis-based medicines are available.

4.7 | Absolute and relative contraindications

Key point: A history of a hypersensitivity reaction to cannabis-based medicines is an absolute contraindication.Pregnancy (contemplating or existing) / lactation and children and adolescents are absolute contraindications apart from exceptional circumstances.
Current or a history of mental disorder, especially substance abuse and dependence, and psychosis are relative contraindications.Seizures and severe cardiac disorders are relative contraindications.

Marijuana does not appear to be a major teratogen; however, a small increased risk of some congenital birth defects may be associated with early pregnancy use. Neurodevelopmental effects have been associated with marijuana use, but it is difficult to control for the effect of confounders (Merlob, Stahl, & Klinger, 2017). The neurodevelopmental data in

humans and animals suggest that prenatal exposure to THC may lead to subtle, persistent changes in targeted aspects of higher-level cognition and psychological well-being (Grant, Petroff, Isoherranen, Stella, & Burbacher, 2018). Pregnant women or women contemplating pregnancy should be encouraged to discontinue use of marijuana for medicinal purposes in favour of an alternative therapy for which there are better pregnancy-specific safety data.

There are limited and inconsistent data on the presence of the constituents of cannabis-based medicines in human milk, the effects on the breastfed infant or the effects on milk production. Because of the possible adverse effects of cannabis-based medicines on the breastfeeding infant, breastfeeding during treatment with cannabis-based medicines is discouraged (Committee on Obstetric Practice, 2017; FDA, 2017).

There is insufficient evidence for the use of cannabinoids or medical cannabis for chronic pain management in children and adolescents (Wong & Wilens, 2017). There is a strong association between early, frequent and heavy recreational use of cannabis in adolescence and poor cognitive and psychiatric outcomes in adulthood (Camchong, Lim, & Kumra, 2017; Levine, Clemenza, Rynn, & Lieberman, 2017). However, strong conclusions cannot yet be drawn as to whether cannabis use alone has a negative impact on the human adolescent brain. Treatment with cannabis-based medicines in children and adolescents should only be performed in exceptional cases. Treatment should be performed in specialized centres/by specialized paediatricians with experience on cannabis-based drugs.

Treatment with cannabis-based medicines in patients with mental disorders should be conducted in close collaboration with a mental healthcare specialist for addiction, in patients with cardiac disorders with a cardiologist and in patients with seizures with a neurologist.

4.8 | Special situations

4.8.1 | Seniors

Key point: Consider a lower starting dose in elderly patients.

Elderly patients may be more sensitive to the neuropsychiatric and postural hypotensive effects of cannabinoids (FDA, 2017).

4.8.2 | Renal and hepatic insufficiency

Key point: Consider a lower starting dose in patients with renal and hepatic insufficiency.

There are very limited data on the benefits and risks of cannabis-based medicines in renal and hepatic insufficiency available. In the absence of available literature, it is the panel expert opinion to recommend lower starting doses.

4.8.3 | Patients with high doses of opioids and benzodiazepines

Patients with high doses of opioids or benzodiazepines.

Key point: Do not prescribe cannabis-based medicines to patients taking high doses of opioids or benzodiazepines.

In the absence of available literature, it is the panel expert opinion that cannabis use could worsen the cognitive impairment caused by high doses of opioids and benzodiazepines. If cannabis is prescribed, it should be prescribed at a low dose and should be discontinued if it affects patients' memory, mood or function. Physicians should consider tapering high opioid (≥90 mg morphine equivalent/day) or benzodiazepine doses, especially in patients with chronic noncancer pain (Kahan et al., 2014).

4.8.4 | Use while driving

Key point: Advise patients not to drive at all if a therapy with cannabis-based medicines is started or modified until a stable dosage for 5–7 days is reached. Advise patients not to drive while under the influence of cannabis-based medicines and not to drink alcohol. Do not prescribe cannabis-based medicines to patients with professional driving (taxi drivers, truck drivers, ambulances).

There are no data available on the association of medical cannabis use and traffic accidents. Systematic reviews of observational studies demonstrated an increased risk of motor vehicle crash, especially for fatal collisions, in the context of recreational use (Asbridge et al., 2012). Risk is higher if alcohol has also been consumed (Martin, Gadegbeku, Wu, Viallon, & Laumon, 2017). With analogy to the European Pain Federation position paper on appropriate opioid use in chronic pain management, we recommend patients to be on stable therapy of at least 5–7 days' duration before driving a car (O'Brien et al., 2017). The Canadian preliminary recommendations for prescribing smoked cannabis for chronic noncancer pain suggested to inform patients not to drink or use sedating drugs while using cannabis and not to drive for at least 3 hr after smoking cannabis, 6 hr after oral ingestion of cannabis and 8 hr if they experience a 'high' (Kahan et al., 2014). The task force

recommends that each physician informs the patient on the current legal situation in the particular country if there any regulations which forbid or allow driving under the use of cannabis-based medicines.

4.8.5 | Use while working

Key point: Recommend a medical assessment for working ability of patients in jobs where there is a potential for harm to oneself or to others.

There are no data available on the association of medical cannabis use and occupational accidents or injuries. There is insufficient evidence to support or refute a statistical association between general, nonmedical cannabis use and occupational accidents or injuries (National Academies of Sciences, Engineering, and Medicine, 2017). Because of the potential risks of cannabis-based medicines and medical cannabis, patients operating machines should be examined for working capacity by an occupational health physician.

4.8.6 | Use while travelling

Key point: Issue a certificate according to §75 of the Schengen Implementing Convention if your patient with cannabis-based medicines is travelling up to 30 days in one of the countries of the Schengen convention. If the patient is travelling to other countries, recommend that the patient to consult the information of the International Narcotis Control Board (International Narcotic Board, 2018).

4.9 | Good clinical practice

4.9.1 | Adequate assessment and supervision of patients with chronic pain potentially treated by cannabis-based medicines

Key points:

1 All patients presenting with chronic pain should be adequately assessed by competent clinicians based on a biopsychosocial approach. The management strategy should be devised and implemented with due regard to best international practice.
2 All prescribing clinicians should be familiar with pain assessment techniques and management guidelines, including the safe and effective use of cannabis-based medicines.
3 Nonspecialists should only prescribe cannabis-based medicines if they have timely access to consultation with a specialist multidisciplinary team in case of particular circumstances that will obligate consultation.
4 Monotherapy with cannabis-based medicines should be avoided. Drug therapy should be combined with physical and/or psychological therapies if appropriate.
5 Within shared decision-making, patients should be informed on the benefits for specific indications, including natural frequencies (event rates) and numbers needed to treat (with duration) as well as on common adverse events in both natural frequency (event rates) and numbers needed to harm. Inform the patient about information brochures on the use of medical cannabis available (e.g., Institute for Responsible Medicine Use and the Office of Medicinal Cannabis of the CIBG, Ministry of Health, Welfare and Sport 2011; Health Canada, 2016; Medical board of California, 2017).
6 The correct dose of any cannabis-based medicines is the lowest possible dose that achieves the desired clinical effect (e.g., pain relief of 30% or more, meaningful improvement of daily functioning) with the minimal side effect profile. For the range of the dosages used in clinical trials and for maximum dosages of finished dosages products and of extemporaneous products, see Table 3.
7 A testing period of maximum 3 months should be considered both by patients and prescribers, to assess treatment efficacy and safety. At the end of this testing period, long-term treatment should only be considered with significant improvement and lack of safety issues.
8 If a satisfactory outcome is achieved, the patient should remain under close medical surveillance for the duration of cannabis-based medicine therapy
9 If the predefined treatment goals are not achieved and/or unacceptable burden of side effects occur and/or signs of abuse and misuse are observed, the specific cannabis-based medicines should be safely withdrawn and alternative options actively explored.
10 Patients and families should be fully informed regarding the use and storage of cannabis-based medicines and fully supported throughout the duration of therapy.
11 Cannabis-based medicines should be dispensed by competent and responsible pharmacists with due regard to local and national regulations and in accordance with best international practice.

TABLE 3 Generic names, brand names, range of dosages used in clinical trials and maximum dosage as detailed in prescription or specialist information (Häuser et al., 2017; Häuser et al., 2018)

Generic name	Brand name	Range of dosages used in clinical trials (mg/day)	Maximum dosage/day of prescription /specialist information (mg)
Delta-9-Tetrahydrocannabinol (THC)	Dronabinol® Marinol®	2.5–10	50
THC/Cannabidiol (CBD) (Nabiximols)	Sativex®	27/25 to 130/120	32.4 mg /30
CBD	Epidiolex®	No studies conducted for chronic pain published	Not available
Nabilone	Canemes®	2–6	6

12 An unique physician should be responsible for treatment prescriptions and follow-up, for safer use.
13 In patients with mental disorders, treatment management should include psychiatrist at the start and follow-up.[2]

The main principles of GCP for prescribing cannabis-based medicines for chronic pain do not differ from the ones for prescribing other drugs, for example opioids, for chronic pain (Häuser, Schug, & Furlan, 2017; O'Brien et al., 2017)

4.10 | Drug interactions

4.10.1 | Concomitant use of centrally acting agents

Key point: Cannabis based medicines can have both pharmacokinetic and pharmacodynamic interactions with other drugs. Reduce the dosage of other centrally acting drugs as far as possible before cannabis-based medicines are used.

Cannabis products contain tens of different constituents with unknown metabolic pathways. The most abundant constituents, THC and CBD, are metabolized mainly in the liver by cytochrome P-450 isoenzymes. In vitro studies indicate that THC is substrate for CYP3A4 and CYP2C9 and CBD and THC for CYP3A4 (Stout & Cimino, 2014). In vitro data suggest a lack of relevant induction of CYPs by THC or CBD (Stout & Cimino, 2014). Both of these cannabinoids inhibit CYP1A1, 1A2 and 1B1 enzymes (Arellano, Papaseit, Romaguera, Torrens, & Farré, 2017). Both cannabinoids may interact with other medications metabolized by the same pathway or by inducers/inhibitors of the isoenzymes. Thus, an inducer of CYP3A4 (e.g., rifampicin or carbamazepine) would decrease, whereas an inhibitor (e.g., ketoconazole) would increase the availability of THC and CBD. Potential effects should be taken into consideration when co-administering THC and /or CBD with compounds which share the CYP3A4 pathway such as rifampicin or ketoconazole (Stott, White, Wright, Wilbraham, & Guy, 2013). Inhibition of CYP3A4 by CBD would increase the availability of drugs such as oxycodone (Arellano et al., 2017; Rong et al., 2018). Both cannabis and tobacco smoking induce CYP4501A2 through induction of theophylline clearance, and the induction effect between the two products is additive (Anderson & Chan, 2016; Wallace et al., 2007). There is a lack of evidence for 'non-smoked' products induce CYP450 1A2.

The clinical relevance of all these interactions is still unknown. Theoretically, medical cannabis and THC can decrease serum concentrations of chlorpromazine, cyclobenzaprine clozapine, duloxetine, haloperidol, naproxen and olanzapine (Anderson & Chan, 2016). Alcohol may increase THC levels (Hartman et al., 2015). Sedative effects of other centrally acting drugs like opioids may be increased by concomitant cannabis administration.

4.10.2 | Perioperative period

Key point: Patients treated with cannabis-based medicines require special attention during the perioperative period.

In anaesthesia, some studies have suggested that there were antagonistic effects between propofol and cannabis, thus requiring increased propofol dosages for induction phase (Flisberg et al., 2009). Cannabis use is also associated with increased sedative effects of anaesthetic drugs (Huu, 2004). Cannabis users may require higher dosages of analgesics for the postsurgery period (Jefferson, Harding, & Cawich, 2013).

4.11 | Special recommendations for prescription of cannabis-based medicines

4.11.1 | Start with oral or oromucosal cannabis-based medicines

Key point: If a patient is suited for a trial with cannabis-based medicines, start with oral or oromucosal cannabis-based medicines (e.g., dronabinol, nabiximols).

The quantity of evidence is larger for oral or buccal cannabis-based medicines (e.g., dronabinol, nabiximols) than for medical cannabis or for cannabis extracts. The randomized controlled studies available did not demonstrate a superiority over nabilone over placebo in pain relief (Häuser, Fitzcharles et al., 2017). The content of ingested THC and/or CBD is better defined in pharmaceutical cannabinoids than in medical cannabis. The bioavailability of inhaled cannabis is more variable than of oral (pills, oils) cannabis-based medicines. Insufficient data are available for the differential indication of different cannabis strains that highly differ in their content of THC and CBD. The risk of misuse (e.g., diversion; use for illicit purposes) is probably higher for inhaled cannabis strains with high content of THC than for oral cannabis-based medicines or for inhaled cannabis strains with a low THC content.

4.11.2 | Trial with cannabis extract or inhaled cannabis

Key point: If oral or oromucosal individual cannabis-based medicines (e.g. dronabinol, nabiximols) do not work, a trial of cannabis extract (oil) or inhaled cannabis can be considered.

The recommendation is in line with the Canadian guidelines on prescribing medical cannabinoids (Allan et al., 2018).

4.11.3 | Do not smoke cannabis

Key point: Advise patients to use medical cannabis as oil extract or via a vaporizer for inhalation (dried cannabis) and not to smoke cannabis. Advise patients to use approved medical devices.

Temperature-controlled, electrically driven vaporizers efficiently decarboxylate inactive acidic cannabinoids and reliably release their corresponding neutral, active cannabinoids. They offer a promising application mode for the safe and efficient administration of medicinal cannabis (Lanz, Mattsson, Soydaner, & Brenneisen, 2016).

Although bronchial biopsies from habitual marijuana smokers have shown precancerous histopathological changes, a large cohort study and a pooled analysis of six well-designed case–control studies have not found evidence of a link between marijuana smoking and lung cancer. The immunosuppressive effects of THC raise the possibility of an increased risk of pneumonia, but further studies are needed to evaluate this potential risk. Several cases series have demonstrated pneumothoraces/pneumomediastinum, as well as bullous lung disease, in marijuana smokers, but these associations require epidemiologic studies for firmer evidence of possible causality (Tashkin, 2018).

In the absence of consistent findings in the literature on an increased risk of lung diseases by cannabis smoking, it is the panel expert opinion to educate patients to stop smoking cannabis and to use a vaporizer.

4.11.4 | Recommended dosages of medical cannabis

Key point: Do not prescribe cannabis flowers with a high (>12.5%) THC content. A dose of no more than one inhalation four times per day to avoid cannabis intoxication and cognitive impairment is recommended.

THC concentrations of medical cannabis strains available vary between 1% and 22%, and CBD concentrations vary between 0.05% and 9% (Häuser et al., 2018). The database to help inform which THC concentration and which ratio of THC to CBD is best in terms of efficacy and safety is very sparse. One crossover RCT found that 25 mg herbal cannabis with 9.4% THC administered as a single smoked inhalation three times daily for five days, significantly reduced average pain intensity compared to a 0% THC cannabis placebo in 22 adult participants with chronic post-traumatic or postsurgical neuropathic pain. Herbal cannabis with 2.5% and 6% THC was not superior to placebo. The subjects in this trial did not experience serious cognitive effects such as confusion and disorientation (Ware, Wang et al., 2010). A systematic review with individual patient data analysis of five RCTs with medical cannabis for neuropathic pain found that the breakdown of responder data by dose suggested an increased effect with increased THC content. THC content of medical cannabis ranged from 1% to 9.4% in the studies analysed. However, declines in attention, psychomotor performance and learning and memory as well as feeling 'high' increased in frequency with increasing dose as well (Andreae et al., 2015). The dosages in 'real live settings' are higher. One 1-year observational study reported that the average dosage of herbal cannabis with 12.5% THC was 2.5 g/day (minimum 0.1 g/d, maximum 14 g/day; Ware, Wang, Shapiro, & Collet, 2015).

The Canadian practice guideline recommended that treatment should be initiated with one inhalation per day and may be increased to no more than one inhalation four times per day to avoid cannabis intoxication and cognitive impairment. A prescription of 400 mg per day (half a joint a day) or 12 g per month (30 days) will allow for four inhalations per day (Kahan et al., 2014).

4.12 | Tools for clinical practice

4.12.1 | Information leaflets

Key point: Use information leaflets of health authorities to inform patients on the potential benefits and risks of cannabis-based medicines.

Informing the patient on the potential benefits and risks of cannabis-based medicines is part of good clinical practice, for example the flyer of The College of Family Physicians in Canada on medical cannabinoids (The College of Family Physicians in Canada, 2018).

4.12.2 | Screening for anxiety and depression

Key point: Consider screening for depression and anxiety, for example by the Patient Health Questionnaire 4.

Screening for psychological distress as part of pain assessment is recommended by recent guidelines on the management of CNCP (O'Brien et al., 2017). With four questions only, the PHQ 4 can be easily completed by the patient and evaluated by the physician. Its sensitivity and specificity to detect anxiety (including post-traumatic stress disorder) and depressive disorder are high (Kroenke, Spitzer, Williams, & Löwe, 2009). The questionnaire can be downloaded by the Internet (http://www.phqscreeners.com/sites/g/files/g10016261/f/201412/English_3.pdf). No permission is required to reproduce, translate, display or distribute.

4.12.3 | Screening for substance abuse

Key point: Consider screening for substance abuse by the CAGE Adapted to Include Drugs.

The use of this questionnaire (Brown & Rounds, 1995) has been recommended if prescribing cannabis-based medicines (Kahan et al., 2014).

4.12.4 | Treatment agreement

Key point: Consider having the patient sign a written treatment agreement.

The use of a written treatment agreement has been recommended by recent guidelines for prescribing cannabis-based medicines (Kahan et al., 2014). An example of a written treatment agreement which can be modified according to the type of cannabis-based medicines use can be downloaded at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4417655/ (Wilsey, Atkinson, Marcotte, & Grant, 2015) and at http://ada i.uw.edu/mcacp/docs/treatmentagreement.pdf.

5 | SUMMARY AND CONCLUSIONS

The current status of evidence and of use of medical cannabis and of cannabis-based medicines for chronic pain in Europe is insufficient. A search in ClinicalTrials.gov as well as the contacts of the authors with pharmaceutical companies and colleagues demonstrated that new studies with cannabis-based medicines for chronic pain syndromes are designed and /or being conducted. The increase in the number of countries that have moved recently towards authorization of medical cannabis or cannabis-based medicines for chronic pain will also afford the opportunity for larger scale empirical and population-level studies which will further inform the evidence base. Therefore, we expect that the quantity and quality of evidence of as well as the clinical experience of physicians medical cannabis and cannabis-based medicines for chronic pain will substantially improve within the next three years. Therefore, we will update the position paper in 2021.

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CONFLICT OF INTERESTS

WH, SP, NKS, BM, SP, MS, CW and SB have no conflict of interests to declare. DPF has received peer-reviewed grant funding from both public bodies and Industry (Randox) for research on cannabinoids and the endocannabinoid system. HGK has served as expert advisor and/or congress speaker for Bionorica SE, Germany, and Trigal GmbH, Austria.

NOTES

[1] Individual therapeutic trial = A treatment which is not recommended by recent medical standards and is used for patients which do not respond to standard medical therapy. The drug may not be approved by regulatory agencies for this indication (off-label use). An individual therapeutic trial with cannabis-based medicines for chronic pain is different to compassionate use**.** Compassionate use is a treatment option that allows the use of an unauthorised medicine. under strict conditions. Products in development can be made available to groups of patients who have a life-threatening, long-lasting

or seriously debilitating disease with no satisfactory authorised therapies and who cannot enter clinical trials (European Medical Agencies, 2014). Cannabis-based medicines might be approved for some chronic pain conditions in some European countries (Krcevski-Skvarc et al., 2018) although they are not established medical treatments.

[2] For screening for anxiety and depressive disorder and substance abuse, see section ‚Tools for clinical practice'

REFERENCES

Abrams, D. I., Hilton, J. F., & Leiser, R. J. (2003). Short-term effects of cannabinoids in patients with HIV-1 infection: A randomized, placebo-controlled clinical trial. *Annals of Internal Medicine*, *139*, 258–266. https://doi.org/10.7326/0003-4819-139-4-200308190-00008

Alexander, S. P., & Kendall, D. A. (2007). The complications of promiscuity: Endocannabinoid action and metabolism. *British Journal of Pharmacology*, *152*, 602–623.

Allan, M., Ton, J. R., Beahm, N. P., Crsip, N., Dockrill, B., Dubin, R. E., … Lindblad, A. J. (2018). Simplified guideline for prescribing medical cannabinoids in primary care. *Canadian Family Physician*, *64*, 111–120.

Anderson, G. D., & Chan, L. N. (2016). Pharmacokinetic drug interactions with tobacco, cannabinoids and smoking cessation products. *Clinical Pharmacokinetics*, *55*, 1353–1368. https://doi.org/10.1007/s40262-016-0400-9

Andreae, M. H., Carter, G. M., Shaparin, N., Suslov, K., Ellis, R. J., Ware, M. A., … Sacks, H. S. (2015). Inhaled cannabis for chronic neuropathic pain: A meta-analysis of individual patient data. *Journal of Pain*, *16*, 1221–1232. https://doi.org/10.1016/j.jpain.2015.07.009

Arellano, A. L., Papaseit, E., Romaguera, A., Torrens, M., & Farré, M. (2017). Neuropsychiatric and general interactions of natural and synthetic cannabinoids with drugs of abuse and medicines. *CNS & Neurological Disorders - Drug Targets*, *16*, 554–566.

Asbridge, M., Hayden, J. A., & Cartwright, J. L. (2012). Acute cannabis consumption and motor vehicle collision risk: Systematic review of observational studies and meta-analysis. *BMJ*, *34*, e536. https://doi.org/10.1136/bmj.e536

Aviram, J., & Samuelly-Leichtag, G. (2017). Efficacy of cannabis-based medicines for pain management: A systematic review and meta-analysis of randomized controlled trials. *Pain Physician*, *20*, E755–E796.

Baek, J. H., Zheng, Y., Darlington, C. L., & Smith, P. F. (2008). Cannabinoid CB2 receptor expression in the rat brainstem cochlear and vestibular nuclei. *Acta Oto-Laryngologica*, *128*, 961–967. https://doi.org/10.1080/00016480701796944

Battista, N., Di Tommaso, M., Bari, M., & Maccarrone, M. (2012). The endocannabinoid system: An overview. *Frontiers in Behavioural Neurosciences*, *6*, 9.

Berdyshev, E. V. (2000). Cannabinoid receptors and the regulation of immune response. *Chemistry and Physics of Lipids*, *108*, 169–190. https://doi.org/10.1016/S0009-3084(00)00195-X

Berman, J. S., Symonds, C., & Birch, R. (2004). Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: Results of a randomised controlled trial. *Pain*, *112*, 299–306. https://doi.org/10.1016/j.pain.2004.09.013

Blake, D. R., Robson, P., Ho, M., Jubb, R. W., & McCabe, C. S. (2006). Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology*, *45*, 50–52. https://doi.org/10.1093/rheumatology/kei183

Bouaboula, M., Poinot-Chazel, C., Bourrie, B., Canat, X., Calandra, B., & Rinaldi-Carmona, M. (1995). Activation of mitogen-activated protein kinases by stimulation of the central cannabinoid receptor CB1. *Biochemical Journal*, *312*, 637–641. https://doi.org/10.1042/bj3120637

Brown, A. J. (2007). Novel cannabinoid receptors. *British Journal of Pharmacology*, *152*, 567–575.

Brown, R. L., & Rounds, L. A. (1995). Conjoint screening questionnaires for alcohol and other drug abuse: Criterion validity in a primary care practice. *Wisconsin Medical Journal*, *94*, 135–140.

Butler, R. K., & Finn, D. P. (2009). Stress-induced analgesia. *Progress in Neurobiology*, *88*, 184–202. https://doi.org/10.1016/j.pneurobio.2009.04.003

Camchong, J., Lim, K. O., & Kumra, S. (2017). Adverse effects of cannabis on adolescent brain development: A longitudinal study. *Cerebral Cortex*, *27*, 1922–1930.

Concannon, R. M., Okine, B. N., Finn, D. P., & Dowd, E. (2015). Differential upregulation of the cannabinoid CB(2) receptor in neurotoxic and inflammation-driven rat models of Parkinson's disease. *Experimental Neurology*, *269*, 133–141. https://doi.org/10.1016/j.expneurol.2015.04.007

Committee on Obstetric Practice (2017). Committee Opinion No. 722: Marijuana Use during pregnancy and lactation. *Obstetrics and Gynecology*, *130*, e205–e209.

Demuth, D. G., & Molleman, A. (2006). Cannabinoid signalling. *Life Sciences*, *78*, 549–563. https://doi.org/10.1016/j.lfs.2005.05.055

Devane, W. A., Dysarz III, F. A., Johnson, M. R., Melvin, L. S., & Howlett, A. C. (1988). Determination and characterization of a cannabinoid receptor in rat brain. *Molecular Pharmacology*, *34*, 605–613.

Devane, W. A., Hanus, L., Breuer, A., Pertwee, R. G., Stevenson, L. A., & Griffin, G. (1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*, *258*, 1946–1949. https://doi.org/10.1126/science.1470919

Devinsky, O., Cilio, M. R., Cross, H., Fernandez-Ruiz, J., French, J., Hill, C., … Friedman, D. (2014). Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*, *55*, 791–802. https://doi.org/10.1111/epi.12631

de Vries, M., van Rijckevorsel, D. C. M., Vissers, K. C. P., Wilder-Smith, O. H. G., & van Goor, H. (2017). Tetrahydrocannabinol does not reduce pain in patients with chronic abdominal pain in a phase 2 placebo-controlled study. *Clinical Gastroenterology and Hepatology*, *15*, 1079–1086. https://doi.org/10.1016/j.cgh.2016.09.147

Di Marzo, V. (2008). Endocannabinoids: Synthesis and degradation. *Reviews of Physiology Biochemistry and Pharmacology*, *160*, 1–24.

Di Marzo, V., Stella, N., & Zimmer, A. (2015). Endocannabinoid signalling and the deteriorating brain. *Nature Reviews Neuroscience*, *16*, 30–42. https://doi.org/10.1038/nrn3876

Fallon, M. T., Albert Lux, E., McQuade, R., Rossetti, S., Sanchez, R., Sun, W., … Kornyeyeva, E. (2017). Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: Two double-blind, randomized, placebo-controlled phase 3 studies. *British Journal of Pain*, *1*, 119–133. https://doi.org/10.1177/2049463717710042

Fasinu, P. S., Phillips, S., ElSohly, M. A., & Walker, L. A. (2016). Current status and prospects for cannabidiol preparations as new

therapeutic agents. *Pharmacotherapy*, *36*, 781–796. https://doi.org/10.1002/phar.1780

Fine, P. G., & Rosenfeld, M. J. (2013). The endocannabinoid system, cannabinoids, and pain. *Rambam Maimonides Medical Journal*, *4*, e0022.

Finn, D. P., Beckett, S. R., Richardson, D., Kendall, D. A., Marsden, C. A., & Chapman, V. (2004). Evidence for differential modulation of conditioned aversion and fear-conditioned analgesia by CB1 receptors. *European Journal of Neuroscience*, *20*, 848–852. https://doi.org/10.1111/j.1460-9568.2004.03509.x

Finnerup, N. B., Attal, N., Haroutounian, S., McNicol, E., Baron, R., Dworkin, R. H., … Wallace, M. (2015). Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. *Lancet Neurology*, *14*, 162–173. https://doi.org/10.1016/S1474-4422(14)70251-0

Fitzcharles, M. A., Baerwald, C., Ablin, J., & Häuser, W. (2016). Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis): A systematic review of randomized controlled trials. *Schmerz*, *30*, 47–61. https://doi.org/10.1007/s00482-015-0084-3

Flisberg, P., Paech, M. J., Shah, T., Ledowski, T., Kurowski, I., & Parsons, R. (2009). Induction dose of propofol in patients using cannabis. *European Journal of Anaesthesiology*, *26*, 192–195. https://doi.org/10.1097/EJA.0b013e328319be59

Gaoni, Y., & Mechoulam, R. (1964). Isolation, structure, and partial synthesis of an active constituent of hashish. *Journal of the American Chemical Society*, *86*, 1646–1647. https://doi.org/10.1021/ja01062a046

Glass, M., Dragunow, M., & Faull, R. L. (1997). Cannabinoid receptors in the human brain: A detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. *Neuroscience*, *77*, 299–318. https://doi.org/10.1016/S0306-4522(96)00428-9

Grant, K. S., Petroff, R., Isoherranen, N., Stella, N., & Burbacher, T. M. (2018). Cannabis use during pregnancy: Pharmacokinetics and effects on child development. *Pharmacology & Therapeutics*, *182*, 133–151. https://doi.org/10.1016/j.pharmthera.2017.08.014

Grotenhermen, F., & Muller-Vahl, K. (2012). The therapeutic potential of cannabis and cannabinoids. *Deutsches Ärzteblatt International*, *109*, 495–501.

Guindon, J., & Beaulieu, P. (2009). The role of the endogenous cannabinoid system in peripheral analgesia. *Current Molecular Pharmacology*, *2*, 5.

Guindon, J., Lai, Y., Takacs, S. M., Bradshaw, H. B., & Hohmann, A. G. (2013). Alterations in endocannabinoid tone following chemotherapy-induced peripheral neuropathy: Effects of endocannabinoid deactivation inhibitors targeting fatty-acid amide hydrolase and monoacylglycerol lipase in comparison to reference analgesics following cisplatin treatment. *Pharmacological Research*, *67*, 94–109. https://doi.org/10.1016/j.phrs.2012.10.013

Hartman, R. L., Brown, T. L., Milavetz, G., Spurgin, A., Pierce, R. S., Gorelick, D. A., … Huestis, M. A. (2015). Cannabis effects on driving longitudinal control with and without alcohol. *Journal of Applied Toxicology*, *36*, 1418–1429.

Häuser, W., Fitzcharles, M. A., Radbruch, L., & Petzke, F. (2017). Cannabinoids in pain management and palliative medicine. *Deutsches Ärzteblatt International*, *114*, 627–634.

Häuser, W., Schug, S., & Furlan, A. (2017). The opioid epidemic and national guidelines for opioid therapy for chronic noncancer pain: A perspective from different continents. *PAIN Reports*, *2*, e599. https://doi.org/10.1097/PR9.0000000000000599

Häuser, W., Petzke, F., & Fitzcharles, M. A. (2018). Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management - An overview of systematic reviews. *European Journal of Pain*, *22*, 455–470. https://doi.org/10.1002/ejp.1118

Häuser, W. & Fitzcharles, M. A. (2018). The perils of overestimating the efficacy of cannabis-based medicines for chronic pain management. *Pain Physician*, *21*, E79–E80.

Herkenham, M., Lynn, A. B., Johnson, M. R., Melvin, L. S., de Costa, B. R., & Rice, K. C. (1991). Characterization and localization of cannabinoid receptors in rat brain: A quantitative in vitro autoradiographic study. *Journal of Neuroscience*, *11*, 563–583. https://doi.org/10.1523/JNEUROSCI.11-02-00563.1991

Hohmann, A. G. (2002). Spinal and peripheral mechanisms of cannabinoid antinociception: Behavioral, neurophysiological and neuroanatomical perspectives. *Chem Physics Lipids*, *121*, 173–190. https://doi.org/10.1016/S0009-3084(02)00154-8

Hohmann, A. G., Suplita, R. L., Bolton, N. M., Neely, M. H., Fegley, D., Mangieri, R., … Piomelli, D. (2005). An endocannabinoid mechanism for stress-induced analgesia. *Nature*, *435*, 1108–1112. https://doi.org/10.1038/nature03658

Howlett, A. C., Mukhopadhyay, S., Shim, J. Y., & Welsh, W. J. (1999). Signal transduction of eicosanoid CB1 receptor ligands. *Life Sciences*, *65*, 617–625. https://doi.org/10.1016/S0024-3205(99)00284-2

Jefferson, D. A., Harding, H. E., & Cawich, S. O. (2013). Postoperative analgesia in the Jamaican cannabis user. *Journal of Psychoactive Drugs*, *45*, 227–232. https://doi.org/10.1080/02791072.2013.803644

Johnson, J. R., Burnell-Nugent, M., & Lossignol, M. (2010). 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*, *39*, 167–179. https://doi.org/10.1016/j.jpainsymman.2009.06.008

Kahan, M., Srivastava, A., Spithoff, S., & Bromley, L. (2014). Prescribing smoked cannabis for chronic noncancer pain: Preliminary recommendations. *Canadian Family Physician*, *60*, 1083–1090.

Krcevski-Skvarc, N., Wells, C., & Häuser, W. (2018). Availability and approval of cannabis-based medicines for chronic pain management and palliative/supportive care in Europe: A survey of the status in the chapters of the European Pain Federation. *European Journal of Pain*, *44*, 440–454. https://doi.org/10.1002/ejp.1147

Kroenke, K., Spitzer, R. L., Williams, J. B., & Löwe, B. (2009). An ultra-brief screening scale for anxiety and depression: The PHQ-4. *Psychosomatics*, *50*, 613–621.

Lanz, C., Mattsson, J., Soydaner, U., & Brenneisen, R. (2016). Medicinal Cannabis. In vitro validation of vaporizers for the smoke-free inhalation of cannabis. *PLoS ONE*, *11*, e0147286. https://doi.org/10.1371/journal.pone.0147286

Levine, A., Clemenza, K., Rynn, M., & Lieberman, J. (2017). Evidence for the risks and consequences of adolescent cannabis exposure. *Journal of the American Academy of Child and Adolescent Psychiatry*, *56*, 214–225. https://doi.org/10.1016/j.jaac.2016.12.014

Lötsch, J., Weyer-Menkhoff, I., & Tegeder, I. (2018). Current evidence of cannabinoid-based analgesia obtained in preclinical and human experimental settings. *European Journal of Pain*, *22*, 471–484. https://doi.org/10.1002/ejp.1148

Martin, J. L., Gadegbeku, B., Wu, D., Viallon, V., & Laumon, B. (2017). Cannabis, alcohol and fatal road accidents. *PLoS ONE*, *12*, e0187320. https://doi.org/10.1371/journal.pone.0187320

Martın-Sanchez, E., Furukawa, T. A., Taylor, J., & Martin, J. L. (2009). Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med*, *10*, 1353–1368. https://doi.org/10.1111/j.1526-4637.2009.00703.x

Matsuda, L. A., Lolait, S. J., Brownstein, M. J., Young, A. C., & Bonner, T. I. (1990). Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature*, *346*, 561–564. https://doi.org/10.1038/346561a0

Mechoulam, R., & Gaoni, Y. (1967). The absolute configuration of delta-1-tetrahydrocannabinol, the major active constituent of hashish. *Tetrahedron Letters*, *12*, 1109–1111. https://doi.org/10.1016/S0040-4039(00)90646-4

Mechoulam, R., Ben-Shabat, S., Hanus, L., Ligumsky, M., Kaminski, N. E., & Schatz, A. R. (1995). Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochemical Pharmacology*, *50*, 83–90. https://doi.org/10.1016/0006-2952(95)00109-D

Merlob, P., Stahl, B., & Klinger, G. (2017). For debate: Does cannabis use by the pregnant mother affect the fetus and newborn? *Pediatric Endocrinology Reviews*, *15*, 4–7.

Munro, S., Thomas, K. L., & Abu-Shaar, M. (1993). Molecular characterization of a peripheral receptor for cannabinoids. *Nature*, *365*, 61–65. https://doi.org/10.1038/365061a0

Mücke, M., Carter, C., Cuhls, H., Prüß, M., Radbruch, L., & Häuser, W. (2016). Cannabinoids in palliative care: Systematic review and meta-analysis of efficacy, tolerability and safety]. *Schmerz*, *30*, 25–36. (German). https://doi.org/10.1007/s00482-015-0085-2

Mücke, M., Philipps, T., Radburch, L., Petzke, F., & Häuser, W. (2018). Cannabis-based medicines for chronic neuropathic pain in adults. *Cochrane Database Systematic Review*, *3*, CD012182.

Naftali, T., Bar-Lev Schleider, L., Dotan, I., Lansky, E. P., Sklerovsky Benjaminov, F., & Konikoff, F. M. (2013). Cannabis induces a clinical response in patients with Crohn's disease: A prospective placebo-controlled study. *Clinical Gastroenterology and Hepatology*, *10*, 1276–1280. https://doi.org/10.1016/j.cgh.2013.04.034

Naftali, T., Mechulam, R., Marii, A., Gabay, G., Stein, A., Bronshtain, M., … Konikoff, F. M. (2017). Low-dose cannabidiol is safe but not effective in the treatment for Crohn's disease, a randomized controlled trial. *Digestive Diseases and Sciences*, *62*, 1615–1620. https://doi.org/10.1007/s10620-017-4540-z

Notcutt, W., Price, M., Miller, R., Newport, S., Phillips, C., Simmons, S., & Sansom, C. (2004). Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'N of 1' studies. *Anaesthesia*, *59*, 440–452. https://doi.org/10.1111/j.1365-2044.2004.03674.x

Noyes Jr, R., Brunk, S. F., Avery, D. A., & Canter, A. C. (1975). The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clinical Pharmacology and Therapeutics*, *18*, 84–89. https://doi.org/10.1002/cpt197518184

Noyes Jr, R., Brunk, S. F., Baram, D. A., & Canter, A. (1975). Analgesic effect of delta-9-tetrahydrocannabinol. *Journal of Clinical Pharmacology*, *15*, 139–143. https://doi.org/10.1002/j.1552-4604.1975.tb02348.x

Nugent, S. M., Morasco, B. J., O'Neil, M. E., Freeman, M., Low, A., Kondo, K., … Kansagara, D. (2017). The effects of cannabis among adults with chronic pain and an overview of general harms: A systematic review. *Annals of Internal Medicine*, *167*, 319–331. https://doi.org/10.7326/M17-0155

O'Brien, T., Christrup, L. L., Drewes, A. M., Fallon, M. T., Kress, H. G., McQuay, H. J., … Wells, J. C. (2017). European Pain Federation position paper on appropriate opioid use in chronic pain management. *European Journal of Pain*, *21*, 3–19. https://doi.org/10.1002/ejp.970

Onaivi, E. S., Ishiguro, H., Gong, J. P., Patel, S., Perchuk, A., & Meozzi, P. A. (2006). Discovery of the presence and functional expression of cannabinoid CB2 receptors in brain. *Annals of the New York Academy of Sciences*, *1074*, 514–536. https://doi.org/10.1196/annals.1369.052

O'Sullivan, S. E. (2007). Cannabinoids go nuclear: Evidence for activation of peroxisome proliferator-activated receptors. *British Journal of Pharmacology*, *152*, 576–582.

Pertwee, R. G. (Ed.) (2015). *Handbook of cannabis*. Oxford, UK: Oxford University Press.

Petzke, F., Enax-Krumova, E. K., & Häuser, W. (2016). Efficacy, tolerability and safety of cannabinoids for chronic neuropathic pain: A systematic review of randomized controlled studies. *Schmerz*, *30*, 62–88. (German). https://doi.org/10.1007/s00482-015-0089-y

Pini, L. A., Guerzoni, S., Cainazzo, M. M., Ferrari, A., Sarchielli, P., & Tiraferri, I. (2012). Nabilone for the treatment of medication overuse headache: Results of a preliminary double-blind, active-controlled, randomized trial. *Journal of Headache Pain*, *13*, 677–684. https://doi.org/10.1007/s10194-012-0490-1

Pinsger, M., Schimetta, W., Volc, D., Hiermann, E., Riederer, F., & Pölz, W. (2006). Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain—a randomized controlled trial. *Wiener Klinische Wochenschrift*, *118*, 327–335 [German]. https://doi.org/10.1007/s00508-006-0611-4

Portenoy, R. K., Ganae-Motan, E. D., & Allende, S. (2012). Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: A randomized, placebo-controlled, graded dose trial. *Journal of Pain*, *13*, 438–449. https://doi.org/10.1016/j.jpain.2012.01.003

Rong, C., Carmona, N. E., Lee, Y. L., Ragguett, R. M., Pan, Z., Rosenblat, J. D., … McIntyre, R. S. (2018). Drug-drug interactions as a result of co-administering Δ(9)-THC and CBD with other psychotropic agents. *Expert Opinion on Drug Safety*, *17*, 51–54. https://doi.org/10.1080/14740338.2017.1397128

Rosenfeld, R. M., Nnacheta, L. C., & Corrigan, M. D. (2015). Clinical consensus statement development manual. *Otolaryngology - Head and Neck Surgery*, *153*, S1–S14.

Sagar, D. R., Jhaveri, M., Richardson, D., Gray, R. A., De Lago, E., Fernandez-Ruiz, J., … Chapman, V. (2010). Endocannabinoid regulation of spinal nociceptive processing in a model of neuropathic pain. *European Journal of Neuroscience*, *31*, 8.

Sagar, D. R., Burston, J. J., Woodhams, S. G., & Chapman, V. (2012). Dynamic changes to the endocannabinoid system in models of chronic pain. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, *367*, 3300–3311. https://doi.org/10.1098/rstb.2011.0390

Schimrigk, S., Marziniak, M., Neubauer, C., Kugler, E. M., Werner, G., & Abramov-Sommariva, D. (2017). Dronabinol is a safe long-term treatment option for neuropathic pain patients. *European Neurology*, *78*, 320–329. https://doi.org/10.1159/000481089

Skrabek, R. Q., Galimova, L., Ethans, K., & Perry, D. (2008). Nabilone for the treatment of pain in fibromyalgia. *Journal of Pain*, *9*, 164–173. https://doi.org/10.1016/j.jpain.2007.09.002

Staquet, M., Gantt, C., & Machin, D. (1978). Effect of a nitrogen analog of tetrahydrocannabinol on cancer pain. *Clinical Pharmacology and Therapeutics*, *23*, 397–401. https://doi.org/10.1002/cpt1978234397

Starowicz, K., & Finn, D. P. (2017). Cannabinoids and pain: Sites and mechanisms of action. *Advances in Pharmacology*, *80*, 437–475. https://doi.org/10.1016/bs.apha.2017.05.003

Stott, C. G., White, L., Wright, S., Wilbraham, D., & Guy, G. W. (2013). A phase I study to assess the single and multiple dose pharmacokinetics of THC/CBD oromucosal spray. *European Journal of Clinical Pharmacology*, *69*, 1135–1147. https://doi.org/10.1007/s00228-012-1441-0

Stout, S. M., & Cimino, N. M. (2014). Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: A systematic review. *Drug Metabolism Reviews*, *46*, 86–95. https://doi.org/10.3109/03602532.2013.849268

Sugiura, T., Kondo, S., Sukagawa, A., Nakane, S., Shinoda, A., & Itoh, K. (1995). 2-Arachidonoylglycerol: A possible endogenous cannabinoid receptor ligand in brain. *Biochemical and Biophysical Research Communications*, *215*, 89–97. https://doi.org/10.1006/bbrc.1995.2437

Tashkin, D. P. (2018). Marijuana and lung disease. *Chest*, epub May 17, pii: S0012-3692(18)30742-6.

Van Sickle, M. D., Duncan, M., Kingsley, P. J., Mouihate, A., Urbani, P., & Mackie, K. (2005). Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science*, *310*, 329–332. https://doi.org/10.1126/science.1115740

Wallace, M., Schulteis, G., Atkinson, J. H., Wolfson, T., Lazzaretto, D., Bentley, H., … Abramson, I. (2007). Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. *Anesthesiology*, *107*(5), 785–796. https://doi.org/10.1097/01.anes.0000286986.92475.b7

Ware, M. A., Fitzcharles, M. A., Joseph, L., & Shir, Y. (2010). The effects of nabilone on sleep in fibromyalgia: Results of a randomized controlled trial. *Anesthesia and Analgesia*, *10*, 604–610. https://doi.org/10.1213/ANE.0b013e3181c76f70

Ware, M. A., Wang, T., Shapiro, S., Robinson, A., Ducruet, T., Huynh, T., … Collet, J. P. (2010). Smoked cannabis for chronic neuropathic pain: A randomized controlled trial. *CMAJ*, *182*, E694–E701. https://doi.org/10.1503/cmaj.091414

Ware, M. A., Wang, T., Shapiro, S., Collet, J. P., & COMPASS study team. (2015). Cannabis for the management of pain: Assessment of Safety Study (COMPASS). *Journal of Pain*, *16*, 1233–1242. https://doi.org/10.1016/j.jpain.2015.07.014

Whiting, P. F., Wolff, R. F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A. V., … Kleijnen, J. (2015). Cannabinoids for medical use: A systematic review and metaanalysis. *JAMA*, *313*, 2456–2473. https://doi.org/10.1001/jama.2015.6358

Wilsey, B., Atkinson, J. H., Marcotte, T. D., & Grant, I. (2015). The medicinal cannabis treatment agreement: Providing information to chronic pain patients through a written document. *Clinical Journal of Pain*, *31*, 1087–1096. https://doi.org/10.1097/AJP.0000000000000145

Woodhams, S. G., Sagar, D. R., Burston, J. J., & Chapman, V. (2015). The role of the endocannabinoid system in pain. *Handbook of Experimental Pharmacology*, *227*, 119–143. https://doi.org/10.1007/978-3-662-46450-2

Woodhams, S. G., Chapman, V., Finn, D. P., Hohmann, A. G., & Neugebauer, V. (2017). The cannabinoid system and pain. *Neuropharmacology*, *124*, 105–120. https://doi.org/10.1016/j.neuropharm.2017.06.015

Wong, S. S., & Wilens, T. E. (2017). Medical cannabinoids in children and adolescents: A systematic review. *Pediatrics*, *140*, pii: e20171818. https://doi.org/10.1542/peds.2017-1818

Zhang, H. Y., Gao, M., Liu, Q. R., Bi, G. H., Li, X., & Yang, H. J. (2014). Cannabinoid CB2 receptors modulate midbrain dopamine neuronal activity and dopamine-related behavior in mice. *Proceedings of the National Academy of Sciences of the United States of America*, *111*, E5007–E5015. https://doi.org/10.1073/pnas.1413210111

WEB REFERENCES

European Medicines Agency. (2014). Compassionate use. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp&mid=WC0b01ac05809f843c. No date of publication.

FDA. (2017). Highlights of prescribing information MARINOL (dronabinol) capsules, for oral use. Revised 08/17. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018651s029lbl.pdf

Health Canada. (2016). Consumer information – Cannabis. https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-use-marijuana/licensed-producers/consumer-information-cannabis-marihuana-marijuana.html

Health Products Regulatory Agency. (2017). Cannabis for medical use. A scientific review. January 31, 2017. http://health.gov.ie/wp-content/uploads/2017/02/HPRA-Report-FINAL.pdf

Huu, T. A. N. (2004). Cannabis (marijuana) and anesthesia. *Anesthesiology Rounds*, https://de.scribd.com/document/81940623/Cannabis-Marijuana-and-Anesthesia

Institute for Responsible Medicine Use and the Office of Medicinal Cannabis of the CIBG, Ministry of Health, Welfare and Sport. (2011). https://english.cannabisbureau.nl/medicinal-cannabis/documents/circulars/2018/02/20/patients-guide-medicinal-cannabis

International Narcotic Board. (2018). General Information for Travellers Carrying Medicines Containing Controlled Substances. http://www.incb.org/incb/en/travellers/general-information.html

Medical board of California. (2017). Guidelines for the recommendation of cannabis for medical purposes. November 2017. www.mbc.ca.gov/…/guidelines_cannabis_recommendation.pdf

National Academies of Sciences, Engineering, and Medicine. (2017). The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Chapter 9: Injury and Death. Washington, DC: The National Academies Press. https://www.ncbi.nlm.nih.gov/books/NBK425742/

National Institute of Health. (2018). National Institute of Drug Abuse. Marijuana as medicine. https://www.drugabuse.gov/publications/drugfacts/marijuana-medicine

The College of Family Physicians in Canada. (2018). Medical cannabinoids. http://www.cfp.ca/content/cfp/suppl/2018/02/13/64.2.111.DC1/MC_Trifold_Handout.pdf

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