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Efficacy, tolerability, and safety of cannabinoids for chemotherapy-induced nausea and vomiting—a systematic review of systematic reviews

Introduction

Prescription and reimbursement of cannabinoids (CBs) for medical purposes are more restricted in Germany than in some other countries of the world, for example, Canada and Israel [1, 9]. Recently, a discussion started in Germany on whether the prescription of CBs for defined medical indications should be made easier. In other countries CBs are approved for chronic pain and for supportive and palliative care [1, 9]. Prevention and control of nausea and vomiting (emesis) are paramount in the supportive care of cancer patients [4, 16]. Despite the advances in antiemetic therapy, nausea and vomiting continue to be a burden for some patients undergoing treatment for malignancies [13]. Chemotherapy-induced nausea and vomiting (CINV) can be divided into the categories of acute, delayed, anticipatory, and breakthrough CINV [7]. For therapy, antiemetic agents are currently differentiated into conventional drugs, for example, comprising prokinetics, neuroleptics or antipsychotics, anticonvulsants, dopamine antagonists and corticoids, and new antiemetics comprising 5HT3- antagonists and neurokinine (NK)-1 receptor antagonists. Nowadays, the antiemetics indicated for CINV with high emesis-inducing potential are 5-HT3 receptor antagonists, dexamethasone, and NK-1 antagonists during the acute emetic phase [20].

CBs are thought to act through different mechanisms compared to other agents given for nausea and vomiting. Both CB1 and CB2 cannabinoid receptors have been demonstrated in the dorsal vagal complex which serves as the integration centre for emetogenic stimuli and their activation results in the inhibition of emesis [6, 28]. Moreover, the blockade of CB 1 cannabinoid receptors induces vomiting, supporting their functional role within the areas of the brain related to nausea and vomiting. Therefore, CBs might be effective in patients that respond poorly to commonly used antiemetics. In 1985, the FDA approved two pharmaceutical CBs, dronabinol and nabilone, for the treatment of CINV not effectively treated by other agents [25]. In Germany, CBs are currently not licensed for any type of CINV.

Within the discussion on potential indications for the medical use of CBs in Germany, the aim of the review is to summarize the efficacy, tolerability, and safety of CBs in the prevention and treatment of CINV in any type of chemotherapy for any type of cancer in patients of all ages compared to placebo or other antiemetics as assessed by systematic reviews of randomized controlled trials.

Methods

The review was conducted according to the recommendations of the Cochrane Collaboration for conducting a Cochrane overview on reviews [8] and of the Joanna Briggs Institute for conducting umbrella reviews [2].

Criteria for considering studies for this review

Types of studies

Systematic reviews should meet the preferred reporting items for systematic reviews and meta-analyses (PRISMA) criteria [12] and include randomized controlled trials (RCTs) with crossover or parallel-group design with active or placebo control groups or both.

Types of participants

Patients presenting with any type of cancer and receiving chemotherapeutic treatment (low, moderate, or high emetic potential), independent of gender, age, country, and clinical setting.

Types of interventions

CBs, either phytocannabinoids such as herbal cannabis (hashish, marihuana), plant-based CBs (nabiximole), or pharmacological synthetic CBs (e.g., cannabidiol, dronabinol, levonantradol, nabilone)

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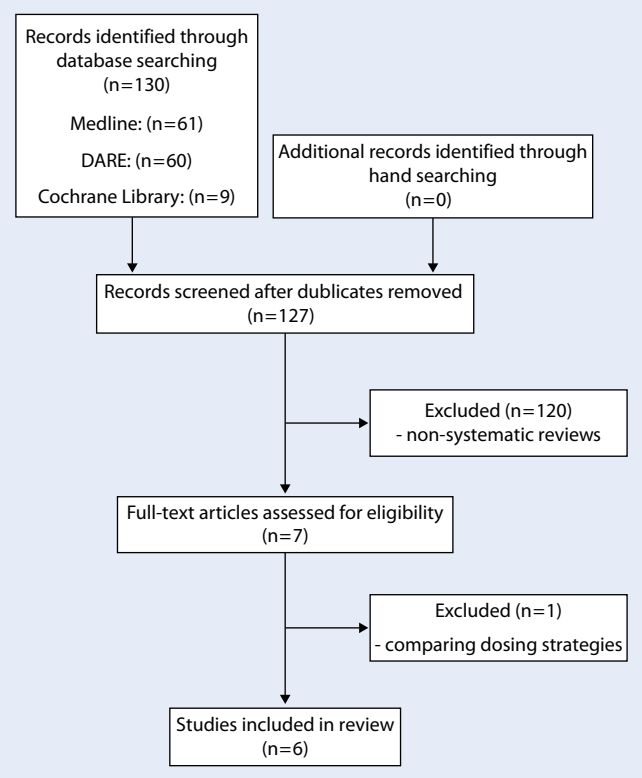

Fig. 1 ◀ Flow diagram for systematic review of studies

at any dose, by any route, compared with other conventional agents or placebo, or both for CINV. Studies evaluating different dosing strategies of CBs were not eligible.

Types of outcome measures

Reviews should summarize at least one of these outcomes:

Efficacy

- Absence of episodes of nausea and vomiting (acute, delayed, anticipatory, and breakthrough)
- Frequency of nausea and vomiting (acute, delayed, anticipatory, and breakthrough)
- Severity of nausea (acute, delayed, anticipatory, and breakthrough)

Tolerability

- Withdrawal due to adverse effects

Safety

- Serious adverse events including deaths

Literature search

The following electronic databases were searched from their inception through to November 30, 2015: Pubmed/MEDLINE, the Cochrane Library, and the Database of Abstracts of Reviews of Effects (DARE). The literature search was constructed around search terms for "chemotherapy induced nausea and vomiting," systematic reviews, and meta-analyses and adapted for each database.

The following search strategy was used on the Pubmed/MEDLINE database: ("systematic review"[All Fields] OR "meta-analysis"[All Fields]) AND ("cannabinoids"[MeSH Terms] OR "cannabinoids"[All Fields] OR "cannabinoid"[All Fields]) AND ("drug therapy"[Subheading] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "chemotherapy"[All Fields]). The Cochrane Library and DARE were searched using the term "cannabinoid." The reference lists of identified reviews were also searched manually for relevant articles.

Review selection

At first all duplicates were removed from the references. Two reviewers (W. Häuser and M. Schäfer) then screened the abstracts of the remaining papers individually and went on to obtain the full papers for potentially eligible reviews. The reviews were then checked in detail with eligible papers being included in this overview. Disagreements were checked with a third reviewer (S. Tafelski) and resolved by agreement.

Data collection

Two reviewers (W. Häuser and M. Schäfer) independently extracted data on review characteristics (aims of the review; search of literature; types of cancer, chemotherapy, interventions, and comparators; demographic data of the study sample; number of studies and patients, information on meta-analysis, and risk of bias assessments). Disagreements were checked with a third reviewer (S. Tafelski) and resolved by agreement.

Methodological quality

Methodological quality of systematic reviews was determined using the assessment of the methodological quality of systematic reviews (AMSTAR) by two independent reviewers (W. Häuser and M. Schäfer). The AMSTAR instrument is an 11-item assessment tool mainly for intervention reviews with good validity and reliability. The AMSTAR determines whether most important contents of systematic reviews have been provided, such as an a priori design, a comprehensive literature search, information about study selection and data extraction, a list of included and excluded studies, characteristics of studies, a quality assessment of included studies, an appropriate method of combining findings or forming conclusions, and a conflict of interest statement [23]. AMSTAR scores 0–4 were rated as low, AMSTAR scores 5–8 as moderate, and AMSTAR scores 9–11 as high quality [22]. Disagreements were checked with a third reviewer (S. Tafelski) and resolved by agreement.

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Efficacy, tolerability, and safety of cannabinoids for chemotherapy-induced nausea and vomiting—a systematic review of systematic reviews

Abstract

Background. There is growing public and legislative body support for the medical use of cannabis products, for example, for chemotherapy-induced nausea and vomiting (CINV), in Germany.

Methods. A comprehensive literature search until November 2015 was conducted in MEDLINE, DARE and Cochrane libraries for systematic reviews of randomized controlled trials (RCTs) comparing herbal or pharmaceutical cannabinoids (CB) versus placebo or conventional antiemetics for CINV. Outcomes were reduction of CINV for efficacy, drop-out rates due to adverse events for tolerability, and serious adverse events for safety. The methodology quality of the systematic reviews was evaluated by the tool assessment of multiple systematic reviews (AMSTAR).

Results. Six systematic reviews of RCTs included the pharmaceutical CBs dronabinol, levonantradol, and nabilone or whole plant extract (e.g., nabiximol) compared with placebo or conventional antiemetics. There was moderate quality evidence on the efficacy of CBs compared to placebo and conventional antiemetics for CINV. There was moderate quality evidence that pharmaceutical CBs were less tolerated and less safe than placebo and conventional antiemetics in CINV. One RCT examining whole plant extract was included into the systematic reviews. No RCT was found comparing CBs with neurokinine−1 receptor antagonists.

Conclusions. With safe and effective antiemetics available, CBs cannot be recommended as first- or second-line therapy for CINV. Some guidelines recommend pharmaceutical CBs as third-line treatment in the management of breakthrough nausea and vomiting. Due to the lack of RCT data and safety concerns, herbal cannabis cannot be recommended for CINV.

Keywords

Cannabinoids · Systematic review of systematic reviews · Randomized controlled trial · Chemotherapy-induced nausea and vomiting · Tolerability · Safety

Wirksamkeit, Verträglichkeit und Sicherheit von Cannabinoiden für die Therapie von Chemotherapie-induzierter Übelkeit und Erbrechen: eine systematische Zusammenfassung systematischer Reviews

Zusammenfassung

Hintergrund. Die medizinische Anwendung von Cannabispräparaten erfährt aktuell eine zunehmende Unterstützung in der Literatur und auch beim Gesetzgeber, z. B. für die Indikation Chemotherapie-induzierte Übelkeit und Erbrechen (CINV).

Methoden. Eine umfassende Literaturrecherche bis einschließlich November 2015 wurde in einschlägigen Datenbanken (MEDLINE, DARE und Cochrane Datenbanken) durchgeführt, um systematische Reviews von randomisierten kontrollierten Studien (RCTs) zu identifizieren, die pflanzliche oder pharmazeutische Cannabinoide hinsichtlich Wirksamkeit, Nebenwirkungen und Verträglichkeit sowie von schwerwiegenden unerwünschten Ereignissen mit Placebo oder herkömmlichen Antiemetika verglichen. Die methodische Qualität der systematischen Übersichtsarbeiten wurde durch ein validiertes Instrument bewertet (AMSTAR).

Ergebnisse. Sechs systematische Übersichtsarbeiten schlossen RCTs mit den Wirkstoffen Dronabinol, Levonantradol und Nabilon sowie ein Pflanzenextrakt (Nabiximol) im Vergleich zu Placebo oder herkömmlichen Antiemetika ein. Die Arbeiten ergaben eine moderate Qualität der Evidenz der Wirksamkeit von Cannabinoiden im Vergleich mit Placebo sowie herkömmliche Antiemetika für die Indikation CINV. Weiterhin besteht eine moderate Qualität der Evidenz, dass Cannabispräparate weniger verträglich und sicher sind als Placebo und herkömmlichen Antiemetika. Insgesamt schlossen die Übersichtsarbeiten eine RCT mit cannabishaltigem Pflanzenextrakt mit ein, dagegen wurde keine Studie identifiziert, die Neurokinin-1-Rezeptorantagonisten mit Cannabisprodukten verglich.

Schlussfolgerungen. Für die Indikation CINV sind sichere und wirksame Antiemetika verfügbar, so dass Cannabinoide nicht als Erstlinien- oder Zweitlinien-Therapeutika empfohlen werden können. Einige Leitlinien enthalten den Hinweis, dass pharmazeutische Cannabinoide in der Indikation Durchbruch –CINV als Drittlinientherapie berücksichtigt werden könnten. Aufgrund der eingeschränkten Datenlage und Sicherheitsbedenken kann pflanzlicher Cannabis nicht für die Therapie von CINV empfohlen werden.

Schlüsselwörter

Cannabinoide · Systematische Übersicht · Randomisierte · Kontrollierte Studie · Chemotherapie-induzierte Übelkeit und Erbrechen · Sicherheit · Verträglichkeit

Data

Overall effect estimates extracted from systematic reviews or other similar numerical data were presented. Where overall effect estimates were presented, the number of studies that informed about the outcome and number of participants (from included studies) as well as the heterogeneity of the results of included reviews were reported.

Results

Literature search

The search of literature yielded 130 hits. After removing three duplicates, papers were assessed for eligibility. Finally, 120

Table 1 Characteristics of systematic reviews and meta-analyses including randomized controlled trials to compare cannabinoids with placebo

Reference	Study population (age, gender)	Type of cancer	Type of chemotherapy	Cannabinoid (dosage/d)	Controls	Methodology quality
Tramer et al. [26]	Mainly adults; two studies included children; no pooled data on age and gender reported	Most studies with various tumors	Most frequently used: adriamycin, cisplatin, cyclosphosphamide, doxorubicine, methotrexate, and vincristine	Nabilone 4 mg Dronabinol 7–10 mg/m^2	Placebo	Oxford score (0–5) Four studies with a score of 5, two studies with a score of 3 and one study with a score of 1
Rocha et al. [17]	No data on demographics reported	Most studies with various tumors	Most frequently used: adriamycin, cisplatin, cyclosphosphamide, doxorubicine, methotrexate, and vincristine	Dronabinol 7–12 mg/m^2 Nabilone 1–5 mg Levonantradol 0.5–1.0 mg	Placebo	Adequacy of randomization One study with low and nine studies with moderate risk of bias
Whiting et al. [30]	Any population with nausea and vomiting due chemotherapy without restrictions	Various malignancies, in some trials underlying disease not reported	Various chemotherapeutic regimens, in some trials chemotherapeuticals not reported	Dronabinol and Nabiximols	Placebo	Cochrane Risk of Bias tool Twenty-three trials with high risk of bias, five trials with unclear risk of bias based on GRADE level "low" for meta-analysis
Smith et al. [24]	Adults with CINV without restriction	Various malignancies, underlying disease not specified	Variety of chemotherapy regimens with low, moderate, and high emetic potential	Nabilone and Dronabinol	Placebo (nine trials, $N=819$ patients)	Cochrane Risk of Bias tool Twenty-three trials showed variable quality, ranging from low to high. GRADE level "low" for most outcomes in meta-analysis

manuscripts did not fulfill inclusion criteria as they did not meet criteria for systematic reviews or focused on other indications for cannabinoid therapy. One systematic review compared adjunctive effects of antiemetic agents and extracted patients with different dronabinol dosing regimens, this systematic review was out of scope [21].

Finally, six systematic reviews were included (**Fig. 1**): Tramer et al. [26]; Rocha et al. [17], Phillips et al. [19], van den Elsen et al. [27], Whiting et al. [30], and Smith et al. [24].

These systematic reviews included the pharmaceutical CBs dronabinol, levonantradol and nabilone or whole plant extracts compared with placebo or conventional antiemetics. Five systematic reviews extracted data on complete control of CINV, two reported on ordinal data from nausea and vomiting scores.

Characteristics of included studies and of systematic reviews

Details of the RCTs included and of the results of the systematic reviews are presented in **Tables 1, 2, 3, 4 and 5**. The most recent literature search in the reviews covered publications up to April 2015 [30]. Included RCTs were published between 1975 and 2012.

Most reviews did not report on the countries or regions in which the RCTs were conducted except Whiting et al. [30]. The RCTs included patients of ages between 3.5 and 82 years. Two systematic reviews focused on specific age groups: Phillips et al. for CINV in childhood [19] and van den Elsen et al. in the elderly [27]. Most sample sizes were small: Only six studies had a sample size of 100 patients and more. Most RCTs included various malignancies. The most frequent chemotherapies were adriamycin, cisplatin, cyclosphosphamide, doxorubicine, methotrexate, and vincristine. The CBs used were dronabinol, levonantradol, nabilone, and whole plant extracts. The dosages ranged between 1 and 7 mg orally for nabilone, 7.5 and 30 mg orally for dronabinol, and 1.5 and 3 mg for levonantradol intramuscularly. Active comparators were classical antipsychotics (prochlorperazine, thiethylperazine, chlorpromazine, haloperidol), prokinetics (metoclopramide, domperidone), dopamine antagonists (alizapride), anticonvulsants (gabapentin), steroids (dexamethasone), and 5HT3- antagonists.

Quantitative synthesis of antiemetic efficacy for CINV was pooled in four reviews conducting meta-analyses. Out of 43 extracted RCTs, quantitative data synthesis was performed including 10 RCTs by Tramer et al. [26], 13 RCTs by Rocha et al. [17], 3 RCTs by Whiting et al. [30], and 3 RCTs by Smith et al. [24]. Two systematic reviews limited their summary to narrative comparisons [19, 27] due to a small number of patients accessible or a large heterogeneity of results.

Assessment of bias

All six reviews assessed the risk of bias: Tramer by the Oxford (Jadad) scale, Rocha reported adequacy of allocation concealment, and Phillips, Whiting and Smith used the Cochrane risk of bias tool [8]. van den Elsen provided a table summarizing risk of bias for included RCTs. The rating of the study quality depended on the assessment system used: For most studies, the risk of bias was low by the Jadad Score, moderate as to the correctness of adequate concealment allocation and high by the Cochrane risk of bias tool.

Three systematic reviews had a high (Phillips, Whiting and Smith [19, 24, 30]) and three had a moderate AMSTAR quality score (see **Table 6**).

Table 2 Results of systematic reviews and meta-analyses including randomized controlled trials to compare cannabinoids with placebo

Reference	Aim of the review	Search of literature	Total number of RCTs included	Total number of patients	Results efficacy; number of trials and participants	Result tolerability	Result safety	Conclusion of authors
Tramer et al. [26]	Efficacy and harm of cannabis in patients having chemotherapy, compared with placebo or conventional antiemetics and profile of adverse effects	Medline, EMBASE, Cochrane libraries, bibliographies to August 2000	Four	Not reported	Complete control nausea RR 1.21 (95 % CI 1.03–1.42); NNT 8.0 (4.0–775) Complete control vomiting RR 1.84 (95 % CI 1.42 to 2.38); NNT 3.3 (2.4–5.7); four studies, 231 patients	Withdrawals RR 4.67 (95 % CI 3.07 to 7.09), 19 studies, 2111 patients	Hallucination RR 6.10 (95 % CI 2.41 to 15.4); ten studies, 859 patients Paranoia RR 8.58 (95 % CI 6.38 to 11.5); six studies, 571 patients	"In selected patients, the cannabinoids tested in these trials may be useful as mood enhancing adjuvants for controlling chemotherapy-related sickness. Potentially serious adverse effects, even when taken short term, orally or intramuscularly, are likely to limit their widespread use"
Rocha et al. [17]	Evaluation of RCTs using *C. sativa* in the treatment of nausea and vomiting in patients with any type of cancer receiving chemotherapy, compared with any type of control group	PUBMED, EMBASE, PSYCINFO, LILACS, CENTRAL from inception December 2006	Two	Not reported	Complete control vomiting, Dronabinol RR 0.47 (95 % CI 0.19–1.16) (two trials; 195 patients)	Not assessed	Not assessed	"The superiority of the antiemetic efficacy of cannabinoids was demonstrated through meta-analysis"
Whiting et al. [30]	Evaluation of benefits and adverse events of medical cannabinoids across a broad range of indications	28 databases (e.g., MEDLINE, Cochrane, EmBase, PubMed, Biosis, OvID, CINAHL, DARE, HTA, NHS EED)	Three	Not reported	Complete control vomiting OR 3.82 [95 % CI 1.55–9.42]	Risk for withdrawal due to AEs: OR 2.94 (95 % CI 2.18–3.96) in 23 trials and 2755 patients	Risk for any adverse event during treatment OR 3.03 95 % CI (2.42–3.80) for 29 trials with 3714 patients; serious adverse events 1.41 (95 % CI 1.04–1.92) for 334 trials with 2755 patients	"There was low quality evidence suggesting that cannabinoids (dronabinol and nabiximol) were associated with improvements in nausea and vomiting due to chemotherapy"
Smith et al. [24]	Evaluation of effectiveness and tolerability of cannabinoids for CINV in adults	CENTARL, PSYCINFO, LILACS, CENTRAL from inception to January 2015	23 (from 1975 to 1991)	Not reported	Absence of nausea and vomiting RR 2.9 (95 % CI 1.8–4.7), three studies, $N = 288$ patients. Preference of participants RR 4.8 (95 % CI 1.7–13), two studies, $N = 256$ patients	Risk for withdrawal due to AEs: RR 6.9 (95 % CI 1.96–24), two trials, $N = 276$ patients	Risk for dysphoria RR 9.0 (95 % CI 0.5–161), two trials, $N = 96$ patients. Risk for sedation RR 4.5 (95 % CI 0.35–58), 2 trials, $N = 139$ patients Other side effects: sedation, euphoria, dizziness, dysphoria, depression, hallucinations, focal dystonia	This review of 23 RCTs found that fewer people experienced CINV with cannabinoids compared with placebo; but effectivity was similar compared with conventional antiemetics. Side effects were more commonly reported with cannabinoids. Quality of evidence is low and included studies do not reflect current standard of chemotherapy and CINV therapy

Table 3 Characteristics of systematic reviews and meta-analyses including randomized controlled trials to compare cannabinoids with conventional antiemetics

Reference	Study population (age, gender)	Type of cancer	Type of chemotherapy	Cannabinoids	Controls	Methodology quality
Tramer et al. [26]	Mainly adults; two studies included children; no pooled data on age and gender reported	Most studies with various tumors	Most frequently used: adriamycin, cisplatin, cyclosphosphamide, doxorubicine, methotrexate, and vincristine	Dronabinol 7.5–15 mg Levonantradol 1.5–3 mg Nabilone 1–7 mg	Prochlorperazine, metoclopramide, thiethylperazine, domperidone, chlorpromazine, haloperidol, alizapride	Oxford score (0–5) Most studies had a score between 3 and 5
Rocha et al. [17]	No data on demographics reported	Mainly patients with various tumors	Most frequently used: adriamycin, cisplatin, cyclosphosphamide, doxorubicine, methotrexate, and vincristine	Dronabinol 7–12 mg/m^2 Nabilone 1–5 mg Levonantradol 0.5–1.0 mg	Alizapride, chlorpromazine, domperidon, prochlorperazine	Adequacy of randomization 4 studies with low and 20 studies with moderate risk of bias
Phillips [19][a]	Only children	Any pediatric malignancy	High-dose cyclophosphamide, high-dose MTX, vincristine, doxorubicin, dacarbazine	Nabilone 0,5–3 or 10 mg/m^2	Prochlorperazine, domperidone, metoclopramide	Cochrane risk of bias tool All studies had at least 2 high risks of bias
van den Elsen et al. [27]	Adult patients	Various malignancies	Wide range of chemotherapeutic regimens	Delta-9-tetrahydrocannabinol (THC)	Prochlorperazine	Consensus-based risk of bias method
Smith et al. [24]	Adults with CINV without restriction	Various malignancies, underlying disease not specified	Variety of chemotherapy regimens with low, moderate, and high emetic potential	Nabilone and Dronabinol	Conventional dopamine antagonist for CINV therapy Prochlorperazine: 11 trials, $N=1221$ patients Metoclopramide: two trials, $N=57$ patients Domperidone: one trial, 38 patients Chlorpromazine: one trial, $N=20$ patients	Cochrane Risk of Bias tool Twenty-three trials showed variable quality, ranging from low to high. GRADE level "low" for most outcomes in meta-analysis

CINV chemotherapy-induced nausea and vomiting.
[a]Systematic review of all antiemetics for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood.

Conclusions from the systematic reviews

Tramer et al. [26] concluded that CBs were more effective than active comparators (prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, and alizapride). The authors calculated the number needed to treat (NNT) and found an NNT of 2–8:1 patient with complete control of CINV. In selected patients, the CBs tested in these trials were described to be potentially useful as mood-enhancing adjuvants for the control of chemotherapy-related sickness. CBs were less tolerated and less safe than controls. The corresponding number needed to harm (NNH) was estimated with NNH of 4–20 for one patient experiencing at least one adverse event. The authors concluded that the side effects of CBs are likely to limit their widespread use.

Rocha et al. [17] concluded that the antiemetic effect of CBs was superior to controls. However, only dronabinol was statistically superior to neuroleptics in the complete control of CINV, but not dronanbinol versus placebo and not levontradol versus neuroleptics. The authors calculated a number needed to treat NNT 3.4 patients with cannabinoid administration for one patient with complete CINV control. The authors did not assess tolerability and safety. They concluded that CBs might be used for patients who are refractory to conventional antiemetics or as auxiliaries to enhance the effect of existent antiemetic medications, if the synergy among CBs, 5-HT3 receptor antagonists, or dexamethasone could be confirmed by future studies.

Phillips et al. [19] concluded that the data on efficacy of CBs versus conventional drugs were inconsistent. They did not pool data because of their heterogeneity. The authors did not assess tolerability and safety compared to controls. They concluded that 5-HT3 antagonists seem more effective than older antiemetic agents. No specific comment on CBs was given.

van den Elsen et al. [27] focused on elderly patients against the background of physiological differences in this specific population. Only one study could be extracted in their trial that showed similar control of CINV for CBs compared with prochlorperazine. Due to the higher adverse event rates related to sedation, dizziness, headache, and psychological side effects, the authors concluded that cannabinoid therapy in the elderly should be administered carefully including a critical evaluation of the risk–benefit ratio for each individual.

Whiting et al. [30] analyzed a wide variety of indications for cannabinoid application. For CINV control the authors described higher therapy response with CBs showing a complete nausea and vomiting response compared with placebo (evaluating three trials, odds ratio of 3.8, and 95 % confidence interval: 1.6–9.4). However, evaluation of adverse events showed that 62 % of 1710 patients in the extracted control groups compared with 81 % of

Table 4 Results of systematic reviews and meta-analyses including randomized controlled trials to compare cannabinoids with conventional antiemetics

Reference	Aims of the review	Search of literature	Total number of RCTs included	Total number of patients	Result efficacy	Result tolerability	Result safety	Conclusion of authors
Tramer et al. [26]	Efficacy and harm of cannabis in patients having chemotherapy, compared with placebo or conventional antiemetics and profile of adverse effects	Medline, Embase, Cochrane libraries, bibliographies to August 2000	Seven	Not reported	Complete control nausea RR 1.38 (95 % CI 1.18 to 1. 62); NNT 6.4 (4.0 to16); seven studies, 422 patients. Complete control vomiting RR 1.28 (95 % CI 1.08 to 1.51); NNT 8.0 (4.5 to 38); six studies, 395 patients	RR 4.67 (95 % CI 3.07 to 7.09); 19 studies, 2111 patients	Hallucination RR 6.10 (95 % CI 2.41 to 15.4); ten studies, 859 patients Paranoia RR 8.58 (95% CI 6.38 to 11.5); six studies, 571 patients	"Across all trials. cannabinoids were more effective than active comparators. In selected patients, the cannabinoids tested in these trials may be useful as mood enhancing adjuvants for controlling chemotherapy related sickness. Potentially serious adverse effects, even when taken short term orally or intramuscularly, are likely to limit their widespread use."
Rocha et al. [17]	Evaluation of RCTs using *C. sativa* in the treatment of nausea and vomiting in patients with any type of cancer receiving chemotherapy, compared with any type of control group	PUBMED, EMBASE, PSYCINFO, LILACS,CENTRAL from inception December 2006	13	Not reported	CINV control Dronabinol versus neuroleptics: RR 0.67 (95 % CI 0.47 to 0.96), NNT 3.4; five studies, 325 patients. Nabilone versus neuroleptics RR = 0.88 (95 % CI 0.72 to 1.08); six studies, 277 patients. Levonantradol versus neuroleptics RR 0.94 (95 % CI 0.75–1.18); three studies, 194 patients	Not assessed	Not assessed	"The superiority of the antiemetic efficacy of cannabinoids was demonstrated through meta-analysis."
Phillips [19]	Evaluation of effectiveness and tolerability of cannabis for CINV in patients with cancer	CENTRAL, MEDLINE, EMBASE, and LILACS, trial registries from their earliest records to February 2008, and ASCO, MASCC, and SIOP conference proceedings from 2001 to 2007	Four	Not reported	Qualitative report only: tetrahydrocannabinol versus prochlorperazine and metoclopramide in nausea: RR 20.7; 95 % CI 17.2–36.2 and for vomiting: RR 19.0; 95 % CI 13.7 to 26.3. Reduced nausea severity compared with domperidone, $p = 0.01$. In one trial with no benefit of THC versus prochlorperazine controlling emesis (RR 1.0; 95 % CI 0.85 to 1.17)	No data reported	Side effects • drowsiness between 28 and 67 % • dizziness between 44 and 60% • mood alteration 5–17 %. Further reports: ocular problems, orthostatic hypotension, muscle twitching, pruritis, vagueness, hallucinations, dry mouth	"The quality of individual studies was moderate, with relatively small numbers and wide confidence intervals limiting conclusions drawn. 5-HT3 antagonists seem more effective than older antiemetic agents, even when those agents are combined with a steroid. " No specific comment on cannabinoids
van den Elsen et al. [27]	Evaluation of safety and efficacy of medical cannabinoids in older subjects	PubMed, EMBASE, CINAHL, and Cochrane Library	One	214	Summary statistics not applicable, no difference for CINV control between active comparator and cannabinoid ($p > 0.05$)	Not reported	Cannabinoid treatment resulted in more adverse effects than placebo or prochlorperazine	"Cannabinoids showed no efficacy on chemotherapy induced nausea and vomiting compared with prochlorperazine."
Smith et al. [24]	Evaluation of effectiveness and tolerability of cannabinoids for CINV in adults	CENTRAL, PSYCINFO, LILACS, CENTRAL from inception to January 2015	Twenty-three (from 1975 to 1991)	Not reported	Absence of nausea and vomiting RR 2.0 (95% CI 0.74–5.4), four studies, $N = 414$ patients for prochlorperazine. Preference of participants RR 2.8 (95 % CI 1.9–4.0), nine studies, $N = 799$ patients	Risk for withdrawal due to AEs: RR 3.2 (95% CI 1.3–8.0), six trials, $N = 740$ patients	Risk for dysphoria RR 7.17 (95% CI 1.33–38.84), three trials, $N = 192$ patients. Risk for sedation RR 1.33 (95 % CI 1.08–1.64), 11 trials, $N = 1055$ patients. Other side effects: sedation, euphoria, dizziness, dysphoria, depression, hallucinations, focal dystonia	This review of 23 RCTs found that fewer people experienced CINV with cannabinoids compared with placebo; but effectivity was similar compared with conventional antiemetics. Side effects were more commonly reported with cannabinoids. Quality of evidence is low and included studies do not reflect current standard of chemotherapy and CINV therapy

CINV chemotherapy-induced nausea and vomiting.

Table 5 AMSTAR rating table of included systematic reviews (low quality—AMSTAR score 0–4; moderate quality—AMSTAR score 5–8; high quality—AMSTAR score 9–11)

Reference	A priori design?	Two data extractor and consensus?	Comprehensive literature search?	Statement on inclusion of grey literature? Language?	List of included and excluded studies?	Characteristics of studies provided, for example, tables?	Quality of risk of bias assessment?	Scientific quality of the included studies used appropriately in formulating conclusions?	Methods used to combine the findings of studies appropriate? Test on heterogeneity	Likelihood of publication bias assessed?	Conflict of interest stated?	Sum
Tramer et al. [26]	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No tests of heterogeneity	No	No	6
Rocha et al. [17]	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	7
Phillips [19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10
Whiting et al. [30]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	9
van den Elsen et al. [27]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	7
Smith et al. [24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10

1779 patients in the intervention group experienced any adverse event resulting in an odds ratio of 3.0 (95 % confidence interval: 2.4–3.8). This resulted in an absolute risk difference of 19 % favoring controls. The corresponding NNH is 6 patients that are treated with one patient expieriencing an adverse event.

Most recently, Smith et al. [24] conducted a meta-analysis focusing on cannabinoid treatment for CINV in adults receiving chemotherapy. The authors included only trials with control groups receiving dopamine antagonists (prochlorperazine, metoclopramide, domperidone, and chlorpromazine). Notably, all included trials were conducted between 1975 and 1991. The authors found a higher response rate for complete control of nausea and vomiting compared with CBs versus placebo (RR 2.9, 95 % CI 1.8–4.7) but no evidence of difference between CBs and conventional antiemetics (RR 2.0, 95 % CI 0.74–5.4). Smith et al. provide analyses of several side effects. They extracted data on risk for study withdrawal due to adverse events. Compared with both placebo and conventional antiemetics, cannabinoid treatment was of higher risk for study withdrawal (RR 6.9 95 % CI 1.96–24 versus placebo; and RR 3.2 95 % CI 1.3–8.0 versus conventional antiemetics). For placebo, the NNT and NNH achieve four and eight patients, respectively. For conventional antiemetics, the NNT and NNH achieve 12 and 16 patients, respectively. However, the authors conclude that they are not very confident with their findings regarding effectiveness of CBs for CINV therapy.

Discussion

Summary of main findings

Systematic reviews provide moderate quality evidence on the efficacy of CBs versus placebo and conventional antiemetics for the therapy of CINV.

Systematic reviews provide moderate quality evidence that pharmaceutical CBs were less tolerated and less safe than placebo and conventional antiemetics.

Due to the lack of sufficient RCTs comparing more recently approved drugs for CINV therapy such as 5HT3 antagonists or NK1- receptor antagonists there is currently insufficient evidence to draw conclusions on the efficacy of CBs compared to these new antiemetics.

Analyzing the results of six systematic reviews, the number needed to treat seems to be approximately NNT four patients for CBs to achieve a complete CINV control compared to placebo or conventional antiemetics. On the other hand, the number needed to harm compared to placebo or conventional antiemetics was approximately NNH six suggesting a very small therapeutic window.

Comparison with other reviews and recent guidelines

Keeley conducted a search of the literature until April 2008 for RCTs and systematic reviews and observational studies for benefits and harms of any antiemetic therapy for nausea and vomiting in cancer patients [14]. They performed a GRADE evaluation of the quality of evidence for interventions with all antiemetics available. For cannabinoids, the systematic review of Tramer was assessed. The authors found moderate quality evidence that CBs are effective for nausea and vomiting in people receiving chemotherapy but may be associated with a high and often unacceptable burden of adverse effects. They concluded that it is unclear if pharmaceutical CBs do more good than harm [14].

The NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology recommended the pharmaceutical CBs dronabinol and nabilone as treatment options for breakthrough nausea and vomiting caused by chemotherapy. ASCO (American Society of Clinical Oncology) guidelines recommended pharmaceutical CBs be reserved for patients intolerant of or refractory to

Table 6 Randomized controlled clinical trials (RCTs) that were included in reviews and meta-analyses listed according to the cannabinoid substance under investigation

RCTs	Tramer 2001	Rocha 2008	Phillips 2011	Whiting 2015	van den Elsen 2014	Smith 2015
Dronabinol						
Chang AE et al. Pediatrics. 1979;79:946–52	X	X				X
Chang AE et al. Ann Intern Med. 1981;91:819–24	X	X				X
Colls BM et al. Lancet. 1980;i:1187–88	X					
Colls BM et al. N Z Med J. 1980;91:449–51	X	X				
Ekert H et al. Med J Australia. 1979a;2:657–59			X			
Ekert H et al. Med J Australia. 1979b;2:657–59			X			
Frytak S et al. Ann Intern Med. 1979;91:82530	X	X		X		X
Gralla RJ Cancer Treat Rep. 1984;68:16372	X	X				X
Harden-Harrison MM et al. Supportive Care in Cancer. Support Care Cancer. 2012;20:S209–10				X		
Kleinman S. et al., 1983; Current Therapeutic Research 1983;33(61):1014–7						X
Kluin-Neleman JC et al. Vet Hum Toxicol. 1979;21:22840	X	X				X
Lane M et al. J Pain Symptom Manag. 1991;6:3529	X	X		X		X
McCabe M et al. Invest New Drugs. 1988;6:2436	X	X		X		X
Meiri E et al. Curr Med Res Opin. 2007;23:533–43				X		
Orr LE et al. Arch Intern Med. 1980;140:14313	X	X		X		X
Sallan SE et al. N Engl J Med. 1975;293:7957	X	X				X
Sallan SE et al. N Engl J Med. 1980;302:1358	X	X		X		
Ungerleider JT et al. Cancer. 1982;50:63645	X	X		X	X	X
Nabilone						
Ahmedzai S et al. Br J Cancer. 1983;48:65763	X	X		X		X
Broder LE et al. Proceedings of the American Association for Cancer Research. 1982;23:514				X		
Chan HS et al. Pediatrics. 1987;79:94652	X	X	X	X		
Crawford SM et al. Med Oncol Tumor Pharmacother. 1986;3:3942	X	X				X
Dalzell AM et al. Arch Dis Child. 1986;61:5025	X	X	X	X		
Einhorn LH et al. J Clin Pharmacol. 1981;21:649	X	X		X		X
George M et al. Biomed Pharmacother. 1983;37:247	X	X		X		X
Hermann TS et al. N Engl J Med. 1979;300:12957	X	X		X		X
Johansson R et al. Cancer Treat Rev. 1982;9:2533	X	X		X		X
Jones SE et al. Cancer Treat Rev. 1982;9:458	X	X		X		X
Levitt M et al. Cancer Treat Rev. 1982;9(suppl B):4953	X	X		X		X
Neidhart JA et al. J Clin Pharmacol. 1981;21:3842	X	X				
Niederle N et al. Klin Wochenschr. 1986;64:3625	X	X				
Niederle N et al. Klin Wochenschr. 1986;64(8):362–365				X		
Niiranen A et al. Am J Clin Oncol. 1985;8:33640	X			X		X
Niiranen A et al. Am J Clin Oncol. 1987;10:325–9		X				
Pomeroy M et al. Cancer Chemother Pharmacol. 1986;17:2858	X	X		X		X
Steele N et al. Cancer Treat Rep. 1980;64:21924	X	X		X		X
Wada JK et al. Cancer Treat Rev. 1982;(Suppl B):3944	X	X		X		X
Levonantradol						
Heim ME et al. Cancer Chemother Pharmacol. 1984;13(2):123–5				X		
Hutcheon AW et al. Eur J Cancer Clin Oncol. 1983a;19:108790	X	X		X		
Hutcheon AW et al. Eur J Cancer Clin Oncol. 1983b;19:108790		X				
Long A et al. Proceedings of the American Society of Clinical Oncology. 1982;1:C-220				X		
Sheidler VR et al. J Clin Pharmacol. 1984;24:155–9		X		X		
Whole plant extract						
Duran et al. Br J Clin Pharmacol. 2010;70(5):656–63				X		

5-HT3 receptor antagonists, NK-1 receptor antagonists and dexamethasone [3].

German guidelines, for example, on breast cancer, did not make any specific recommendation for a drug class for CINV [15]. The 2013 guideline of the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology did not mention CBs anymore [20].

Recent research has not further explored CBs in CINV since 2012. Only one study was extracted comparing CBs with 5-HT3 receptor antagonists and no study with NK-1 receptor antagonists as comparator. RCTs assessing the additional benefit of CBs to current standard antiemetic therapy are sparse [5].

Network meta-analyses comparing "old" antiemetics such as CBs, prokinetics, and first-generation neuroleptics with "new" antiemetics such as 5-HT3 receptor antagonists, NK-1 receptor antagonists, and atypical antipsychotic drugs (e.g., quetiapine) have not been conducted. A network meta-analysis would be difficult because the response criteria used in studies with CBs, prokinetics, and first-generation neuroleptics would not meet present day standards [5].

To date, the incidence of CINV despite prophylactic treatment with guideline recommended first-line antiemetics remains up to 20% of patients [4, 18]. CINV altered life quality of patients and is one of the leading concerns of patients related to chemotherapy [16]. Due to this significant number of patients affected by this symptom, optimization of adjunctive antiemetic therapy is still of high relevance for patients. Therefore, the importance of CBs as third- or fourth-line medication (alternative medication) still needs to be determined. In this context, data evaluating the role of CBs as an adjunctive treatment option compared with current standard therapy of CINV is needed. Based on the most recent review of Smith et al. [24] and against the background of limited evidence in the literature the role of CBs compared with atypical neuroleptics currently in medical use is not sufficiently clear [11, 29].

Limitations

The methodology of systematic reviews inherits limitations that are also present in this study. First, the inclusion of studies is restricted to trials that fulfill predefined inclusion criteria and are published in accessed databases. As an example, in this study alternative data sources were not included into the search strategy. Currently, there are specific data sources that may provide additional information; exemplarily the International Association for Cannabinoid Medicines or Cochrane CAM (Complementary and Alternative Medicine) Reviews. Additionally, this study was intended to provide an overview on published systematic reviews in the field; hence, data bases were not searched for new RCTs not included in the summarized reviews. Similarly, comparing dosing strategies for cannabinoid formulations was not the only primary focus of this study, it was also to provide additional information regarding efficacy, tolerability, and safety. Especially for safety and tolerability, RCTs may not provide optimal information: Sample size is most commonly too small and observation period is too short in these trials to find signals of side effects that are not very common. Here, observational studies may provide additional information.

Conclusions for clinical practice

With safe and effective agents such as 5-HT3 receptor antagonists and NK-1 receptor antagonists, pharmaceutical CBs have no place as a first- or second-line treatment of CINV. Use of pharmaceutical oral CBs should be limited to the management of breakthrough or refractory nausea and vomiting caused by chemotherapy. In Germany, the use of pharmaceutical oral CBs is possible within individualized patient off-label use (according to § 4 AMG—German medical drug legislation). The failure of established medical therapies and careful information of the patient on the potential risks and benefits should be documented. Because of the lack of its availability in Germany and safety concerns [10], herbal cannabis is not a medical treatment option for CINV [25].

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Compliance with Ethical Standards

Conflict of interest. All authors declare that they have no conflicts of interest concerning the specific subject of this study. ST received lecture fees from Roche Deutschland GmbH and Pfizer Deutschland GmbH. MS received speaking fees from TEVA and Grünenthal and is a member of the committe of experts of the Federal Institut for Pharmaceuticals and Medical Products. Winfried Häuser has received speaking fees from Grünenthal, MSD Sharp & Dohme and Pfizer.

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