ORIGINAL ARTICLE

Cannabinoids in Pain Management and Palliative Medicine

An Overview of Systematic Reviews and Prospective Observational Studies

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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:
Häuser W, Fitzcharles MA, Radbruch L, Petzke F: Cannabinoids in pain management and palliative medicine—an overview of systematic reviews and prospective observational studies. Dtsch Arztebl Int 2017; 114: 627–34. DOI: 10.3238/arztebl.2017.0627

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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

BOX

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.

* 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).

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) und 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 ClinicalTrials.gov und 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

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

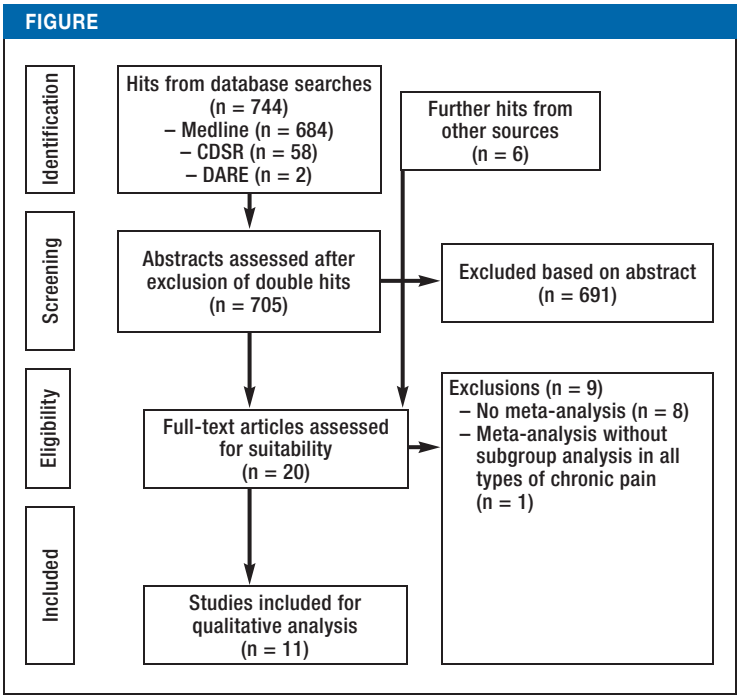
One SR analyzed 1 RCT evaluating medical marijuana administered as a joint compared to a cigarette not containing tetrahydrocannabinol (THC) in 21 patients with Crohn's disease over a period of 8 weeks. While no significant differences were found with regard to remission rate and incidence of adverse 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 $p \leq 0.05$. 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).

FIGURE



Results of literature search
CDSR, Cochrane Database of Systematic Reviews;
DARE, Database of Abstracts of Reviews of Effects

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

TABLE 1

Characteristics of the randomized controlled trials with cannabinoids included in the systematic reviews

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

* Systematic review from the authors' working groups
CBD, cannabidiol; RoB, Cochrane Collaboration risk-of-bias tool; THC, tetrahydrocannabinol

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) *(eTable 5)*.

Prospective long-term observational studies

Three prospective long-term studies were identified *(eTable 6)*. 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 2

Results of systematic reviews of randomized controlled trials with cannabinoids for chronic neuropathic pain

First author Year (Reference)	Databases Period of literature search	Efficacy [95% CI] Number of studies/patients (with quantitative data synthesis)	Tolerability and safety [95% CI] Number of studies/patients (with quantitative data synthesis)	Authors' conclusion
Andreae, 2015 (17)	Cochrane CENTRAL, PubMed, Embase and AMED, date not stated, manual search in the abstracts of the Conference on Retroviruses and Opportunistic Infections 2011, of the International AIDS Conference and of the World Congress of Pain 2010	OR (≥ 30% pain relief): 3.2 [1.59; 7.24] NNTH: 5.6 [3.4; 13.7] 5/509	No quantitative data synthesis	Inhaled cannabis appears to result in short-term relief of neuropathic pain in 1 of 5–6 patients treated.
Jawahar, 2013 (18)	CINAHL, PubMed, CPCI-S, clinicaltrials.gov until December 2012	SMD: 0.08 [0.74; 0.89] 3/565	No quantitative data synthesis	Due to the comparatively small number of studies evaluating multiple-sclerosis patients with chronic pain, no specific treatment recommendations can be made.
Petzke, 2016 (20)*[1]	PubMed, Cochrane CENTRAL und clinicaltrials.gov until November 2015	All cannabinoids pooled: SMD: −0.10 [−0.20; −0.00]; 13/1565 Subgroup analysis: THC/CBD spray: SMD: −0.09 [−0.20; 0.03]; 9/1433 Medical marijuana: SMD: −0.19 [−0.68; 0.31]; 1/84*[2] All cannabinoids pooled: RD, ≥30 % pain relief: 0.10 [0.03; 0.16]; NNTB: 10 [6; 33]; 9/1346 Subgroup analysis: THC/CBD spray: RD: 0.08 [0.02; 0.15]; NNTB: 12 [6; 50]; 9/1 289 Medical marijuana: RD: 0.29 [0.05; 0.52]; NNTB: 4 [2; 20]; 1/56*[2]	All cannabinoids pooled: RD (discontinuation due to adverse events): 0.04 [0.01; 0.07]; NNTH: 25 [16; 100]; 11/1572 All cannabinoids pooled: RD (central nervous system adverse events): 0.38 [0.18; 0.58]; NNTH: 3 [2. 6]; 9/1304 All cannabinoids pooled: RD (psychiatric disorders): 0.11 [0.06; 0.16]; NNTH: 9 [6; 17]; 9/1304 No statistically significant difference between all cannabinoids pooled and placebo with regard to incidence of serious adverse events	Short-term and mid-term treatment may be considered in selected patients with chronic neuropathic pain after failure of first- and second-line therapy.

*[1] Systematic review from the authors' working groups
*[2] Erratum in (20); results corrected by authors
AMED, Allied and Alternative Medicine; CBD, cannabidiol; CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; CPCI-S, Conference Proceedings Citation Index-Science; CI, confidence interval; NNTB, number needed to treat for an additional benefit; NNTH, number needed to treat for an additional harm; OR, odds ratio; RD, risk difference; SMD, standardized mean difference; 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 nabilone 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 und 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 marihuana 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.

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.

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

Manuscript received on 6 April 2017; revised version accepted on 21 June 2017

Translated from the original German by Ralf Thoene, MD

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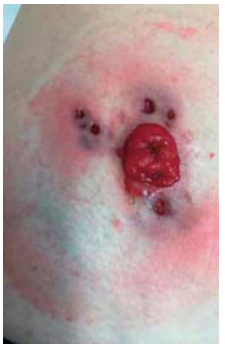
Supplementary material
For eReferences please refer to:
www.aerzteblatt-international.de/ref3817

eTables, eBox:
www.aerzteblatt-international.de/17m0627

CLINICAL SNAPSHOT

Peristomal Lesions in Crohn's Disease: Are They Always Fistulae?

A 34-year-old woman with ileocolonic and perianal Crohn's disease received a loop ileostomy because of a supralevator abscess and multiple perianal fistulae. She was treated thereafter with dual immunosuppression by means of a TNF-α inhibitor (adalimumab) combined with azathioprine. About eight weeks after surgery, the patient developed peristomal inflammation with small oozing lesions. Peristomal fistula formation was suspected, and treatment was begun with ciprofloxacin and metronidazole, but there was no improvement. Her leukocyte count and CRP values were only mildly elevated. Ileocoloscopy revealed no more than a mild mucosal erythema without aphthous or ulcerative changes; there was no evident fistular opening. Ultrasonography and MR enterography did not reveal any fistula passageways either. Peristomal pyoderma gangrenosum was ruled out by skin biopsy. Swabs taken for microbiological diagnosis were positive for methicillin-resistant Staphylococcus aureus (MRSA). The lesions healed within two weeks after local antiseptic measures with octenidine and povidone-iodine.



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Conflict of interest statement: The authors state that they have no conflict of interest.

Cite this as: Schäffler H, Lamprecht G, Witte M: Peristomal lesions in Crohn's disease: are they always fistulae? Dtsch Arztebl Int 2017; 114: 634. DOI: 10.3238/arztebl.2017.0634

Translated from the original German by Ethan Taub, M.D.

Supplementary material to:

Cannabinoids in Pain Management and Palliative Medicine

An Overview of Systematic Reviews and Prospective Observational Studies

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Dtsch Arztebl Int 2017; 114: 627–34. DOI: 10.3238/arztebl.2017.0627

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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)

First author Year (Reference)	a-priori design?	Duplicate study selection and data extraction?	Comprehensive literature search?	"Gray" literature included?	List of included and excluded studies?	Characteristics of the included studies presented, e.g. as a table?	Scientific quality of the included studies assessed and documented?	Scientific quality of the included studies used appropriately in formulating conclusions?	Methods used to combine the findings of studies appropriate?	Likelihood of publication bias assessed?	Conflict of interest included?	Total
Andreae 2015 (17)*1	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	10
Fitzcharles 2016 (22)*2	no	yes	yes	yes	yes	yes	yes	yes	no*3	no	no	7
Fitzcharles 2016 (23)*2	no	yes	yes	yes	yes	yes	yes	yes	no*3	no	yes	8
Jawahar 2013 (18)	no	yes	yes	yes	no	yes	yes	yes	yes	no	yes	8
Krishnan 2009*1 (24)	yes	yes	yes	yes	yes	yes	yes	no	no*3	no	no	7
Ludge 2013*1 (25)	yes	yes	yes	yes	yes	yes	yes	no	no*3	no	no	7
Mücke 2016 (19)*2	no	yes	yes	yes	yes	yes	yes	no	yes	yes	no	8
Petzke 2016 (20)*2	no	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	9
Volz 2016 (26)*2	no	yes	yes	yes	yes	yes	yes	no	no*3	yes	yes	8
Walitt*1/*2 2016 (27)	yes	yes	yes	yes	yes	yes	yes	yes	no*3	no	yes	9
Whiting 2015 (21)*1	yes	yes	yes	yes	no	no	yes	yes	yes	yes	no	8

*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

First author Year (Reference)	Databases and period of literature search	Efficacy	Tolerability and safety	Authors' conclusion
Fitzcharles 2016 (22) *1	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.	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	Dizziness, cognitive problems, vertigo, and nausea were reported by half of the patients	The current evidence is inadequate to recommend cannabinoids for the treatment of pain associated with rheumatic diseases
Fitzcharles 2016 (23)*1	CENTRAL, PubMed, www.cannabis-med.org and clinicaltrials.gov until April 2016	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 in 30 patients with musculoskeletal pain	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).	The current evidence is inadequate to recommend cannabinoids for the treatment of pain associated with rheumatic diseases.
Walitt 2016 (27)*1	CENTRAL, Medline and Embase until April 2016; 3 study registries; contact with study authors	Greater pain relief in FMS patients by nabilone compared with placebo in a study with 40 FMS patients*2 No statistically significant difference between nabilone and amitriptyline with regard to pain relief in a study with 32 FMS patients	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	There is no unbiased and high-quality evidence available to show benefits of nabilone in FMS patients.

*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

First author Year (Reference)	Databases and period of literature search	Efficacy	Tolerability and safety	Authors' conclusion
Volz 2016 (26)*	CENTRAL, Medline, PubMed, Scopus and PsycINFO as well as clinicaltrials.gov until April 2015 Study duration at least 2 weeks	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 ($p<0.05$) relief of abdominal pain and improved appetite The results of 2 RCTs evaluating pharmaceutical cannabis products, one in patients with IBD and the other with chronic pancreatitis, had not yet been published at that time	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.	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.

* 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

First author Year (Reference)	Databases and period of literature search	Efficacy [95% CI] Number of studies/patients	Tolerability and safety [95% CI] Number of studies/patients	Authors' conclusion
Mücke 2016 (19)*	CENTRAL, PsycINFO, PubMed, Scopus and clinicaltrials.gov until April 2015	RD (≥30% pain relief): 0.07 [–0.0; 0.16] 2/387	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	Due to inadequate data, it is currently not possible to make recommendations for the use of cannabis or cannabinoids.
Whiting 2015 (21)	28 databases and gray literature until April 2015	OR (≥30% pain relief): 1.41 [0.99; 2.00] 2/387	No separate analysis for cancer pain	No specific conclusion for cancer pain

* 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

Reference	Databases and period of literature search	Efficacy [95% CI] Number of studies/patients	Tolerability und safety [95% CI] Number of studies/patients	Authors' conclusions
Krishnan 2009 (24)	Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG), The Cochrane Library, Medline, Embase, PsycINFO, CINAHL und LILACS until April 2008	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	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.	No evidence is available to support the efficacy of cannabinoids in patients with symptoms of dementia.
Lutge 2013 (25)	CENTRAL/CCTR, Medline and Embase until July 2012	No statistically significant difference in weight gain of ≥2 kg between dronabinol and placebo (RR: 2.09 [0.72; 6.06]) 1/139	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	No evidence is available to support the efficacy and safety of the medicinal use of marijuana in HIV/AIDS.
Mücke 2016 (19)*	CENTRAL, Medline, PubMed, Scopus and PsycINFO as well as clinicaltrials.gov until April 2015 Duration at least 2 weeks	Cancer 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 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	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	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.

* Systematic review from the authors' working groups
CI, confidence interval; RCT, randomized controlled trial; RD, risk difference; RR, risk ratio; SMD, standardized mean difference

eTABLE 6

Cannabinoids in pain medicine – prospective long-term studies

First author Year (Reference) Setting and time period of study	Inclusion criteria	Exclusion criteria	Substance used and dosing	Study duration Number of patients	Efficacy [95% CI]	Tolerability and safety
Hoggart 2015 (28) 66 study centers in 4 countries (65 European centers) October 2005 until June 2007	Diabetic polyneuropathy Postherpetic neuralgia Complex regional pain Syndrome type 2 Focal nerve lesion Patients had tolerated study medication in randomized controlled trial and principal investigator expected benefits from continuation of THC/CBD therapy.	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	Median of daily dose of THC/CBD spray: 6–8 puffs (16.2–21.6 mg THC/15–20 mg CBD)	38 weeks 380 patients	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.	234/380 patients completed the study The study was discontinued by 23% of patients because of adverse events, in 7% because of serious adverse events 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%).
Ware 2015 (29) 7 Canadian pain centers January 2004 until July 2008	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	Pregnancy, breastfeeding; history of psychosis; unstable ischemic heart disease or arrhythmia; unstable bronchopulmonary disease	Medical marijuana (12.5% THC); mean daily dose 2.5 g (minimum 0.1 g, maximum 14 g)	52 weeks 215 patients in cannabis group and 216 patients in control group (pharmacological pain therapy without cannabis)	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])	77/215 patients of the cannabis group and 34/216 of the control group completed the study. 10/215 patients in the cannabis group discontinued the study due to adverse events. 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]). The rate of serious adverse events was 13% in the cannabis group und 19% in the control group. Moreover, the non-adjusted incidence rate of psychiatric conditions was higher in the cannabis group compared with the control group: 2.31 [1.45; 5.16] (57 versus 24 reported events). In comparison with the control group, a higher rate of anxiety (4.6% vs. 0.9%), euphoria (4.2% vs. 0%) and paranoia (0.9% vs. 0%) was observed.

First author Year (Reference) Setting and time period of study	Inclusion criteria	Exclusion criteria	Substance used and dosing	Study duration Number of patients	Efficacy [95% CI]	Tolerability and safety
Haroutounian 2016 (30) June 2010 until January 2013 University hospital pain clinic in Israel	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	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	Mean monthly medical marijuana dose 43.2 g (SD 17.9) (THC and CBD content not specified)	26 weeks 206 patients Most common diagnoses: chronic musculoskeletal pain in several anatomical regions (n = 62, 30.1%), peripheral neuropathic pain (n = 49, 23.8%), radicular back pain (n = 39, 18.9%)	Reduction of pain severity score by median 7.50 [6.75; 7.75] to 6.25 [5.75; 6.75]) on 11-point scale	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

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

eBOX

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.