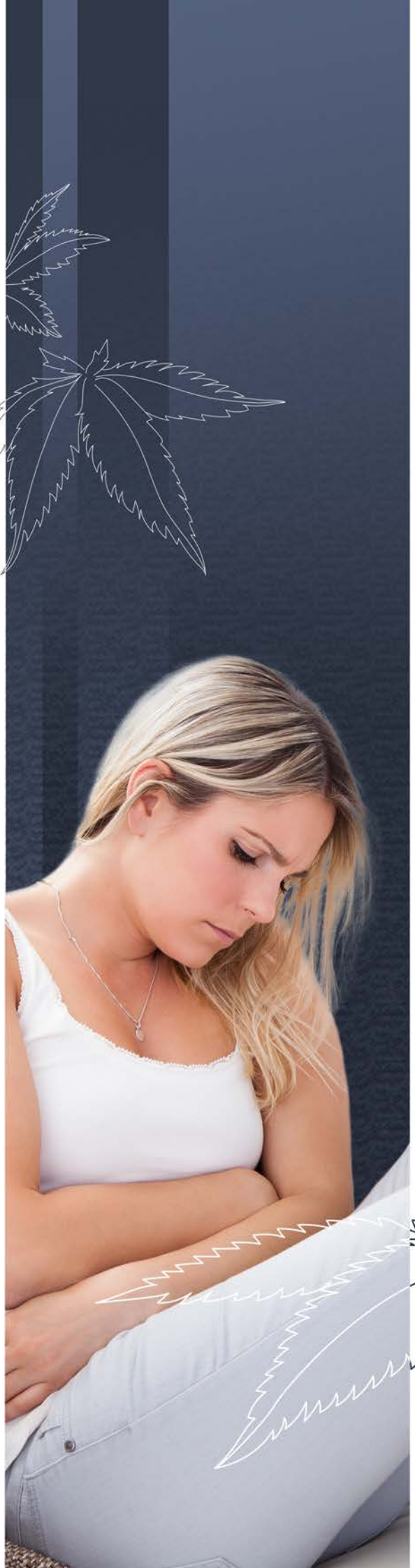

Australian Government
Department of Health
Therapeutic Goods Administration

Guidance
for the use of
medicinal cannabis
for the prevention or management of
nausea and vomiting
in Australia

Version 1, December 2017

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Introduction

A set of guidance documents has been made available to assist doctors and their patients who choose to prescribe medicinal cannabis in Australia under current access schemes. These have been developed based on reviews of available evidence for the use of medicinal cannabis in five different settings. Included is an overview addressing the evidence base for medicinal cannabis therapy generally as well as specific documents relating to medicinal cannabis in the treatment of palliative care, epilepsy, chemotherapy-induced nausea and vomiting (CINV), multiple sclerosis (MS) and chronic pain.

This document reflects the evidence supporting the use of medicinal cannabis in nausea and vomiting and the recommendations of the Nausea and Vomiting Working Group.

Note: These guidance documents are based on evidence available at the time of publication and will be updated as new evidence emerges. Each document should be read in conjunction with the '*Guidance to the use of medicinal cannabis in Australia—Overview*'.

Review method

The Australian Government Department of Health commissioned a team from the University of New South Wales, University of Sydney and University of Queensland under the coordination of the National Drug and Alcohol Council (NDARC) to review the available evidence for the use of medicinal cannabis in the above five settings.

The researchers conducted a review of previously published reviews from multiple databases such as Medline, Embase, PsychINFO and EBM Reviews based on PRISMA[123]. PRISMA is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and is an evidence-based minimum set of items for reporting on randomised controlled trials (RCTs). These guidelines have been developed because of concern for low quality trials and aim to improve the quality of medical research, remove bias and improve transparency and accurate reporting of findings. Searches were guided by a specialist Librarian using specific search terms and were limited to studies published between 1980 and early 2017. Two reviewers independently examined titles and abstracts for relevance using Covidence Software and the Cochrane Risk of Bias Tool was used to assess studies, aiming to increase accuracy. The GRADE (grading of recommendations, assessment, development and evaluation) approach, an internationally recognised standard applying to weighting of evidence in scientific and medical literature was used to evaluate the quality of evidence.

In July 2017, the department also convened five separate Working Groups to consider the available evidence for the use of medicinal cannabis in the treatment of each of the settings. The five groups consist of individuals from a wide range of backgrounds and organisations, including senior staff from each state and territory Department of Health, fifteen healthcare professional organisations, clinical staff from twenty-nine hospitals and healthcare systems, fourteen outpatient or Primary Health Networks and eighteen consumer representative groups.

Management of nausea and vomiting

Nausea and vomiting may occur in distinct clinical settings of varying aetiology, with either acute or chronic duration of symptoms, including:

- chemotherapy-induced nausea and vomiting (CINV)
- radiotherapy-induced nausea and vomiting (RINV)
- cancer-associated nausea and vomiting
- chronic disease-associated nausea and vomiting
- palliative care
- post-operative nausea and vomiting (PONV)
- nausea and vomiting arising from long-term concomitant medication administration
- pregnancy.

Where clinical practice guidelines exist for the management of nausea and vomiting occurring in each of these specific circumstances, these should be considered the current standard of care.

The current, internationally recognised, clinical practice guidelines for the prevention and management of CINV and RINV are produced by the American Society of Clinical Oncology (ASCO), Multinational Association for Supportive Care in Cancer (MASCC) and European Society of Medical Oncology (ESMO). These serve as the standard for patient management[1,2].

National and international guidelines for the prevention and management of CINV/RINV developed for the Australian context, in addition to specific cancer treatment protocols are presented on the eviQ website (www.eviq.org.au). Herein, specific antiemetic recommendations are documented for each chemotherapy or radiotherapy treatment protocol.

The prevention and management of CINV in children with cancer is addressed in the Children's Oncology Group Guidelines (2017) and is included within the MASCC/ESMO Guidance[3,4].

The standard management of CINV is directed according to the relative emetogenicity of the chemotherapeutic regimen being received[5,6,7,8].

There are reports that several medicinal cannabis products have relieved the symptoms of CINV when compared to placebo. Of the International Clinical Practice Guidelines, only the ASCO clinical practice guideline for CINV contains a statement regarding the use of medicinal cannabis in the management of CINV, for use after registered therapies have been tried and failed. Only one product is registered by the US Food and Drug Administration (dronabinol, trade name Syndros) for "nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments".

There is currently no evidence from in-human studies that medicinal cannabis has any anti-cancer activity.

Chronic disease-associated nausea and vomiting may occur in a diverse range of conditions, including AIDS-defining illnesses, gastroparesis, intestinal motility disorders, and cyclical vomiting syndrome.

The management of acute PONV in Australia is typically according to locally developed hospital guidelines. The management of acute PONV is outside the scope of this document.

Owing to its safety profile, the use of medicinal cannabis in pregnancy is contraindicated. The management of nausea and vomiting in pregnancy is outside the scope of this document.

There is currently only one cannabinoid (nabiximols/Sativex) that is listed on the Australian Register of Therapeutic Goods (ARTG). This product is not indicated for the management of nausea and vomiting.

Caveats

This document provides guidance for health professionals in the use of an unapproved medicine, in the context of limited evidence of efficacy for the treatment of nausea and vomiting. It also addresses the tension between patient autonomy and the underlying therapeutic principle to 'do no harm' and intends to support patients who may wish to use an unapproved therapeutic good.

The scope of the document is broad given the limited evidence available and does not encompass all clinical conditions where nausea and vomiting may occur.

In addition to the limited evidence for benefit of pharmaceutical grade medicinal cannabis products in the treatment of nausea and vomiting, there are further caveats:

1. Guidance can only relate recommendations to the condition, drug and dose which have been studied. For example, evidence of efficacy in nausea from one product, and dose, should not be extrapolated to treatment of vomiting with the same product and dose.
2. There are limitations in how the clinical evidence was obtained and reviewed.
3. Dose–response information for efficacy is lacking, in particular for starting doses. This is particularly relevant when applying data obtained from younger adults to the elderly, or people with hepatic or renal impairment.
4. Dose–response information for toxicity is also lacking, particularly for side effects which may occur at different doses and before efficacy is evident.
5. There is no dose equivalence for safety or efficacy data between medicinal cannabis products or between specific products and registered medicines which are current standard therapy.
6. There is an absence of information regarding drug-drug interactions, for medicines of any class, arising from medicinal cannabis administration
7. There is no long-term animal or human data on which to model or predict toxicity. This is most relevant for use in pregnant women, children and young adults.
8. For paediatric patients, there is no standardised dose regimen, no efficacy data presented separate from that for adults, no information on the interaction with other medicines, and no information on the relative incidence of adverse events in children as compared to adults. Thus the use of medicinal cannabis in children with nausea and/or vomiting from any cause is not supported.
9. As noted previously, use of medicinal cannabis for the treatment of nausea and vomiting in pregnancy is contraindicated.

As with all therapies, medical practitioners must exercise their professional judgment in determining if medicinal cannabis products are an appropriate treatment for an individual patient, and obtain informed consent from them before administration. At this time, the use of medicinal cannabis for the treatment of nausea and vomiting in managing the adult patient's symptoms should be considered only where conventional treatments have been appropriately tried and proven unsuccessful.

Recommendations

The most recently registered classes of medicines for the treatment of nausea and vomiting which are efficacious have superseded those against which medicinal cannabis products have been studied. Medicinal cannabis products are therefore likely to be inferior to newer agents. It is recommended that the treating physician initiate medicinal cannabis only after an accepted clinical algorithm has been appropriately followed and demonstrated to have failed, and where not otherwise contraindicated.

In the absence of high-quality evidence, the treating physician should consider the risks and benefits of either medicinal cannabis monotherapy, or co-prescription of medicinal cannabis with registered medicines.

There is a paucity of evidence for the use of medicinal cannabis to prevent the onset of nausea and vomiting.

The published clinical evidence is of moderate quality at best. There is no current high quality evidence for advocating medicinal cannabis in the treatment of established nausea and vomiting in adults in any clinical situation where registered antiemetics have not already been used according to accepted condition-specific clinical practice guidelines.

Pharmacokinetic and pharmacodynamic interactions of medicinal cannabis products with chemotherapy and other medications are predicted but as yet not fully elicited. There is an absence of data as to an accepted duration which may be considered a suitable period to determine efficacy.

Medicinal cannabis may be assessed to treat intractable symptoms which are ineffectively managed by other modalities, but should be stopped if significant adverse effects occur or lack of benefit is demonstrated. This therapeutic use is experimental.

Patients and prescribing clinicians should be aware of adverse events—such as somnolence, dizziness, euphoria or gastro-intestinal disturbance—that may impact the overall aims of therapy. Adverse events, and revision of the dosing of medicinal cannabis, should be evaluated and managed on a case-by-case basis by the treating physician.

Oversight by the Therapeutic Goods Administration (TGA) of the quality of medicinal cannabis preparations, including the quantity and compositions of cannabinoids supplied in products, is important to protect the health of the Australian public.

Recommendation

High-THC medicinal cannabis products can sometimes be effective for nausea and vomiting and should only be prescribed only after newer standard approved treatments have failed and where otherwise not contraindicated.

Efficacy

The role of therapeutic substances for nausea and vomiting is in either prophylactically preventing these symptoms from occurring to treat breakthrough symptoms, or to treat established symptoms occurring despite other therapies. Various studies on the use of medicinal cannabis in the treatment of nausea and vomiting treatment have addressed:

- as primary end points: complete control of nausea and vomiting, complete control of nausea and complete control of vomiting,
- as secondary end points: subjective experience of appetite, subjective feeling of nausea, patient preference for medicinal cannabis versus comparator (in cross-over trials).

Although there are significant limitations of this data (unknown product constituents in some, route of administration and doses, substantial age of the clinical evidence), a potential benefit in CINV in comparison to placebo has been suggested.

Note that there is no consistently reported beneficial effect of medicinal cannabis in the management of vomiting occurring without nausea.

There are low to moderate quality reports that dronabinol, as compared to placebo, may increase appetite in people living with AIDS-defining illnesses. To date, improvement in appetite has not been clearly demonstrated from the use of either levonantradol in patients with CINV, or tetrahydrocannabinol (THC) cannabidiol in patients with cancer-associated anorexia.

Dosage and administration

There is no data to recommend either a specific starting dose or maintenance dose according to the clinical condition being treated. There is little information on dose–response in the treatment of nausea and vomiting. In general, starting doses should be low, and the dose titrated in response to lack of efficacy, until toxicity outweighs any benefit.

Nabilone and dronabinol have some limited evidence of efficacy in achieving complete control of nausea and vomiting. However, comparative data with current best therapies which are registered in Australia (e.g. 5-hydroxytryptamine (HT) 3 antagonists, neurokinin (NK) 1 receptor antagonists, cyclizine, steroids) are unavailable. It is hoped that current trials of medicinal cannabis being undertaken in Australia (including a CINV study being funded by the NSW Government) may address some of the significant data limitations. The link to the ANZ Clinical Trials Registry for this and other trials on medicinal cannabis is http://www.anzctr.org.au/TrialSearch.aspx?searchTxt=cANNABIS&isBasic=True .

Recommended review process for auditing patient outcomes

The prescribing doctor should collect pharmacovigilance information. This will help refine guidance documents and provide additional cumulative safety data.

Tolerance and withdrawal from treatment

- In the studies included in the review, patients who received medicinal cannabis were more likely to withdraw from clinical trials for any reason, i.e. either lack of efficacy or adverse effects, than those who received either a prescribed antiemetic or a placebo[9,10,11,12].
- Poor compliance to treatment with medicinal cannabis delivered by smoking, with 24 per cent of patients withdrawing due to lack of tolerance of the method of administration[13].
- In children with CINV treated with nabilone, study withdrawal due to the onset of drowsiness, dizziness, hallucinations mood change or hallucinations were commonly occurring (in >1 per cent to <10 per cent), or very commonly occurring (in >10 per cent) of patients observed. In addition, the onset of debilitating adverse effects of nabilone was shown to result in deferral of the patient's scheduled chemotherapy regimen[14,15].
- When medicinal cannabis was combined with another antiemetic therapy, there was no difference in treatment withdrawals compared to patients receiving the other antiemetics as a monotherapy[16,17]. However, there is no evidence to support a synergistic effect of medicinal cannabis with any other registered class of antiemetics.

Recommended duration of medication trial

In the absence of strong evidence for specific dosing and administration information of specific preparations of cannabis in managing nausea and vomiting, the treating physician who elects to initiate therapy should assess the clinical condition of the patient and monitor response to treatment.

There is little evidence based on the studies identified in the systematic review to inform decisions about the timing of therapy, duration of therapy and timing of treatment discontinuation.

Safety

Adverse effects

Details of the incidence and severity of adverse events with most medicinal cannabis products are lacking, as reported in the literature.

Based on the available studies, the most commonly reported adverse events in the use of medicinal cannabis in nausea and vomiting include in order of frequency:

- dysphoria and or depression (13 per cent of patients)
- hallucinations (6 per cent of patients)
- paranoid delusions (5 per cent of patients)
- drowsiness (proportion not reported)
- dry mouth (proportion not reported).

Drug–drug interactions

There are no data regarding drug–drug interactions with therapeutic anti-nausea and vomiting agents of any class. Data is insufficient to provide specific advice to prescribers regarding the need for dose modification of prescription medicines co-administered with medicinal cannabis in adult patients.

There is evidence that for children administered nabilone for CINV, their chemotherapy regimen had to be delayed due to the onset of adverse effects due to medicinal cannabis[18].

There is no data regarding the appropriate starting dose, or maintenance dose, of any medicinal cannabis product for patient groups who may be considered at greater risk of adverse effects—for example, the elderly, patients with hepatic or renal impairment, or those at the extremes of body weight.

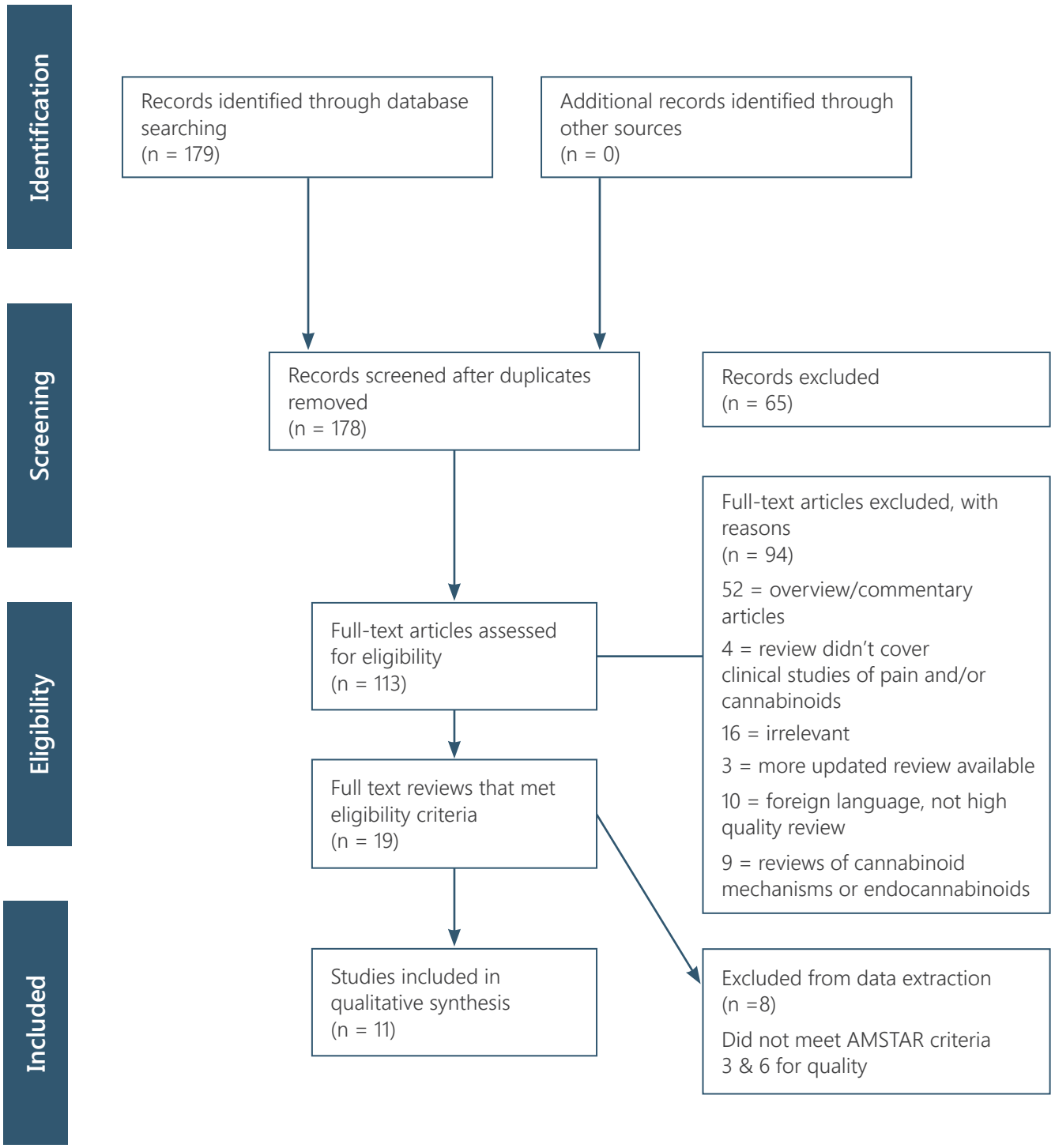
Stopping rules

There is little information on dose-response. Starting doses should be low, and the dose increased in response to lack of efficacy until toxicity outweighs any benefit.

NDARC Review

(See Appendix A)

Figure 1. PRISMA Chart



Overview

Key to grades—adapted from the Mayo Clinic[1]

A Strong scientific evidence for this use
B Good scientific evidence for this use
C Unclear scientific evidence for this use
D Fair scientific evidence against this use (it may not work)
F Strong scientific evidence against this use (it likely does not work)

Place in therapeutic hierarchy

There is an absence of high-quality evidence for the use of medicinal cannabis for patients with acute onset nausea and vomiting, where it would be expected that currently registered medicine(s) would be prescribed. The efficacy of the most recently registered antiemetics has surpassed that of the registered medicines used as comparators in studies of medicinal cannabis.

Furthermore, off-label uses of registered medicines which have off-target anti-nausea effects may be considered appropriate for the treatment of CINV, as is consistent with published clinical practice guidelines.

Treatment in specific disease settings

Chemotherapy-induced nausea and vomiting

Patients with CINV should first be treated according to the ASCO, MASCC/ESMO (2016) clinical practice guidelines, nationally accepted guidelines (eviQ) or other recognised locally-accepted treatment guidelines.

There is an absence of reliable evidence of the efficacy of medicinal cannabis in the treatment of CINV according to the relative emetogenicity of chemotherapeutic regimens, or in comparison with currently available antiemetic therapies, which would be sufficient for clinicians to consider the use of medicinal cannabis ahead of those medicines described in the clinical practice guidelines above.

Studies assessing complete control of nausea and vomiting in patients with CINV

Evidence

The NDARC review (see Appendix A) identified ten reviews (comprising 57 studies) which assessed the outcome of complete control of CINV. However, these studies assessed medicinal cannabis products against medicines which were historically used (and some of which have been superseded), or against placebo.

Overall, there was moderate-quality evidence that the pharmaceutical cannabinoid products dronabinol and nabilone were more effective than placebo, and at least as effective as the antiemetics with which they were compared to antiemetics (prochlorperazine, metoclopramide, thiethylperazine, domperidone, chlorpromazine, haloperidol, alizapride) at achieving complete control of nausea and vomiting in CINV[20,21,22,23,24].

There was more mixed evidence for the effectiveness of other cannabinoids in CINV. One review included low quality evidence, based on a small sample size, that nabiximols were more effective than placebo in achieving complete control of nausea[25]. Three reviews provided low to moderate quality evidence that levonatradol did not exhibit superior antiemetic efficacy to the antiemetics prochlorperazine and chlorpromazine in CINV[26,27,28].

There were mixed conclusions in the reviews regarding the use of cannabinoids to control nausea and vomiting in CINV. One of the highest quality reviews concluded that there was low quality evidence that dronabinol and nabiximols reduced CINV[29]. In contrast, another moderate quality review concluded that dronabinol or THC were not more effective than placebo[30]. Further, the review concluded that while dronabinol had better acute antiemetic efficacy, cannabinoids nabilone and levonantradol did not have superior antiemetic efficacy to "conventional" antiemetics[31].

A high quality Cochrane review concluded on the basis of four studies that there was low quality evidence favouring the use of medicinal cannabis in treating CINV[32].

Control of nausea in patients with CINV

Evidence

Complete control of nausea was typically measured by self-report ratings on visual analogue scales (VAS). Six reviews reported data on nausea in patients receiving cannabinoids for patients with CINV and late-stage AIDS-defining illness[33,34,35,36,37].

Overall, there was moderate quality evidence that nabilone was more effective than placebo, and at least as effective as the active comparators prochlorperazine, metoclopramide, domperidone and chlorpromazine, in completely controlling nausea in CINV[118,11,12]. Four reviews included five individual studies that provided low to moderate quality evidence for a mostly positive effect of dronabinol in controlling nausea for CINV[38,39,40].

One high quality review reported a combined analysis of the effectiveness of nabilone, THC and dronabinol at controlling nausea in CINV. It found no difference in the proportion of patients reporting no nausea after receiving cannabinoids compared to patients receiving placebo[41]. In contrast, a low quality review (AMSTAR 4 of 11) concluded that medicinal cannabis was more effective than active comparators and placebo in completely controlling CINV[42]. The review reported a combined analysis of nabilone, dronabinol and levonantradol which indicated that medicinal cannabis was more effective than placebo (RR=1.21, NNT=8.0) and active comparators (prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, alizapride) (RR=1.38, NNT=6.4). These differences were small, however.

Complete control of vomiting in patients with CINV

Evidence

Complete control of vomiting in CINV was measured as either the reported absence of vomiting, or the number of reported episodes of vomiting. Most studies for this outcome were measured in response to the administration of chemotherapy and were included in five reviews[43,44,45,46,47].

There was low to moderate quality evidence reporting the effectiveness of nabilone and dronabinol as more effective than placebo in completely controlling vomiting in CINV (total of 23 studies in five reviews[48,49,50,51].

There was limited evidence that levonantradol (one study, in two reviews[52,53]) and cannabis sativa (one study, in one review[54]) were more effective than placebo in achieving complete control of vomiting in CINV[55,56,57]. One low quality review concluded that smoked cannabis sativa was significantly better than placebo in controlling vomiting for patients experiencing CINV[58]. No specific conclusions were drawn about levonantradol but moderate quality evidence suggested that it may reduce vomiting in CINV compared to active comparators and placebo[59,60].

Subjective experience of effect on nausea in patients with CINV

Evidence

Several reviews reported data on the effects of medicinal cannabis on subjective measures of nausea using VAS scales in patients experiencing CINV[61,62,63]. Three reviews included eight studies of low to moderate quality that reported dronabinol was as effective as prochlorperazine at reducing nausea for patients with CINV[64,65,66]. In four reviews there was low to moderate quality evidence that nabilone was more effective than placebo, and at least as effective as the antiemetics prochlorperazine and domperidone, with which it was compared, in reducing nausea in CINV[67,68,69]. One review included one study of low quality that reported THC extract reduced nausea in CINV[70].

One review included one study with evidence of unclear quality that found no difference between smoked cannabis sativa and active comparator thiethylperazine in self-reported (or nurse observed) nausea severity in patients experiencing CINV[71]. The review did not state whether either drug was successful in reducing or controlling nausea. One review included a moderate quality study[72] which reported that CINV patients receiving levonantradol experienced less nausea and vomiting than patients receiving prochlorperazine[73].

Subjective experience of effect on appetite in patients with CINV

Evidence

There are nine studies reporting effects on appetite during use in patients with CINV, all of which are Grade C evidence. These arise from use with nabilone (seven studies of low to moderate quality reported mixed results), THC (one low quality study had mixed results) and Levonantradol (one low quality study demonstrated no significant difference compared to an active comparator).

Nausea and vomiting in patients with chronic conditions

Evidence

Evidence regarding the use of medicinal cannabis products for chronic disease management is limited to patients with cancer (in a non-palliative setting) or for individuals with AIDS-defining illness.

Complete control of nausea in patients with cancer or individuals with AIDS-defining illness

Evidence

There was some moderate-quality evidence for nabilone being more effective for controlling nausea in individuals with late-stage AIDS-defining illness as compared to placebo[74].

Subjective experience of nausea in cancer palliative care and late-stage AIDS

Evidence

Several reviews have reported on subjective experience of nausea in patients with advanced cancer, and late-stage AIDS-defining illness[75,76,77,78,79,80,81]. One review included one moderate quality study which reported that a THC:CBD combination was more effective than placebo in reducing nausea in patients with cancer-related anorexia. The authors noted that these trials did not consistently observe benefits or drawbacks when adding CBD and THC to therapy[82].

Subjective experience of change in appetite in individuals with AIDS or cancer

Evidence

Appetite was measured in some studies of patients experiencing CINV[83,84,85]. There was low to moderate quality evidence reporting mixed effectiveness of nabilone and THC at improving appetite in patients experiencing CINV[86,87].

Two reviews reported individual studies of the effects of cannabis sativa on appetite in patients experiencing CINV or AIDS-related nausea[88,89,90,91]. One review reported moderate quality evidence of a non-significant difference in appetite between levonantradol and an active comparator chlorpromazine in patients experiencing CINV[92]. No reviews drew specific conclusions on the potential for cannabinoids to increase appetite in patients experiencing CINV.

Subjective experience of effect on appetite in patients with cancer or individuals with HIV/AIDS-defining conditions

Evidence

Subjective experience of effect on appetite was most often measured in studies in which medicinal cannabis was administered to individuals with HIV/AIDS[93,94,95].

There was a small amount of low to moderate quality evidence that dronabinol was more effective than placebo at improving appetite in individuals with AIDS-defining conditions. No reviews drew specific conclusions on the potential for cannabinoids to increase appetite in patients experiencing cancer, or AIDS-related nausea.

Dosage

There is an absence of dose recommendations for the management of nausea and vomiting in children.

There is an absence of dose recommendations for the management of nausea and vomiting in patients with concomitant hepatic or renal impairment. There is also an absence of dose recommendations for the management of nausea and vomiting in elderly patients.

There is an absence of information regarding drug–drug interactions and recommendations for dose modification in any patient group.

Dosage for CINV in adults

Clinical reviews reported the use of Dronabinol for the treatment of CINV using dose between 2.5mg and 20mg between one and four times a day[96,97,98,99,100,101,102,103,104,105,106].

The use of nabilone for the treatment of CINV was reported in reviews using doses between 1mg and 10mg one to five times a day. However, in studies reporting effectiveness, doses between 1mg and 4mg at one to four times a day were used[107,108,109,110,111,112,113,114,115,116].

Reviews reported patients receiving THC for CINV had received 10mg between four and eight times a day, or 10mg/m^2 body surface area at four to six times a day.

Levonantradol was administered at 0.5mg to 4mg between one and four times a day.

Use of nabiximols was included in one study of 16 participants who received 2.7mg THC: 2.5mg CBD between two and eight times a day.

Dosage for cancer-related nausea and vomiting in adults[117]

In observational studies of effectiveness, doses of Dronabinol used ranged 2.5mg to 10mg at two to three times a day. One observational study of the use of nabilone reported use of doses between 0.5mg and 10mg one to two times a day.

Summary

Dosage forms, variations in route of administration and standardisation

Cannabinoid product	Condition	Preparation	Administration	Standardised
Dronabinol	**CINV***	**Capsule**	**Oral**	**Yes**
	HIV	Capsule	Oral	Yes
	Cancer-associated N&V	Capsule	Oral	Yes
Nabilone	**CINV*, Cancer-associated N&V***	**Capsule**	**Oral**	**Yes**
	HIV/AIDS	Capsule	Oral	Yes
THC	**CINV***	**Capsule**	**Oral**	**Yes**
Levonantradol	**CINV***	**Dissolved formula**	**Intramuscular injection**	**Yes**
Nabiximols/ THC:CBD	**CINV***	**Liquid**	**Oromucosal spray**	**Yes**
	Cancer—effect on appetite	Liquid	Oromucosal spray	Yes
Herbal cannabis	**CINV***	**Cigarette**	**Inhalation**	**Not specifie**
	HIV/AIDS	Cigarette	Inhalation	Not specified

*No studies of these medicinal cannabis products have been performed against the most recently approved antiemetics which are considered the most efficacious available, in adequately designed and performed randomised clinical trials.

Dronabinol

Dronabinol was administered in a standardised oral capsule form for patients experiencing CINV, nausea and vomiting associated with AIDS-defining conditions, or other cancer-related nausea and vomiting[118].

Nabilone

Nabilone was administered in a standardised oral capsule form for patients experiencing CINV, nausea and vomiting associated with AIDS-defining conditions, or cancer-related nausea and vomiting.

THC

Cannabidiol was administered in an oral capsule form for patients experiencing CINV, and other conditions that reduced appetite.

Cannabis sativa

Cannabis sativa was administered in herbal cigarette form for patients experiencing CINV and nausea and vomiting associated with AIDS-defining conditions. It is uncertain how successfully these products were standardised.

Other cannabinoids

Levonantradol was administered as a standardised intramuscular injection for patients experiencing CINV. Nabiximols or THC:CBD mixture was administered as a standardised oromucosal spray for patients experiencing CINV or cancer-related appetite suppression.

Appendix A

NDARC Review

Studies were assessed for their quality based on the criteria that the Cochrane Collaboration uses to evaluate possible methodological flaws in clinical trials.

This review comprised a comprehensive 'review of reviews' of high quality systematic reviews assessing the effectiveness of cannabinoids in treating nausea and vomiting. The objectives were to identify the cannabinoids used, including plant and pharmaceutical formulations, and assess their ability to completely control nausea and/or vomiting, as well as addressing subjective feelings of nausea and appetite. The review also considers tolerability and safety data, as reported by patient study withdrawals and reported adverse events. Each included review had to address at least one of the outcomes defined on the basis of clinical experience[119], namely:

Primary outcomes:

- The complete control of nausea and vomiting (absence of nausea and vomiting without the use of rescue medication) in the acute phase (within 24 hours of treatment with chemotherapy) and in the delayed phase (after 24 hours of treatment with chemotherapy) of nausea and vomiting.
- Complete control of vomiting (absence of episodes of vomiting without use of rescue medication) in the acute and delayed phases of nausea and vomiting.
- Complete control of nausea (absence of episodes of nausea without use of rescue medication) in the acute and delayed phases of nausea and vomiting.

Secondary outcomes:

- Subjective experience of appetite (using self-reported scoring system such as visual analogue scale).
- Subjective experience of nausea (also using self-reported scoring system such as visual analogue scale, for number, duration and severity of episode).
- Study withdrawal due to any reason.
- Cross-over studies only: participant preference for one or other of the interventions (cannabis or control).
- Adverse effects, including 'feeling high', sedation, euphoria, dizziness, heightened sense of anxiety or agitation (dysphoria), depression, hallucinations, paranoia, hypotension, focal dystonia, extrapyramidal effects and oculogyric crisis.

The following secondary outcomes for nausea and vomiting associated with HIV/AIDS as suggested by Lutge et al[120].

- Subjective experience of appetite (using a visual analogue scale)
- Subjective experience of nausea (also using self-reported rating on a visual analogue scale, for number, duration and severity of episode)

Inclusion criteria

1. Types of participants: The review considered studies that included participants of any age, with any type of nausea and vomiting but the primary focus was on emesis occurring in cancer patients undergoing chemotherapy.
2. Types of intervention: The review considered reviews of studies that evaluate plant based and pharmaceutical cannabinoids administered to prevent or treat nausea and vomiting, particularly related to cancer treatment and secondarily in cancer and AIDS-related nausea. The review considered studies of: tetrahydrocannabinol; cannabidiol; combination tetrahydrocannabinol + cannabidiol; cannabis sativa; and where evidence exists, other cannabinoids e.g. tetrahydrocannabinolic acid (thca), cannabidiolic acid, cannabidivarin, and the synthetic delta-9-tetrahydrocannabinol formulations nabilone and dronabinol).
3. Types of studies: We included reviews of both experimental and epidemiological study designs and so included randomized controlled trials, non-randomized controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case control studies and analytical cross sectional studies.

Exclusion criteria

Papers describing mechanisms of cannabinoid action, commentaries and clinical overviews that did not present the results of studies were not included in the review.

Review quality was assessed using the AMSTAR measurement tool of methodological quality of systematic reviews[121]. The AMSTAR tool documents assessed risk of bias at the review level. To identify reviews conducted methodologically, and to minimise bias at the review level in study selection, each identified review was required to meet criterion 3 and 6 of the AMSTAR tool at a minimum. This reflects reviews that were conducted with a comprehensive search and those that, at a minimum, describe the characteristics of the included studies.

The review assessed risk of bias of each study using aspects of bias recommended by the Cochrane Collaboration. These are:

- selection bias (randomisation, allocation concealment)
- performance bias
- detection bias
- attrition bias due to incomplete outcome data, and
- reporting bias[122].

Studies were defined as high quality if they had six to seven factors with low risk of bias, as moderate quality if they had three to five factors with low risk of bias, and as low quality if only zero to two factors of the seven were classified as low risk of bias.

After excluding duplicates, the literature search returned 179 publications (see Figure 1). Sixty two were excluded during screening of abstracts. One hundred and eighteen publications were assessed for eligibility, of which 94 did not match the inclusion criteria.

In total, eleven studies were included in the systematic analysis, assessing the effects of various medicinal cannabis products on relevant outcomes.

Table 1. Summary of evidence for cannabis and cannabinoids for the treatment of nausea and vomiting

	Complete control of nausea and vomiting	Complete control of nausea	Complete control of vomiting	Subjective experience of nausea	Subjective experience of appetite	Patient preference	Withdrawals	Adverse events
Cannabis sativa/extract	2 studies (No RCT)	No studies	No studies	1 study (1 RCT)	2 studies (1 RCT)	No studies	1 study (No RCT)	No studies
Findings	Mixed effect			Positive effect	Mixed effect		24% withdrew	
Quality of evidence	Unclear			Unclear	Unclear to low quality		Unclear quality	
Risk of bias	Unclear				Unclear risk			
Conclusion	Insufficient evidence			Insufficient evidence	Insufficient evidence		Insufficient evidence	
Dronabinol	21 studies (20 RCT)	8 studies (6 RCT)	11 studies (9 RCT)	11 studies (11 RCT)	6 studies (6 RCT)	4 studies (4 RCT)	1 study (1 RCT)	12 studies (12 RCT)
Findings	Positive effect	Positive effect	Positive effect	Positive effect	Mixed effect	Positive effect	More likely to withdraw	AEs > comparator
Quality of evidence	Moderate quality	Low to moderate quality	Low to moderate quality	Low to moderate quality	Low to moderate quality	Low to moderate quality	Moderate quality	Low to moderate quality
Risk of bias	Low to high risk	Low to high risk	Low to high risk	Low to high risk	Low to high risk	Unclear risk	Low to high risk	Low to high risk
Conclusion	As effective as traditional antiemetics	More effective than placebo	More effective than placebo	As effective as traditional antiemetics	More effective than placebo for AIDS; insufficient CINV	Patients prefer dronabinol	Insufficient evidence	More likely to experience mild to moderate AEs
Oral THC	No studies	No studies	1 study (1 RCT)	1 study (1 RCT)	1 study (1 RCT)	No studies	No studies	No studies
Findings			Positive effect	Positive effect	No change			
Quality of evidence			Low quality	Low quality	Low quality			
Risk of bias			Unclear risk	Unclear risk	Unclear risk			
Conclusion			Insufficient evidence	Insufficient evidence	Insufficient evidence			

	Complete control of nausea and vomiting	Complete control of nausea	Complete control of vomiting	Subjective experience of nausea	Subjective experience of appetite	Patient preference	Withdrawals	Adverse events
Nabilone	16 studies (15 RCT)	8 studies (6 RCT)	12 studies (12 RCT)	12 studies (12 RCT)	7 studies (7 RCT)	14 studies (14 RCT)	12 studies (12 RCT)	12 studies (12 RCT)
Findings	Positive effect	Positive effect	Mixed results	Positive	Mixed results	Positive effect	More patients withdrew	AEs > comparator
Quality of evidence	Very low to moderate quality	Low to moderate quality	Low to moderate quality	Low to moderate quality	Low to moderate quality	Low to moderate quality	Low to moderate quality	Very low to moderate quality
Risk of bias	Low to high risk	High risk	Low to high risk	Low to high risk	Low to high risk	Low to high risk	Low to high risk	Low to high risk
Conclusion	As effective as traditional antiemetics	More effective than placebo	Possibly more effective than placebo	As effective as traditional antiemetics	Insufficient evidence	Patients prefer nabilone	More likely to withdraw	More likely to experience mild to moderate AEs
THC:CBD	No studies	No studies	No studies	1 study (1 RCT)	1 study (1 RCT)	No studies	No studies	No studies
Findings				No effect	No effect			
Quality of evidence				Moderate quality	Moderate quality			
Risk of bias				Low risk	Low risk			
Conclusion				Insufficient evidence	Insufficient evidence			
Nabiximols	1 study (1 RCT)	No studies	No studies	No studies	No studies	No studies	No studies	1 study (1 RCT)
Findings	Positive effect							AEs = comparator
Quality of evidence	Low quality							Low quality
Risk of bias	High risk							High risk
Conclusion	Insufficient evidence							Insufficient evidence
Levonantradol	3 studies (3 RCT)	No studies	1 study (1 RCT)	1 study (1 RCT)	1 study (1 RCT)	2 studies (2 RCT)	No studies	2 studies (2 RCT)
Findings	Mixed results		Possible effect	Possible effect	No effect	Mixed results		AEs > comparator
Quality of evidence	Low to moderate quality		Moderate quality	Low quality	Moderate quality	Low to moderate quality		Moderate quality
Risk of bias	High risk		High risk	High risk	Unclear risk	High risk		High risk
Conclusion	Insufficient evidence		Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence		Insufficient evidence

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