Cannabinoids in Pain Management and Palliative Medicine

An Overview of Systematic Reviews and Prospective Observational Studies

Winfried Häuser, Mary-Ann Fitzcharles, Lukas Radbruch, Frank Petzke

SUMMARY

Background: There are conflicting interpretations of the evidence regarding the efficacy, tolerability, and safety of cannabinoids in pain management and palliative medicine.

Methods: We conducted a systematic review (SR) of systematic reviews of randomized controlled trials (RCT) and prospective long-term observational studies of the use of cannabinoids in pain management and palliative medicine. Pertinent publications from January 2009 to January 2017 were retrieved by a selective search in the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and Medline. The methodological quality of the SRs was assessed with the AMSTAR instrument, and the clinical relevance of quantitative data syntheses was assessed according to the standards of the Cochrane Collaboration.

Results: Of the 750 publications identified, 11 SRs met the inclusion criteria; 3 of them were of high and 8 of moderate methodological quality. 2 prospective long-term observational studies with medical cannabis and 1 with tetrahydrocannabinol/cannabidiol spray (THC/CBD spray) were also analyzed. There is limited evidence for a benefit of THC/CBD spray in the treatment of neuropathic pain. There is inadequate evidence for any benefit of cannabinoids (dronabinol, nabilone, medical cannabis, or THC/CBD spray) to treat cancer pain, pain of rheumatic or gastrointestinal origin, or anorexia in cancer or AIDS. Treatment with cannabis-based medicines is associated with central nervous and psychiatric side effects.

Conclusion: The public perception of the efficacy, tolerability, and safety of cannabis-based medicines in pain management and palliative medicine conflicts with the findings of systematic reviews and prospective observational studies conducted according to the standards of evidence-based medicine.

► Cite this as:

As of 10 March 2017, according to the provisions of the “Act to Amend Narcotic Drugs Provisions and Other Related Provisions”, physicians in Germany may prescribe cannabinoids—with costs covered by statutory health insurances—for patients with severe diseases and no alternative treatment options available, as dried cannabis flowers (so-called medical cannabis or medical marijuana), standardized extracts (compounded medication dronabinol, finished medicinal product THC/CBD [tetrahydrocannabinol/cannabidiol] spray) or synthetic THC analog (finished medicinal product nabilone) (1) (Box). Recently, an article in Deutsches Ärzteblatt stated that chronic—especially neuropathic—pain, spasticity in multiple sclerosis and loss of appetite, nausea and vomiting are considered “established” indications for cannabis-based medicines (2).

Systematic reviews (SRs) with quantitative analyses (meta-analysis) of randomized clinical trials (RCTs) and overviews of SRs have the highest level of evidence in evidence-based medicine (3). Long-term efficacy and long-term risk can be assessed by prospective observational studies (4).

Thus, the aim of this paper is to identify potential indications for, but also risks of cannabinoids in pain management and palliative medicine, based on systematic reviews of RCTs and prospective long-term (≥ 6 months) observational studies.

Methods

This overview was prepared according to the recommendations of the Pain Palliative and Supportive Care Group of the Cochrane Collaboration (5), of the Cochrane Collaboration on the compilation of a Cochrane Overview on Reviews (6) and of the Joanna Briggs Institute on the conduction of umbrella reviews (7). For detailed information about the methods (literature search, inclusion criteria, endpoints, methodological quality, data extraction) refer to the eBox.

The analytic methods and inclusion criteria used were defined a priori (PROSPERO 2017; CRD 42017058875).

The methodological quality of the SRs was assessed using the AMSTAR rating (e1). The 11 items of
**AMSTAR**—a measurement tool to assess systematic reviews—are listed in eTable 1. AMSTAR scores of 0–4, 5–8 and 9–11 were rated as low, moderate and high methodological quality, respectively (e2).

**Results**

**Literature search**

Systematic reviews: Altogether 750 publications were identified by database searches and manual searches. Twenty full-text articles were assessed for suitability. Eight SRs were excluded as they lacked quantitative data analysis without giving reasons for this omission (8–15). One SR was excluded because the quantitative data synthesis was performed based on data on all types of chronic pain without subgroup analysis (16). Eleven SRs were included in our qualitative analysis, comprising 5 SRs with quantitative data analysis (17–21) and 6 without quantitative analysis due to insufficient data quantity and/or quality (22–27) (Figure). Six of the 11 included SRs had been prepared by our own working groups (19, 20, 22, 23, 26, 27).

Prospective observational studies: Our database search yielded 7 hits in Medline, 30 hits in Clinical-Trials.gov and 2 hits in the manual search. Three studies met the inclusion criteria (28–30).

**Study characteristics**

An overview of the SRs included in this review is provided in Table 1. Two SRs required a minimum study duration (double-blind period) of 2 weeks (19, 20) for inclusion; 1 SR required a study duration of at least 4 weeks (23). The remaining studies had no study duration–based inclusion criteria.

Methodological quality of the RCTs analyzed in the SRs varied widely. The methodological quality of 3 SRs (17, 20, 27) was high, while it was moderate in the remaining SRs (eTable 1).

**Neuropathic pain**

Three SRs (17, 18, 20) analyzed up to 25 RCTs with 1837 participants and with study duration between 5 hours and 15 weeks (Table 2). In the meta-analysis on the use of medical marijuana, a clinically relevant number needed to treat for an additional benefit (NNTB) of 6 was calculated for pain relief of at least 30%. The authors concluded that medical marijuana was effective in reducing neuropathic pain in the short term (duration of the analyzed studies varied between 1 and 14 days) (17). One SR of all cannabinoids used to treat neuropathic pain, including “gray literature“, found an NNTB of 10 in a pooled analysis for this outcome parameter. In the subgroup analysis, the difference between the mean pain relief achieved with medical marijuana and that achieved with placebo was not statistically significant. However, with regard to a minimum pain relief of 30%, medical marijuana proved to be superior to placebo; this difference was both statistically significant and clinically relevant. Tetrahydrocannabinol/cannabidiol (THC/CBD) spray was superior to placebo with

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**Cannabis-based medicines and their availability in Germany**

- **Medical cannabis (so-called medical marijuana)**
  - Currently, 14 types of cannabis flowers can be prescribed, with THC concentrations varying between 1% and 22% and CBD concentrations varying between 0.05% and 9%. Dosing information for specific indications is not available.
  - The German Narcotic Drugs Act sets the maximum amount that can be prescribed within a 30-day period at 100 g cannabis in form of flowers, regardless of THC content.

- **Medicinal products containing cannabis plant extracts**
  - A THC/CBD-containing oromucosal spray, available as a formulated medicinal product, was approved in 2011 for the indication moderate to severe spasticity in multiple sclerosis which did not respond adequately to other anti-spasticity treatments and showed significant clinical improvement following a treatment trial. Posology: 1 puff 2.7 mg THC/2.5 mg CBD; maximum of 12 puffs/day.
  - THC-containing capsules and oil are not permitted under the German Narcotic Drugs Act. These can be prescribed for individual therapeutic trials as compounded medications in the form of drops, capsules or inhalation solution and be prepared by pharmacies. Specific indications are not stated. The recommended daily doses range between 5 and 30 mg.

- **Synthetic cannabinoids**
  - A synthetic THC analog (nabilone) was approved in Germany in December 2016 for the indication of nausea and vomiting in patients undergoing chemotherapy and not adequately responding to other medications and is available as a formulated medicinal product. The recommended dosage is 2–4 mg/day.

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* Cannabis (Latin: hemp) is a collective term for substances from the female hemp plant of the genus Cannabis sativa. Cannabinoids are a collective term for substances from the resin of the hemp plant. The female hemp plant contains more than 100 phytocannabinoids. The best characterized phytocannabinoids are the psychotropic tetrahydrocannabinol (THC) and the primarily anti-inflammatory cannabidiol (CBD).
regard to mean pain relief (but not statistically significant) and at least 30% pain relief (statistically significant). The NNTB for at least 30% pain relief was clinically not relevant.

In the pooled analysis of all cannabinoids, the number needed to harm (NNH) of 25 was clinically not relevant for adverse event–related study discontinuation. No statistically significant differences were found with regard to the rate of serious adverse events between the cannabinoid and placebo groups. The authors concluded that cannabinoids can be used as third-line therapy in carefully selected patients, if they were to be used at all (20).

One SR of multiple sclerosis studies found no statistically significant difference compared to placebo with regard to mean pain relief. The authors concluded that the number of available studies was too small to allow for recommendations for cannabinoids (18).

**Pain associated with rheumatic diseases**

Three SRs analyzed a total of 4 RCTs, comprising 1 RCT evaluating THC/CBD spray in 58 patients with rheumatoid arthritis, 2 RCTs with 72 patients with fibromyalgia and 1 RCT with 30 patients with musculoskeletal pain. The authors for all 3 SRs concluded that the current evidence base is inadequate to recommend cannabinoids for the treatment of pain associated with rheumatic diseases (22, 23, 27) (eTable 2).

**Visceral pain**

One SR analyzed 1 RCT evaluating medical marijuana administered as a joint compared to a cigarette not containing tetrahydrocannabinol (THC) in 21 patients with Crohn’s disease over a period of 8 weeks. While no significant differences were found with regard to remission rate and incidence of adverse events, a significant reduction in abdominal pain (p<0.05) and improvement in appetite was observed. The authors concluded that individual therapeutic trials of THC in patients with Crohn’s disease to alleviate pain and loss of appetite should only be considered after non-response to all established pharmacotherapy options and with a careful risk–benefit assessment (26) (eTable 3).

An additional study of the effect of oral THC in chronic pancreatitis was published subsequent to the literature search. This 3-month study evaluating 65 patients with pain associated with chronic pancreatitis reported the following: there was no statistically significant superiority of oral THC over placebo with regard to pain relief (31).

**Cancer pain**

Two SRs (19, 21) analyzed the same 2 RCTs with 307 patients and a study duration of 2 and 3 weeks, respectively (eTable 4). In both quantitative analyses, the significance levels of the cannabinoid–placebo comparison with regard to at least 30% pain relief were just above the threshold of p ≤ 0.05. No statistically significant differences in tolerability and safety were found between cannabinoid and placebo (19). One SR concluded that given the limited data available it was not possible to recommend the use of cannabinoids to treat cancer pain (19).

**Appetite, weight and nausea/vomiting in advanced diseases**

Two SRs analyzed a total of 6 RCTs with 350 patients with HIV/AIDS and study duration between 3 and 12 weeks. All studies were conducted prior to the introduction of highly active antiretroviral therapy (HAART). One SR identified clinically relevant increases in appetite and weight. No statistically significant differences with regard to tolerability and safety were found between cannabinoids and placebo (19). Both SRs concluded that insufficient evidence was available to support the use of cannabinoids to symptomatically treat loss of appetite, nausea and weight loss in patients with HIV/AIDS (19, 24).

One SR analyzing 3 RCTs with 441 cancer patients found no statistically significant differences with regard to increases in appetite, weight and calorie intake compared to placebo. The authors concluded that there is not sufficient evidence to recommend the use of cannabinoids for symptomatic treatment of loss of appetite and loss of weight in cancer patients (19).

Two SRs evaluating 1 RCT of dronabinol in 15 patients with Alzheimer-type dementia over a period of 12 weeks concluded that from published data the
efficacy (calorie intake, body weight), tolerability and safety of cannabinoids cannot be determined and that there is no evidence to recommend the use of cannabinoids in patients with dementia (19, 24).

Prospective long-term observational studies
Three prospective long-term studies were identified (eTable 5). Altogether 380 of 439 patients who had been enrolled in either an RCT evaluating painful diabetic polyneuropathy or an RCT evaluating neuropathic pain of various causes agreed to participate in a 38-week observational trial assessing THC/CBD spray. At least half of the patients reported pain relief of ≥ 30% and at least one-third of patients had pain relief of ≥ 50% at all time points. Altogether 23% of patients discontinued the study because of adverse events. In 11% of patients, serious adverse events were observed (28).

A Canadian prospective 1-year observational study compared 215 patients with non-cancer pain treated with standardized medical marijuana (12.5% THC) with 216 pain patients not treated with cannabis. In the cannabis group, a statistically significant pain relief compared with baseline of –0.92 points on an 11-step scale (95% confidence interval: [–0.62; –1.23]) was found, while this was not the case in the

table 1

<table>
<thead>
<tr>
<th>First author Year (Reference)</th>
<th>Medical indication (number of studies)</th>
<th>Number of studies/patients</th>
<th>Duration of randomized double-blind study phase (minimum; maximum)</th>
<th>Cannabinoids used (number of studies)</th>
<th>Methodological quality of the included studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreae 2015 (17)</td>
<td>Chronic neuropathic pain</td>
<td>5/178</td>
<td>5 hours, 2 weeks</td>
<td>Medical marijuana (joint, vaporizer) (5)</td>
<td>RoB: 1 study with low, 2 studies with moderate and 2 studies with high risk of bias</td>
</tr>
<tr>
<td>Fitzcharles 2016 (22)*</td>
<td>Fibromyalgia (2) Rheumatoid arthritis (1) Musculoskeletal pain (1)</td>
<td>4/160 – 72 fibromyalgia – 58 rheumatoid arthritis – 30 musculoskeletal pain</td>
<td>4, 8 weeks</td>
<td>Nabilone oral (3) THC/CBD spray (1)</td>
<td>RoB: 3 studies with high and 1 study with low risk of bias</td>
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<tr>
<td>Fitzcharles 2016 (23)*</td>
<td>Fibromyalgia (2) Rheumatoid arthritis (1) Osteoarthritis (1)</td>
<td>4/204 – 72 fibromyalgia – 58 rheumatoid arthritis – 74 osteoarthritis</td>
<td>4, 8 weeks</td>
<td>Nabilone oral (2) THC/CBD spray (1) Fatty acid amide hydrolase (FAAH) inhibitor oral (1)</td>
<td>RoB: 3 studies with high risk of bias; risk of bias could not be determined for 1 study</td>
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<td>Jahawar 2013 (18)</td>
<td>Neuropathic pain, except for trigeminal neuralgia, in multiple sclerosis (3)</td>
<td>3/400</td>
<td>4, 12 weeks</td>
<td>Dronabinol oral (1) THC/CBD spray (2)</td>
<td>Classification scheme of the American Academy of Neurology: 2 class-1 studies and 1 class-3 study</td>
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<tr>
<td>Krishnan 2013 (24)</td>
<td>Dementia (1)</td>
<td>1/15</td>
<td>12 weeks</td>
<td>Nabilone oral (1)</td>
<td>RoB: high risk of bias</td>
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<td>Lutge 2013 (25)</td>
<td>HIV/AIDS</td>
<td>7/350</td>
<td>3, 7 weeks</td>
<td>THC-containing cigarettes (6) Dronabinol oral (6)</td>
<td>RoB: 3 studies with moderate and 4 studies with high risk of bias</td>
</tr>
<tr>
<td>Mücke 2016 (19)*</td>
<td>Cancer (5) HIV/AIDS (3)</td>
<td>5/758 – 3/102</td>
<td>2, 11 weeks – 3, 12 weeks</td>
<td>Dronabinol oral (2) THC/CBD spray (5) Dronabinol oral (2) THC-containing cannabinoids (1)</td>
<td>RoB: 3 studies with moderate and 5 studies with high risk of bias</td>
</tr>
<tr>
<td>Petzke 2016 (20)*</td>
<td>Chronic neuropathic pain</td>
<td>15/1 619</td>
<td>2, 14 weeks</td>
<td>Dronabinol oral (1) Nabilone oral (2) Medical marijuana (joint) (2) THC/CBD spray (10)</td>
<td>RoB: 2 studies with low and 13 studies with moderate risk of bias</td>
</tr>
<tr>
<td>Volz 2016 (26)*</td>
<td>Crohn’s disease</td>
<td>1/21</td>
<td>8 weeks</td>
<td>THC cigarette (1)</td>
<td>RoB: high risk of bias</td>
</tr>
<tr>
<td>Walitt 2016 (27)*</td>
<td>Fibromyalgia</td>
<td>2/72</td>
<td>4, 6 weeks</td>
<td>Nabilone oral (2)</td>
<td>RoB: 2 studies with moderate risk of bias</td>
</tr>
<tr>
<td>Whiting 2015 (21)</td>
<td>Cancer pain</td>
<td>2/307</td>
<td>2, 3 weeks</td>
<td>THC/CBD spray (2)</td>
<td>RoB: 1 study with high and 1 study with unclear risk of bias</td>
</tr>
</tbody>
</table>

* Systematic review from the authors’ working groups
CBD, cannabidiol; RoB, Cochrane Collaboration risk-of-bias tool; THC, tetrahydrocannabinol
control group with $-0.18$ [0.13; $-0.49$]. The extent of pain relief of $<1$ point is not clinically relevant (5). The rate of non-serious adverse events was increased in the group treated with medical marijuana (adjusted incidence rate: 1.73 [1.41; 2.13]), but not the rate of serious adverse events (adjusted incidence rate: 1.08 [0.57; 2.04]). Only 7% of patients in the cannabis group were cannabis-naive, i.e. had never consumed cannabis before, compared with 64% in the control group. The authors stated that their study did not allow conclusions to be drawn regarding the safety of medical marijuana in cannabis-naive patients with chronic non-cancer pain (29).

A 1-year observational study examining the efficacy of medical marijuana and conducted in Israel recruited 216 patients with non-cancer pain. The reduction in pain severity scores from median 7.50 [6.75; 7.75] to 6.25 [5.75; 6.75] on an 11-step scale was clinically relevant. The study was discontinued by 5.3% patients because of adverse events. The rate of serious adverse events was 1% (30).

**Discussion**

Applying the quality criteria of evidence-based medicine, we found inadequate evidence to support the “established” indications claimed by proponents of medical marijuana therapy, such as chronic cancer pain or loss of appetite, nausea and vomiting in advanced disease stages. Likewise, there was no evidence to support the claimed positive effects in patients with internal disorders (arthritis, ulcerative colitis) (2). The current evidence with regard to cancer pain, loss of appetite, or nausea and vomiting in patients with HIV and dementia, as well as...
rheumatoid arthritis showed no clear benefit from the use of cannabinoids compared with placebo. There are no controlled trials for ulcerative colitis. Two RCTs investigating THC-containing cigarettes (e3) and oral CBD (e4), respectively, showed no statistically significant effects on disease activity in patients with Crohn’s disease.

By contrast, sufficient evidence is available for neuropathic pain. A meta-analysis based on individual patient data on the use of medical marijuana to treat neuropathic pain found an NNTB of 6 for pain relief of at least 30% (17). This finding meets the criteria for a clinically relevant benefit (4). However, the validity of the finding is limited by small sample sizes (23–50 participants/study) and short study durations (3 studies <1 week, 2 studies conducted over a period of 2 weeks). With small study sizes, therapeutic effects may be overestimated (e5). The European Medicines Agency (EMA) requires two studies with a minimum of 12 weeks’ duration for approval of a medication for pain management (e6).

In the SR on all cannabinoids, requiring a study duration of at least 2 weeks, a subgroup analysis found no superiority with regard to mean pain relief for medical marijuana compared with placebo (20). The NNTB of 12 for pain relief of at least 30% by THC/CBD spray was not clinically relevant (20). On clinicaltrials.gov, 3 RCTs with nabiximol and 1 RCT with medical marijuana for neuropathic pain are registered, but their results have not yet been reported (20). Should these not yet published studies yield negative results, a pooled analysis would be even less favorable for cannabinoids.

Two SRs found no statistically significant increase in the incidence of serious adverse events for cannabinoids in comparison with placebo in neuropathic (20) or cancer pain (19). The NNTH of 25 for discontinuation due to adverse events calculated in the SR on neuropathic pain was clinically not relevant. However, this SR identified a clinically relevant NNTH of 3 for central nervous system adverse events and an NNTH of 9 for psychiatric disorders (20). Likewise, the 3 prospective observational studies on medical marijuana and THC/CBD spray detected frequent central nervous and psychiatric adverse events (28–30).

Our more reserved view of the role of cannabinoids in pain management and palliative medicine is in line with current European guideline recommendations. The Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain (IASP) issued a weak recommendation against the use of cannabinoids (32). The guideline of the British National Institute for Health and Care Excellence (NICE) made a negative recommendation for the use of THC/CBD spray in multiple sclerosis, as it is not cost-effective (33). The German guideline (34) and the European League Against Rheumatism (EULAR) (35) issued negative recommendations for cannabinoids in fibromyalgia syndrome. By contrast, the Canadian guideline on neuropathic pain made a recommendation for cannabinoids as a third-line therapy with short-term or mid-term treatment duration (36) and an open recommendation for cannabinoids in fibromyalgia patients with severe insomnia (37). The American Academy of Neurology recommended that THC/CBD spray or oral THC may be given as a treatment trial for pain associated with multiple sclerosis. It was concluded that data are inadequate to support or refute use of medical marijuana (38). The authors of this review are not aware of any national or European guidelines recommending the use of cannabinoids in palliative medicine.

Data from existing studies do not allow for clear recommendations to guide prescribing physicians on how to dose medical marijuana, either with regard to THC:CBD ratio or to dosing for specific indications. In countries such as Canada and Israel where the option to prescribe herbal cannabis for medicinal purposes has been available for several years, the majority of physicians reported inadequate understanding of medical marijuana in general and, more specifically, poor knowledge of how to prescribe cannabinoids (e7, e8). Given the negative health impact of tobacco smoking, the German Medical Association advised against treatment with medical marijuana in the form of joints (39). According to the authors’ clinical experience, persons inexperienced in the recreational use of marijuana find it difficult to inhale medical marijuana via a vaporizer.

Outlook

A JAMA editorial titled “Is the cart before the horse” pointed out that the approval of medical marijuana in several US federal states was based on low-quality evidence, public opinion and political agenda. According to the author of this editorial, such disregard for the medicines agencies’ drug approval standards is unprecedented (40). In Germany, the process followed a similar pattern. In anticipation of this change in the law, the German Medical Association argued against allowing the prescription of medical marijuana, stating that the available evidence was inadequate to support this move (39). The German Pain Society (DSG, Deutsche Schmerzgesellschaft) and the German Society of Palliative Medicine (DGP, Deutsche Gesellschaft für Palliativmedizin) have, however, welcomed the law change, contending that existing barriers to the reimbursement of cannabis-containing compounded medications and formulated medicinal products will be eased. Currently available data provide sufficient evidence, according to evidence-based medicine criteria, to support the use of THC/CBD spray in carefully selected neuropathic pain patients who have shown insufficient response to standard pharmacotherapy. The results of 3 long-term observational studies support the observed benefit and tolerability of THC/CBD spray and medical marijuana in selected patients with chronic non-cancer pain syndromes. However, the use of all cannabinoids for any indication in pain management and palliative
medicine should be regarded as an individual therapeutic trial, except for two approved indications (THC/CBD spray for spasticity in multiple sclerosis and nabilone for chemotherapy-induced vomiting). Cannabinoids, however, should not be used in isolation as the only treatment, but in combination with physiotherapy and pain-related psychotherapy (e9).

In Italy, all prescriptions of THC/CBD spray for spasticity in multiple sclerosis are linked to a web-based registry of the Agenzia Italiana del Farmaco, designed to prospectively collect data on the efficacy and tolerability of this medication (e10). It is to be hoped that the accompanying research required by the “Act to Amend Narcotic Drugs Provisions and Other Related Provisions” which was enacted on March 10, 2017 will be designed to assemble evidence based information with regard to the efficacy, tolerability and safety of medical marijuana for specific indications.

Conflict of interest
The authors declare that no conflict of interest exists.

Translators from the original German by Ralf Thoene, MD

REFERENCES

KEY MESSAGES

- Limited evidence is available to support the use of tetrahydrocannabinol/cannabidiol spray for the treatment of chronic neuropathic pain.
- According to the quality criteria of evidence-based medicine, the available evidence for cannabinoids is inadequate for the indications of loss of appetite in patients with cancer or HIV/AIDS, fibromyalgia syndrome, Crohn’s disease, musculoskeletal pain, rheumatoid arthritis, chronic pancreatitis, and cancer pain.
- The use of cannabinoids in pain management and palliative medicine should be regarded as individual therapeutic trials, except for chronic neuropathic pain.
- Cannabinoid use in pain management and palliative medicine may cause relevant central nervous system (e.g. dizziness) and psychiatric adverse events (e.g. confusion, psychosis).
- Approval of medical marijuana as a prescribable medicinal product in Germany was granted even though the approval requirements of the European Medicines Agency (EMA) for medicinal products intended for pain management (at least 2 controlled studies with adequate power and a duration of at least 12 weeks) were not met.


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**eREFERENCES**


**eTABLE 1**

Assessment of methodological quality of systematic reviews on controlled trials with cannabinoids in pain management and palliative medicine using the AMSTAR instrument (e1) (in alphabetical order)

<table>
<thead>
<tr>
<th>First author</th>
<th>Year (Reference)</th>
<th>a-priori design?</th>
<th>Duplicate study selection and data extraction?</th>
<th>Comprehensive literature search?</th>
<th>&quot;Gray&quot; literature included?</th>
<th>List of included and excluded studies?</th>
<th>Characteristics of the included studies presented, e.g. as a table?</th>
<th>Scientific quality of the included studies assessed and documented?</th>
<th>Scientific quality of the included studies used appropriately in formulating conclusions?</th>
<th>Methods used to combine the findings of studies appropriate?</th>
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<td>Voil 2016 (26)*3</td>
<td>no yes yes yes yes yes yes yes no no3 yes yes 8</td>
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<td>Wallitt*1/2 2016 (27)</td>
<td>yes yes yes yes yes yes yes yes no no3 no yes yes 9</td>
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<td>Whiting 2015 (21)*1</td>
<td>yes yes yes yes no no yes yes yes yes no 8</td>
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</table>

*1 a-priori design: protocol, ethics committee approval or research question published before study start.
*2 systematic reviews from the authors’ study groups
*3 no meta-analysis due to inadequate quantity and/or quality of data
AMSTAR, measurement tool to assess systematic reviews
### eTABLE 2

#### Efficacy of cannabinoids in pain associated with rheumatic diseases—systematic reviews of randomized controlled trials

<table>
<thead>
<tr>
<th>First author</th>
<th>Year (Reference)</th>
<th>Databases and period of literature search</th>
<th>Efficacy</th>
<th>Tolerability and safety</th>
<th>Authors’ conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitzcharles 2016</td>
<td>(22) *1</td>
<td>Medline, Embase, BIOSIS Previews, Web of Science, Scopus, CENTRAL, DARE, CINAHL, PsycINFO, AMED, clinicaltrials.gov, International Clinical Trials Registry Platform (current controlled trial), Natural Standard, websites of various regulatory agencies responsible for the approval of medicinal products and medical devices, until January 2015.</td>
<td>THC/CBD reduced pain at rest and during motion in 58 patients with rheumatoid arthritis. Nabilone led to pain relief in 40 FMS patients. Nabilone improved sleep quality, but did not reduce pain in 32 FMS patients. Study terminated early because FAAH1 inhibitor showed no effect in 75 patients with osteoarthritis.</td>
<td>Dizziness, cognitive problems, vertigo, and nausea were reported by half of the patients. No statistically significant difference between nabilone and placebo with regard to mean pain relief in the analysis of published data by the authors of the systematic review (27).</td>
<td>The current evidence is inadequate to recommend cannabinoids for the treatment of pain associated with rheumatic diseases.</td>
</tr>
<tr>
<td>Fitzcharles 2016</td>
<td>(23)*1</td>
<td>CENTRAL, PubMed, <a href="http://www.cannabis-med.org">www.cannabis-med.org</a> and clinicaltrials.gov until April 2016</td>
<td>No statistically significant difference between nabilone and placebo with regard to pain relief (calculations of the authors of this review based on the data presented) in 40 FMS patients. No statistically significant difference between nabilone and amitriptyline with regard to pain relief in a study with 32 FMS patients. THC/CBD spray was significantly superior to placebo in reducing morning resting pain and pain on motion, but not in reducing overall and current pain intensity in 58 patients with rheumatoid arthritis. No statistically significant difference between nabilone and placebo with regard to pain relief in a study with 32 FMS patients and between nabilone and placebo by 30 patients with musculoskeletal pain.</td>
<td>In the nabilone group, 3 of 20 patients and in the placebo group 1 of 20 patients discontinued study participation because of adverse events. While 1 of 32 patients in the FMS group discontinued the study due to adverse events, none did so in the amitriptyline group. Neither the 2 FMS studies nor the rheumatoid arthritis study reported serious adverse events in the cannabinoid group. In the musculoskeletal pain study, 1 serious adverse event occurred in the nabilone group (dizziness-related fall with fracture).</td>
<td>The current evidence is inadequate to recommend cannabinoids for the treatment of pain associated with rheumatic diseases.</td>
</tr>
<tr>
<td>Walitt 2016</td>
<td>(27)*1</td>
<td>CENTRAL, Medline and Embase until April 2016; 3 study registries; contact with study authors</td>
<td>Greater pain relief in FMS patients by nabilone compared with placebo in a study with 40 FMS patients.</td>
<td>Higher discontinuation rate due to adverse events in the nabilone group (4/52) compared with the control group (1/20 with placebo and 0/32 with amitriptyline). No serious adverse events.</td>
<td>There is no unbiased and high-quality evidence available to show benefits of nabilone in FMS patients.</td>
</tr>
</tbody>
</table>

*1 systematic review from the authors’ working groups

*2 no statistically significant difference between nabilone and placebo with regard to mean pain relief in the analysis of published data by the authors of the systematic review (27)

CBD, Cannabidiol; FAAH1, fatty-acid amide hydrolase; FMS, fibromyalgia syndrome; THC, tetrahydrocannabinol
### eTABLE 3

**Efficacy of cannabinoids in visceral pain—systematic review of randomized controlled trials**

<table>
<thead>
<tr>
<th>First author</th>
<th>Year (Reference)</th>
<th>Databases and period of literature search</th>
<th>Efficacy</th>
<th>Tolerability and safety</th>
<th>Authors’ conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volz</td>
<td>2016 (26)*</td>
<td>CENTRAL, Medline, PubMed, Scopus and PsycINFO as well as clinicaltrials.gov until April 2015</td>
<td>1 RCT with medical marijuana evaluating 21 patients with Crohn’s disease over a period of 8 weeks; no statistically significant difference in remission rate; significant (p&lt;0.05) relief of abdominal pain and improved appetite</td>
<td>1 RCT with Crohn’s disease: No difference in tolerability was found between medical marijuana and placebo. Serious adverse events, such as neuropsychiatric symptoms and withdrawal symptoms after discontinuation of cannabis, were not observed. Data on potential addictive behavior were collected but not published by the authors. No information was provided about the patients’ fitness for work during the study.</td>
<td>Currently, considering an individual therapeutic trial of tetrahydrocannabinol in gastroenterology is limited to symptomatic relief of pain and loss of appetite in patients with Crohn’s disease, but only after failure of all established pharmacotherapy options and careful risk–benefit assessment.</td>
</tr>
</tbody>
</table>

* Systematic review from the authors’ working groups

IBD, inflammatory bowel disease; RCT, randomized controlled trial

### eTABLE 4

**Efficacy of cannabinoids in cancer pain—systematic reviews of randomized controlled trials**

<table>
<thead>
<tr>
<th>First author</th>
<th>Year (Reference)</th>
<th>Databases and period of literature search</th>
<th>Efficacy [95% CI]</th>
<th>Tolerability and safety [95% CI] Number of studies/patients</th>
<th>Authors’ conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mücke</td>
<td>2016 (19)*</td>
<td>CENTRAL, PsycINFO, PubMed, Scopus and clinicaltrials.gov until April 2015</td>
<td>[RD (≥30% pain relief): 0.07 [–0.0; 0.16] 2/387]</td>
<td>Discontinuation rate due to adverse events: RD: 1.15 [0.80; 1.60]; 4/825 Serious adverse events: RD: 1.12 [0.86; 1.46]; 4/825</td>
<td>Due to inadequate data, it is currently not possible to make recommendations for the use of cannabis or cannabinoids.</td>
</tr>
<tr>
<td>Whiting</td>
<td>2015 (21)</td>
<td>28 databases and gray literature until April 2015</td>
<td>[OR (≥30% pain relief): 1.41 [0.99; 2.00] 2/387]</td>
<td>No separate analysis for cancer pain</td>
<td>No specific conclusion for cancer pain</td>
</tr>
</tbody>
</table>

* Systematic review from the authors’ working groups

CI, confidence interval; OR, odds ratio; RD, risk difference; SMD, standardized mean difference
## ETABLE 5

### Efficacy of cannabinoids in palliative medicine—systematic reviews of randomized controlled trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Databases and period of literature search</th>
<th>Efficacy [95% CI]</th>
<th>Tolerability and safety [95% CI]</th>
<th>Authors’ conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krishnan 2009 (24)</td>
<td>Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG), The Cochrane Library, Medline, Embase, PsycINFO, CINAHL, und LILACS until April 2008</td>
<td>1 RCT with dronabinol in 18 patients with dementia In 1 RCT, the way data were presented made it impossible to use them for further analyses</td>
<td>No serious adverse events were reported even though 1 patient had experienced a generalized tonic-clonic seizure after the first dose of dronabinol. Compared with placebo, more patients treated with dronabinol suffered from dizziness, fatigue and euphoria.</td>
<td>No evidence is available to support the efficacy of cannabinoids in patients with symptoms of dementia.</td>
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<td>Lutge 2013 (25)</td>
<td>CENTRAL/CCTR, Medline and Embase until July 2012</td>
<td>No statistically significant difference in weight gain of ≥2 kg between dronabinol and placebo (RR: 2.09 [0.72; 6.06]) 1/139</td>
<td>In 3 RCTs, no study discontinuations due to adverse events were reported. One RCT reported 1 treatment discontinuation due to acute cannabis-induced psychosis and 1 due to intractable tobacco-related cough; 4/185</td>
<td>No evidence is available to support the efficacy and safety of the medicinal use of marijuana in HIV/AIDS.</td>
</tr>
<tr>
<td>Mücke 2016 (19)*</td>
<td>CENTRAL, Medline, PubMed, Scopus and PsycINFO as well as clinicaltrials.gov until April 2015 Duration at least 2 weeks</td>
<td>Cancer&lt;br&gt;Calorie intake: SMD: 0.2 [−0.66; 1.06]; 1/21 Appetite: SMD: 0.81 [−1.14; 2.75] 3/441 Nausea/vomiting: SMD: 0.21 [−0.10; 0.52]; 1/177 AIDS&lt;br&gt;Appetite: SMD: 0.57 [0.11; 1.03] 1/76 Weight change: SMD: 0.57 [0.22; 0.92]; 2/192 Nausea/vomiting: SMD: 0.20 [−0.15; 0.54]; 1/130</td>
<td>Discontinuation rate due to adverse events Cancer: RD: 1.15 [0.80; 1.66] 4/825 AIDS: RD: 1.87 [0.60; 5.84] 2/206 Serious adverse event Cancer: RD: 1.12 [0.86; 1.46] 4/825 AIDS: RD: 4.51 [0.54; 37.45] 2/206</td>
<td>Due to inadequate data, it is currently not possible to make recommendations for the use of cannabis or cannabinoids. In patients with cancer pain showing no adequate response to opioid therapy, an individual therapeutic trial over some days with dose titration may be indicated.</td>
</tr>
</tbody>
</table>

* Systematic review from the authors’ working groups

CI, confidence interval; RCT, randomized controlled trial; RD, risk difference; RR, risk ratio; SMD, standardized mean difference
### TABLE 6

**Cannabinoids in pain medicine – prospective long-term studies**

<table>
<thead>
<tr>
<th>First author</th>
<th>Year (Reference)</th>
<th>Setting and time period of study</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Substance used and dosing</th>
<th>Study duration</th>
<th>Efficacy (95% CI)</th>
<th>Tolerability and safety</th>
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<tbody>
<tr>
<td>Hoggart 2015</td>
<td>66 study centers in 4 countries (65 European centers)</td>
<td>October 2005 until June 2007</td>
<td>Diabetic polyneuropathy, Postherpetic neuralgia, Complex regional pain Syndrome type 2, Focal nerve lesion</td>
<td>History of serious psychiatric, epileptic, renal, hepatic or cardiovascular disorders; history of alcohol or substance abuse; hypersensitivity to study medication; women of childbearing age without contraception</td>
<td>Median of daily dose of THC/CBD spray: 6–8 puffs (16.2–21.6 mg THC/15–20 mg CBD)</td>
<td>38 weeks</td>
<td>380 patients</td>
<td>At least half of the patients reported pain relief of ≥30% and at least one-third of patients pain relief of ≥50% at all time points.</td>
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<td>Ware 2015</td>
<td>7 Canadian pain centers</td>
<td>January 2004 until July 2008</td>
<td>Age ≥18 years, Chronic non-cancer pain of moderate to severe intensity over a period of at least 6 months; conventional treatments not indicated or not effective</td>
<td>Pregnancy, breastfeeding; history of psychosis, unstable ischemic heart disease or arrhythmia, unstable bronchopulmonary disease</td>
<td>Medical marijuana (12.5% THC); mean daily dose 2.5 g (minimum 0.1 g, maximum 14 g)</td>
<td>52 weeks</td>
<td>215 patients in cannabis group and 216 patients in control group (pharmacological pain therapy without cannabis)</td>
<td>Pain relief by 0.92 [−0.62; −1.23] points on an 11-point scale in the cannabis group, but not in the control group (−0.18 [0.13; −0.49])</td>
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<td>234/380 patients completed the study</td>
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<td>The study was discontinued by 23% of patients because of adverse events, in 7% because of serious adverse events</td>
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<td>The most common adverse events (by organ system) were related to the central nervous system (42%), the gastrointestinal tract (36%), general and local conditions (24%), infections (23%), and psychiatric disorders (21%).</td>
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<tr>
<td>First author Year (Reference)</td>
<td>Setting and time period of study</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Substance used and dosing</td>
<td>Study duration</td>
<td>Efficacy [95% CI]</td>
<td>Tolerability and safety</td>
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<tr>
<td>Haroutounian 2016 (30)</td>
<td>June 2010 until January 2013</td>
<td>Age ≥18 years; Pain for more than 3 months; inadequate pain relief or intolerable adverse events with at least two substance classes in full dose</td>
<td>Inability to understand the treatment-related risks; history of drug abuse or drug dependency; concomitant mental illness; history or family history of schizophrenia or psychosis; high risk for lack of compliance; pregnancy or breastfeeding</td>
<td>Mean monthly medical marijuana dose 43.2 g (SD 17.9) (THC and CBD content not specified)</td>
<td>26 weeks</td>
<td>206 patients</td>
<td>Reduction of pain severity score by median 7.50 [6.75; 7.75] to 6.25 [5.75; 6.75] on 11-point scale</td>
<td>176/206 patients completed the study. 11 patients terminated the study because of adverse events (sedation, difficulty concentrating). 2 serious adverse events: elevated liver enzymes; admission to emergency department for confusion</td>
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</table>

CBD, cannabidiol; CI, confidence interval; SD, standard deviation; THC, tetrahydrocannabinol
Methods

Literature search
The literature search for systematic reviews (SRs) was conducted in the databases Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Medline for the period January 2009 to January 2017, using the search terms “systematic review”, “meta-analysis”, “cannabis”, “chronic pain” and “palliative care”. In the Medline database, the following search strategy was used: (“Palliative Care”[Mesh] OR “Palliative Medicine”[Mesh]) OR “Chronic Pain”[Mesh]) AND (“Cannabis”[Mesh] OR “Medical Marijuana”[Mesh]) AND (“Review Literature as Topic”[Mesh] OR “Review”[Publication Type] OR “Meta-Analysis as Topic”[Mesh]). In addition, we searched in Medline using the search terms (“Palliative Care”[Mesh] OR “Palliative Medicine”[Mesh]) OR “Chronic Pain”[Mesh]) AND (“Cannabis”[Mesh] OR “Medical Marijuana”[Mesh]) AND (“safety”[MeSH Terms] OR safety [Text Word]) and in clinical trials.gov using the search terms ((Cannabis OR cannabinoids) AND chronic pain) for prospective observational studies (duration ≥ 6 months).

The reference sections of the identified SRs were checked for further SRs. We interviewed experts in pain management and palliative medicine with regard to further SRs and long-term studies on this topic.

Inclusion criteria

● Study type: SRs of randomized controlled trials (RCTs) (parallel, cross-over and enriched enrollment randomized withdrawal (EERW) trial designs) as well as prospective cohort studies ≥ 6 months. We included SRs with quantitative data analysis or which stated explicit reasons for not performing a quantitative data synthesis. We excluded qualitative (narrative) SRs without quantitative data synthesis and/or without information about the reasons why this had not been performed.

● Indications: chronic cancer and non-cancer pain and symptomatic treatment of further somatic symptoms (e.g. loss of appetite, dyspnea) of advanced diseases (e.g. cancer, dementia, AIDS). We included SRs on defined clinical entities (e.g. cancer pain, neuropathic pain) and excluded SRs combining several clinical entities (e.g. all types of chronic pain) without subgroup analysis. No age or country restrictions applied.

Endpoints
The SRs and long-term studies should report a quantitative outcome parameter for at least one of the following endpoints:

● Efficacy:
  - Mean pain intensity at end of treatment or change in pain intensity at end of treatment versus baseline or at least 30% pain relief at end of treatment versus baseline.
  - Mean reduction of symptoms other than pain (e.g. dyspnea, loss of appetite) at end of treatment. Standardized mean differences (cannabinoids vs. placebo) >0.2 (4) or a number needed to treat for an additional benefit (NNTB) of ≤ 10 (5) were regarded as clinically relevant effects.

● Tolerability: discontinuation rate due to adverse events

● Safety: serious adverse events, including deaths: A number needed to treat for an additional harm (NNTH) of ≤10 was regarded as clinically relevant harm (5).

Methodological quality
As a quantitative criterion of robust evidence we chose inclusion of at least 400 patients in a quantitative analysis (meta-analysis) of the study results and/or availability of an RCT with at least 200 patients per study arm (4).

Data extraction
The following characteristics of the SRs were extracted independently by two authors (WH, MAF, FP); any disagreements were resolved by consensus: medical indication; number of included RCTs/patients; duration of RCT; type of control; instrument for and results of measurement of methodological quality of included RCTs; databases and period of literature search; results for efficacy, tolerability and safety; authors’ conclusions; AMSTAR rating. Due to the heterogeneity of conditions and outcome parameters, we did not plan a priori to perform quantitative data synthesis.