Cost-effectiveness of medicinal cannabis for management of refractory symptoms associated with chronic conditions: A systematic review of economic evaluations

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Concise description of the study: A comprehensive review of economic evaluations of medicinal cannabis for alleviating refractory symptoms associated with chronic conditions.

Highlights

- An increasing number of patients are interested in or are using cannabis for medical reasons; however, little is known about whether these products represent good value for money.
- This paper comprehensively examined the current evidence regarding cost-effectiveness of medicinal cannabis products.
- There is a need to generate adequate clinical and cost-effectiveness evidence prior to introducing these drugs into clinical practice.

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Abstract

Objectives: Although there is a growing body of evidence suggesting that cannabinoids may relieve symptoms of some illnesses, they are relatively high-cost therapies compared to illicit growth and supply. This paper aimed to comprehensively review economic evaluations of medicinal cannabis for alleviating refractory symptoms associated with chronic conditions.

Methods: Seven electronic databases were searched for articles published up to September 6, 2020. The quality of reporting of economic evaluations was assessed using the CHEERS checklist. The extracted data were grouped into subcategories according to types of medical conditions, organized into tables and reported narratively.

Results: This review identified 12 cost-utility analyses (CUA) conducted across a variety of diseases including multiple sclerosis (MS) (n=8), pediatric drug-resistant epilepsies (n=2), and chronic pain (n=2). The incremental cost-effectiveness ratio varied widely from cost-saving to more than USD $451,800 per QALY depending on the setting, perspectives, types of medicinal cannabis and indications. Nabiximols is a cost-effective intervention for MS spasticity in multiple European settings. Cannabidiol was found to be a cost-effective for Dravet syndrome, in a Canadian setting whereas a CUA conducted in a USA setting deemed cannabidiol to be not cost-effective for Lennox-Gastaut Syndrome. Overall study quality was good, with publications meeting 70% to 100% (median 83%) of CHEERS checklist criteria.

Conclusion: Medicinal cannabis-based products may be cost-effective treatment options for MS spasticity, Dravet syndrome and neuropathic pain, although the literature is nascent. Well-designed clinical trials and health economic evaluations are needed to generate adequate clinical and cost-effectiveness evidence to assist in resource allocation.

Keywords: Cannabinoids; medicinal cannabis; economic evaluation; cost-effectiveness

Introduction

Patient interest in the use of cannabis and cannabinoids to treat a variety of conditions including management of intractable symptoms associated with advanced medical conditions has increased over the last decade [1]. The increased patient demand has also been accompanied by renewed scientific interest in the therapeutic effects of cannabis, and several clinical trials have recently evaluated the medical use of cannabinoids [1,2]. Although the evidence base is limited and inconsistent, findings from systematic reviews of currently available controlled clinical trials suggests that cannabinoids, when used as either adjunctive treatment or drug of last resort, relieve some of symptoms of some illnesses such as chemotherapy induced nausea and vomiting [1], neuropathic pain and spasticity in multiple sclerosis (MS) [3,4], chronic non-cancer pain [5,6], and intractable childhood epilepsy [7] for some patients. Medicine regulatory authorities in certain countries have already granted marketing authorisations, on the basis of an evolving yet limited evidence base, to a wide variety of plant-derived and synthetic cannabinoid-containing preparations for various indications. These products predominantly contain tetrahydrocannabinol (THC) and/or cannabidiol (CBD) in various concentrations and dosage forms, and includes drugs such as dronabinol (a synthetic version of THC), nabilone (a synthetic THC analogue), and nabiximols (a cannabis plant extract containing a roughly 1:1 ratio of THC and cannabidiol).

Although an increasing number of patients are interested in or are using cannabis for medical reasons, the additional cost and resource utilisation associated with medicinal cannabinoids should first be justified against its overall benefit to the patient, providers, health system prior to introducing these drugs into specialist and primary health care settings. This is particularly so as adverse events from such medicines also cause morbidity. Cost-effectiveness analysis (CEA) is often conducted to systematically examine economic efficiency and value for money of adopting a new strategy or a new drug along with its impacts on patient care and outcomes. Herzog *et al* (2017) conducted a systematic review of costs and benefits of medicinal cannabis for the management of chronic illness (last search date: December 2016), and found only a handful of full economic evaluations limited to the management of MS spasticity [8]. However, several cost-effectiveness analyses have since been published for various conditions including for pediatric drug-resistant epilepsies [9,10] and neuropathic pain [11]. The aim of this review was, therefore, to update the previously published systematic review and provide a comprehensive overview of the cost-effectiveness of medicinal cannabis for the management of refractory symptoms associated with chronic conditions (e.g. pediatric drug-resistant epilepsy, MS

spasticity, chronic pain, anorexia-cachexia, cancer-related nausea and intractable pain in advanced cancer patients). The findings will serve to inform the subsequent development of a within-trial and modelled economic evaluation to determine costs and benefits of prescribed medicinal cannabis for symptom control in advanced cancer patients in Australia.

Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline and the study protocol was registered on PROSPERO (CRD42020209372).

Data sources and search strategy

A comprehensive literature search was undertaken using multiple databases (from inception of each databases up to September 6, 2020): PubMed/MEDLINE, EMBASE, PsycINFO, CINHAL, Econlit, Centre for Reviews and Dissemination databases (Database of Abstracts of Reviews of Effects and the NHS Economic Evaluation Database), CEA Tufts, and Google Scholar to capture all full economic evaluations related to the use of medicinal cannabis for the management of refractory symptoms associated with chronic conditions. This was followed by complementary searches including forward and backward citation searches of included articles, manual search of health technology agency and government websites, and Google search to further locate eligible articles that were not identified in the database search. We have also rerun the database search in November 5, 2020 to check for updates. The keywords used in the search strategy were built on two key concepts of the subject as: 1) Cannabis products (“cannabis”, “medical cannabis”, “medical marijuana”, “tetrahydrocannabinol”, “cannabidiol”, “dronabinol”, “nabilone” “nabiximol”), and 2) Economic evaluations (“economic evaluation”, “Costs and Cost Analysis", “Cost utility”, “Cost-effectiveness”, “Cost-benefit”, “pharmacoeconomics”, “health technology assessment”, “Quality-Adjusted Life Years”, “Disability Adjusted Life Years”, “economic model”), and tailored to each database. Boolean operators and truncations varied depending on the database. No restrictions on year of publication was applied. The full search strategy is presented in a Supplementary file.

Eligibility screening

Studies were included if they were 1) full economic evaluations (both within-trial and model-based), or 2) health technology assessments that include a full economic evaluation. Studies comparing cost-effectiveness of cannabis based medicines (e.g. cannabidiol and/or tetrahydrocannabinol [THC], and synthetic THC formulations nabilone and dronabinol) as an adjunct or complementary therapy with standard treatment (both pharmacologic and non-pharmacologic treatments) for management of intractable symptoms associated with chronic conditions (e.g. advanced cancer, dementia, or chronic conditions with an intractable symptoms such as pediatric drug-resistant epilepsy, multiple sclerosis associated spasticity) were included. We excluded grey literature, methodology papers, literature reviews, studies published in languages other than English and conference or dissertation abstracts without the full text available for retrieval. Prior to excluding conference abstracts, dissertation abstracts and other relevant articles without full text, a repeated email contact was made with authors requesting for full text. The articles identified were then exported to COVIDENCE, and two independent reviewers (DE and SS) screened all titles, abstracts and full texts based on the eligibility criteria. Any discrepancies and/or disagreements between reviewers were resolved through discussion and consensus. The detailed search strategy and eligibility screening are presented in Figure 1. A list of excluded studies along with justification for exclusion is provided in supplementary file.

[INSERT Figure 1]

Reporting quality of studies The reporting quality of each included study was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [12]. Developed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force, the CHEERS checklist provides a guidance for researchers, editors and peer reviewers regarding optimal reporting of health economic evaluations. The checklist consists of 24 items subdivided into six main categories: (1) title and abstract, (2) introduction, (3) methods, (4) results, (5) discussion, and (6) "other." Studies were scored independently by two of the authors (DE and SS) as having met the criteria in full (designated as "Yes" and given a score of 1), do not fulfil (designated as "No" and given a score of 0)

or not applicable ("NA"). Any disagreements were resolved through consensus, and, if necessary, in consultation with a third reviewer.

Data extraction and synthesis

Two reviewers (DE and SS) independently extracted detailed information about the study characteristics and key study findings from each included study using a published data extraction form, after tailoring to our review objective and the study designs of included articles [13]. A third reviewer resolved any disagreements. The final data extraction form included two main sections: 1) study characteristics (e.g. publication details, country, study design, sample size, intervention/comparator, study perspective, analytical approach etc.), and 2) study design and main outcomes (resource use, costs, effects, measurement, valuation methods, total and incremental quality-adjusted life years, incremental cost-effectiveness ratios [ICER], uncertainty and sensitivity analyses, author's conclusions). Where possible, standardised ICER (cost estimates adjusted to US$ in 2018) were calculated using CCEMG - EPPI-Centre Cost Converter v.1.6 [14]. For model-based economic evaluations, details about the model structure (e.g. health states, time horizon, and cycle length) and model inputs (e.g. resource use and utility values) were extracted. For studies that reported probabilistic sensitivity analyses, we summarised the key model parameters reported the sensitivity analyses, and their impact on the overall ICER estimate. The extracted data were grouped into subcategories according to types of medical conditions, organized into tables and reported narratively.

Results

General characteristics of studies

After removal of duplicates and publications that did not meet the inclusion criteria, a total of 10 articles were included (Figure 1). The studies were conducted between 2012 and 2020 and majority of them were from UK [15-19], USA [10,11] or Italy [20,21]. Characteristics of included studies are presented in Table 1 and 2. Multiple sclerosis (MS) associated spasticity was the most common disease state for which cost-effectiveness of medicinal cannabis were evaluated (n=7) [15-17,19-23]. The remaining studies were conducted in patients with pediatric drug-resistant epilepsies (Dravet syndrome – DS [9] and Lennox-Gastaut Syndrome – LGS [10]) and chronic pain [11,18].

Study design, perspective, time horizon and discount rates

All studies applied cost-utility analysis (CUA), with majority of studies (n=10) being CUAs based on a Markov model [9-11,16-19,21-23]. The remaining studies were CUAs conducted alongside a clinical trial [15] or based on real world patient-level data from a national registry [20]. All included studies were analysed using a healthcare payer perspective. All except one studies included 'standard of care (SoC)' in both intervention and comparator arms while the Mantovani et al 2020 study [20] compared Cannabinoid Oromucosal Spray with "no treatment" instead of the SoC. One study [9] considered a societal perspective in their sensitivity analysis alongside a payer perspective. The time horizons ranged from 6 months to lifetime. Discount rates were reported in eight of the studies [9-11,15-17,21,23]. For the remaining studies, discounting was either not reported [22] or not applicable as the main analysis considered a time horizon of 6 months [20].

[INSERT TABLE 1]

Reporting of costs and effectiveness

Table 2 shows the costs included in the analyses, and measurement and valuation of preference-based health outcomes. While the types of costs included depended on the study setting and study perspectives, drug costs, direct medical costs (e.g. laboratory tests and monitoring) and health system-related costs (e.g., homecare workers, general practitioners) were the key inputs for the cost analysis in majority of the studies. All studies described the approach used to estimate unit costs and cost calculations. Several sources were used to derive data regarding costing of resource use including from literature review (e.g. previous economic evaluations, resource utilization study) [9-11,16,17,21-23] and Ex-factory price for drugs [9,20]. All studies clearly described the choice of outcomes and used QALY as the summary health outcome measure. All but one study [11] reported valuation of preference-based outcomes. Most of the effectiveness data were collected from randomised controlled trials (RCTs) [10,15,16,18,19,21,23] and observational data [20,22], or were estimated based on a literature review [9,17]. In majority of the studies, health-state utilities were estimated from utility values provided in the literature (e.g. EQ-5D utility values collected in clinical trials [16,17,20-23], whereas one study obtained utility values from the patients using the time trade-off method [9].

[INSERT TABLE 2]

Cost-effectiveness outcomes according to disease conditions and drivers of ICER estimates

Economic evaluation results are summarised in Table 3. Eleven studies reported incremental cost-effectiveness ratios (ICERs) as the final economic evaluation outcome, and clearly stated the willingness to pay (WTP) threshold used [9-11,16,17,20] or referred to the National Institute for Health and Care Excellence (NICE)'s threshold (i.e. £20 000 - £30 000 per QALY gained) to determine cost-effectiveness [18,19,21-23]. One study compared incremental costs and QALYs but did not calculate ICER as the intervention (oral Δ9-THC, maximum 28 mg/day for progressive MS) was not shown to be effective [15]. The ICERs varied widely from cost-saving [23] to more than USD $451,800 per QALY [10] depending on the setting, perspectives, types of medicinal cannabis and indications.

Multiple Sclerosis

Nabiximols for the management of MS spasticity were deemed to be cost-effective in six studies conducted in Germany [22,23], Italy [20,21], Spain [23], and UK [16,19] settings and not cost effective in one study conducted in the UK setting [17]. All except one study (five out of seven studies) that found nabiximols to be a cost-effective intervention were industry funded. The remaining two studies were funded by the UK government, and reported conflicting conclusions (not cost-effective by Lu et al study [17] and cost-effective in a study commissioned by the UK's National Institute for Health and Care Excellence[19]). An economic evaluation conducted alongside a clinical trial in the UK (CUPID Trial) [15] found that oral Δ9-THC (dronabinol) had significant additional costs with no improvement in health outcomes for patients with progressive MS (i.e. dominated by usual care and thus not cost-effective).

Pediatric drug-resistant epilepsy

A study conducted in USA [10] comparing cannabidiol with the usual care for the management of LGS concluded that cannabidiol is not a cost-effective option for this patient population at a WTP threshold of USD $150,000/QALY (ICER: $451,800 per QALY gained). On the other hand, a study from Canada (using a Canadian public health care system perspective and a WTP of CAD $50,000 per QALY gained)

found adjunctive cannabinoid oil to be cost-effective option for patients with DS (ICER: CAD $32,399 per QALY gained) [9].

Chronic pain

Two studies [11,18] evaluated cost-effectiveness of medicinal cannabinoids for chronic pain. The National Institute for Health and Care Excellence in the UK conducted CUA of THC / CBD spray as an add on therapy for patients with chronic pain (compared with usual care alone) using a Markov model. In addition to THC / CBD spray, the model considered other medicinal cannabinoids (i.e. oral dronabinol, oral nabilone and oromucosal THC) in sensitivity analyses. According to findings from the base case and sensitivity analyses, THC / CBD spray (ICER: £151,431/QALY gained) and all other medicinal cannabinoids were found to be not cost-effective interventions for chronic pain including for all treatment and condition specific subgroups. Another study evaluated cost-effectiveness of a standardized herbal cannabis product (12.5% THC) for chronic neuropathic pain in USA setting [11], and found it to be a cost-effective intervention (ICER: $48,594 per QALY gained) when augmenting second-line treatment.

Findings from sensitivity analyses

All except one [15] studies reported the results of one-way and/or probabilistic sensitivity analyses. Uncertainty in health state utilities (e.g. pain state utility, adverse events) was the largest contributor to uncertainty in the model outcomes in five studies [10,11,17,21,23]. Other model parameters with the greatest influence on model outcomes were variations in drug cost [10,11,17,22,23] and dose [11,17,21,23], adherence to therapy [11], and other costs such as costs of physiotherapy sessions [23], homecare support [16,23] and hospitalisations [16]. Findings from sensitivity analysis in one of the studies where Nabiximols was considered to be not cost-effective for MS spasticity [17] suggest that it could be cost-effective if a dose much lower than the mean dose reported in randomised controlled trials provided patients with adequate benefits, and if there was a substantial difference in utilities between responders and non-responders. Similarly, findings from sensitivity analysis of a study conducted in a UK setting (a range of medicinal cannabinoids for chronic pain) suggest that for the ICER to be within the commonly accepted cost-effectiveness threshold (£30,000 per QALY gained), medicinal cannabinoids must be at least 8 times more effective or 6 times less expensive than the usual care. All other model parameters reported in sensitivity analyses did not significantly change ICER estimates.

Assessment of the reporting quality of studies

The assessment of the reporting quality of each study using the CHEERS checklist is provided in Supplementary file. Overall, the reporting quality of the included studies varied from 70% to 100% (median 83%). The study perspective was clearly stated in all the studies. While all model-based studies explicitly stated the modelling approach, none of them gave reasons for the specific type of decision-analytical model used. Among the modelling studies where the specified time horizon exceeded one year (n = 7), one study did not specify that costs and outcomes were discounted [22] while the remaining studies applied discount rates in accordance with national guidelines and ranged from 1.5% to 3.5% per annum. The item that least complied with the CHEERS were on characterizing heterogeneity, compliant only in 2 out of 10 articles.

[INSERT TABLE 3]

Discussion

In this study, we sought to summarise the currently available evidence on the economic evaluation of use of a variety of medicinal cannabinoids for various disease conditions, with the intention of guiding future within-trial economic evaluation aimed at assessing the cost-effectiveness of oral medicinal cannabinoids to relieve symptom burden in the palliative care of patients with advanced cancer. This review identified 12 CUA conducted across a variety of diseases including multiple sclerosis, Dravet syndrome, Lennox-Gastaut Syndrome, and chronic pain.

This body of evidence showed that THC / CBD spray is a cost-effective intervention in managing MS spasticity when used either as an adjunctive treatment or drug of last resort, reported to be cost-effective in six out of seven studies. An abstract on CUA of THC / CBD spray conducted in a Belgium setting reported that for patients with MS spasticity, adding THC / CBD spray to standard spasticity care dominated the standard spasticity care alone, with cost savings of € 7530/patient and a QALY gain of 0.162 over the 5 year time horizon [24]. The findings are also in line with a recently published systematic review which concluded that prescribed cannabis-based products are a potentially cost-effective add-on treatment for MS spasticity [8]. However, some of the evaluations that reported THC /

CBD spray to be a cost-effective treatment for MS spasticity have a several methodological limitations which potentially introduce uncertainty to the ICER estimate. For example, an industry-funded CUA conducted in a UK setting found that THC / CBD spray plus standard of care was £3,836 more expensive and produced 0.35 more QALYs over a 30-year time horizon compared to standard of care alone, making it cost-effective at the £20,000- £30,000 per QALY threshold. However, the model has several limitations including i) extrapolating short-term RCT data from Novotna et al. 2011 [4] (4 plus 12 weeks) to a 30-year model time horizon; ii) missing important parameters such as adverse events (thus favouring to the THC / CBD spray strategy); iii) relying on subjective estimates for resource use; iv) attributing all cost to spasticity alone while some of the costs might overlap with the management MS patients; and v) potential conflict of interest as it was funded by THC / CBD spray manufacturer. Furthermore, one of the studies [20] compared Cannabinoid Oromucosal Spray with "no treatment" instead of the SoC and assumed no costs or utility value change for the "no treatment" option. Although omitting the SoC in both intervention and comparator arms may not affect the overall cost estimate, this approach could potentially favour the cannabinoid strategy since utility values for some patients (including those with uncontrolled and resistant MS spasticity) will likely deteriorate with 'no treatment'.

In Australia, similar cost-effectiveness claims were indicated in a submission made by Novartis Pharmaceuticals Australia Pty Ltd in 2013 (resubmitted again by Emerge Health Pty Ltd in 2020) to the Pharmaceutical Benefits Advisory Committee (PBAC) to list Sativex (nabiximols 10 mL; comparator: oral anti-spasticity treatment alone) for the adjunctive treatment of drug-resistant, moderate-to-severe MS spasticity. In both submissions, the PBAC did not recommend listing of nabiximols the Pharmaceutical Benefits Scheme, and noted in the decision that i) treatment effects are likely overestimated due to the design of the key clinical trial, and ii) ICER was uncertain due to 'substantial structural issues and unrealistic assumptions' in the economic model [25].

A study conducted in a USA setting found a cannabis whole-plant product containing 12.5% THC cost-effective for management of chronic neuropathic pain as an add-on treatment [11] whereas a study conducted in a UK setting found a range of medicinal cannabinoids (THC / CBD spray, oral dronabinol, oral nabilone and oromucosal THC) not cost-effective interventions for the management of chronic pain, with ICERs more than £150,000/QALY gained [18]. The high ICER in the later study [18] can partially be attributed to the modest treatment effects relating to symptom alleviation and the high and ongoing cost of treatment with THC / CBD spray and other medicinal cannabinoids. In addition, the lack

of high-quality long-term data for almost all parameters in the model, extrapolation of data on some parameters from indirect sources (e.g. adverse event disutility), and lack of robust estimates of costs and resource use and reliance on expert opinion in the model have direct influence on the ICER estimate. However, these and other model parameters were tested in the probabilistic sensitivity analysis under various assumptions, and the findings remained the same – a 0% probability that THC / CBD spray is cost-effective for chronic pain [18]. A conference paper reported findings from a trial based CUA of THC / CBD spray plus SoC compared to SoC alone for neuropathic pain in patients with MS. The analysis was conducted from a Canadian provincial government payer perspective over a one-year time horizon and found an ICER of $70,103 per QALY gained. However, it was difficult to critically examine the analysis as it was a conference abstract and we were unable to retrieve the full text of the study [26].

The conclusion regarding the cost-effectiveness of CBD preparations for drug-resistant pediatric epilepsies (DS and LGS) is mixed. While a Canadian study found CanniMed Oil, a CBD dominant preparation (1:20 mg/ml), to be a cost-effective intervention for patients with DS, another CUA conducted in a USA setting deemed the use of CBD oral solution not cost-effective for patients with LGS. This could be partially explained by the difference in the WTP threshold used in the USA (USD $110,000 to $300,000 per QALY) Canada (CAD $50,000 per QALY gained). Following the recent registration of Epidyolex, a cannabidiol product, for use as adjunctive therapy of seizures associated with LGS or DS on the Australian Register of Therapeutic Goods (ARTG) as an Orphan drug, it was considered for listing on the Pharmaceutical Benefits Scheme (sponsored by Chiesi Australia, formerly Emerge Health). However, PBAC deferred making a recommendation due to uncertainty in the magnitude of the benefit of Epidyolex, and the need for further clarity on the clinical place of cannabidiol to 'inform the appropriate initial and continuing restriction criteria, cost-effectiveness and financial implications of listing cannabidiol' [27].

The main shortcomings in publication quality as assessed by the CHEERS checklist were lack of reasoning for the type of decision analytic model used, and lack of reporting on characterizing heterogeneity. In addition, all but one study did not consider a societal perspective, either in the base case or sensitivity analysis. This could have a significant impact on the strength of the cost-effectiveness conclusion as some relevant cost categories that fall outside the healthcare system might have been excluded. For example, indirect costs including informal care or care provided by patient-

remunerated staff are major contributors to the total costs associated with the management of MS [28]. Productivity losses in patients with MS can also be substantial as it predominantly affects adults of working age (diagnosed between the ages of 20 and 45) [29]. However, these cost categories were not considered in all the studies that deemed THC / CBD spray as a cost-effective intervention for MS spasticity.

Another key limitation of several studies included in this review was that they relied on proxy cost data from health professionals and expert opinion to estimate resource use, which might create issues with accuracy resulting from response biases such as recall bias and potential over-estimation of resource consumption [30] with a direct implication on the validity of ICER estimate. Similarly, four out of the six economic evaluations of nabiximols for MS spasticity included in this review estimated treatment efficacy based on same clinical trial conducted by Novotna et al [4] and the remaining studies used observational studies or patient records. Novotna et al study [4] was a 19-week follow-up RCT in patients with MS spasticity not fully relieved with the standard of care. The inclusion criteria specified that patients had spasticity ≥4 in Numeric Rating Scale (NRS) at baseline which suggest that patients with very low NRS or very high NRS may not have been represented. With this, it is unclear how the models in some of the studies (e.g. Gras et al) calculated the transition probabilities from this RCT, nor it was explored in the probabilistic sensitivity analysis. The strength of the clinical evidence and the plausibility of clinical outcomes extrapolated beyond the study duration was seldom discussed in most of the studies. It is also worth mentioning that most of the evaluations that reported THC / CBD spray to be a cost-effective treatment for MS spasticity were industry-funded, further introducing selection bias and uncertainty to the ICER estimate.

Although the clinical evidence regarding the role of medicinal cannabinoids for various medical conditions is growing, the current evidence base is mixed and inconsistent. This is reflected in recently published systematic reviews on the clinical benefit of medicinal cannabinoids for MS spasticity which have reported contrasting findings [31]. In such situations where the evidence base is contentious and uncertain, using selected RCT(s) for deriving treatment effects and/or utility weights for economic evaluations will certainty suffer from bias with a direct implication on the ICER estimate. For example, the industry-funded CUA study of nabiximols for MS spasticity [16] derived treatment effects from a single RCT (Novotna et al. 2011 [4]) and used utilities measured using the EQ-5D data from the same trial, which may have led to an overestimate of cost-saving from nabiximols (ICER of £10,891 per QALY).

This contrasts with the recent CUA conducted by UK's National Institute for Health and Care Excellence [19] which have used four different RCTs for deriving treatment effects and reported an ICER of £19,512 per QALY gained. Although ICER estimates from both studies fall within the UK's commonly accepted WTP threshold of £20,000- £30,000 per QALY, the difference in ICER estimates demonstrate how failing to consider all available evidence can potentially lead to over/under estimation of clinical benefits (i.e. utilities) from the use of a medicinal cannabis product, thereby affecting its cost-effectiveness.

Generally, there is a need for a larger, better-designed clinical trials with longer-term follow-up of participants to ascertain the role of medicinal cannabis in medical conditions where there is no/insufficient evidence. It is important that these clinical trials include measures of various utility-based health related quality of life (HRQoL) measures which are important to estimate benefit in terms of QALYs. In Australia, over 40 observational and RCTs of medicinal cannabis have been registered by Australian New Zealand Clinical Trials Registry (as of November 2020) for a range of indications including for symptom control in people with MS, advanced cancer, chronic pain, sleep disorder, neurological disorders, and mental disorders. Evidence from such well-designed RCTs will provide data on the safety, efficacy, and relative effectiveness of medicinal cannabinoids. This will, in turn, facilitate economic evaluations to establish whether products that are clinically effective also represent good value for money.

Strength and limitations

While we have employed rigorous and standard approaches to summarise and present empirical data on cost-effectiveness of medicinal cannabis from published literature, our review is not without limitations. We excluded studies reported in languages other than English and studies for which the full text was unavailable (e.g., conference abstracts), which may have limited our study findings. The inherent subjectivity of assessing the quality of reporting of economic evaluations [32] is another key limitation of this review although we have used a second reviewer to reduce the subjectivity in scoring. The CHEERS Checklist is a guidance for the reporting economic evaluations, rather than assessing the quality of published economic evaluations, and thus this review is limited to assessing what has been reported. As most of the conditions included in this review (particularly MS) have undergone a big pharmaceutical development in the last few years, the number of therapeutic alternatives for these patients have increased in recent years. This could affect the definition of appropriate comparisons for

the economic evaluations, thus affecting the external validity of the existing economic evaluations (and the conclusions of this review).

Conclusion

Our findings suggest that medicinal cannabis-based products may be cost-effective treatment options for a variety of medical conditions and symptoms including MS spasticity, Dravet syndrome and neuropathic pain, albeit considerable uncertainty in the ICER estimates. Model parameters with the greatest influence on ICER estimates were uncertainties in health state utilities, variations in drug cost and dose, and consideration of other costs such as homecare support. Well-designed clinical trials and health economic evaluations are needed to generate adequate clinical and cost-effectiveness evidence regarding use of medicinal cannabis products in various disease conditions in order to inform clinical practice and assist in resource allocation and/or public reimbursement decisions.

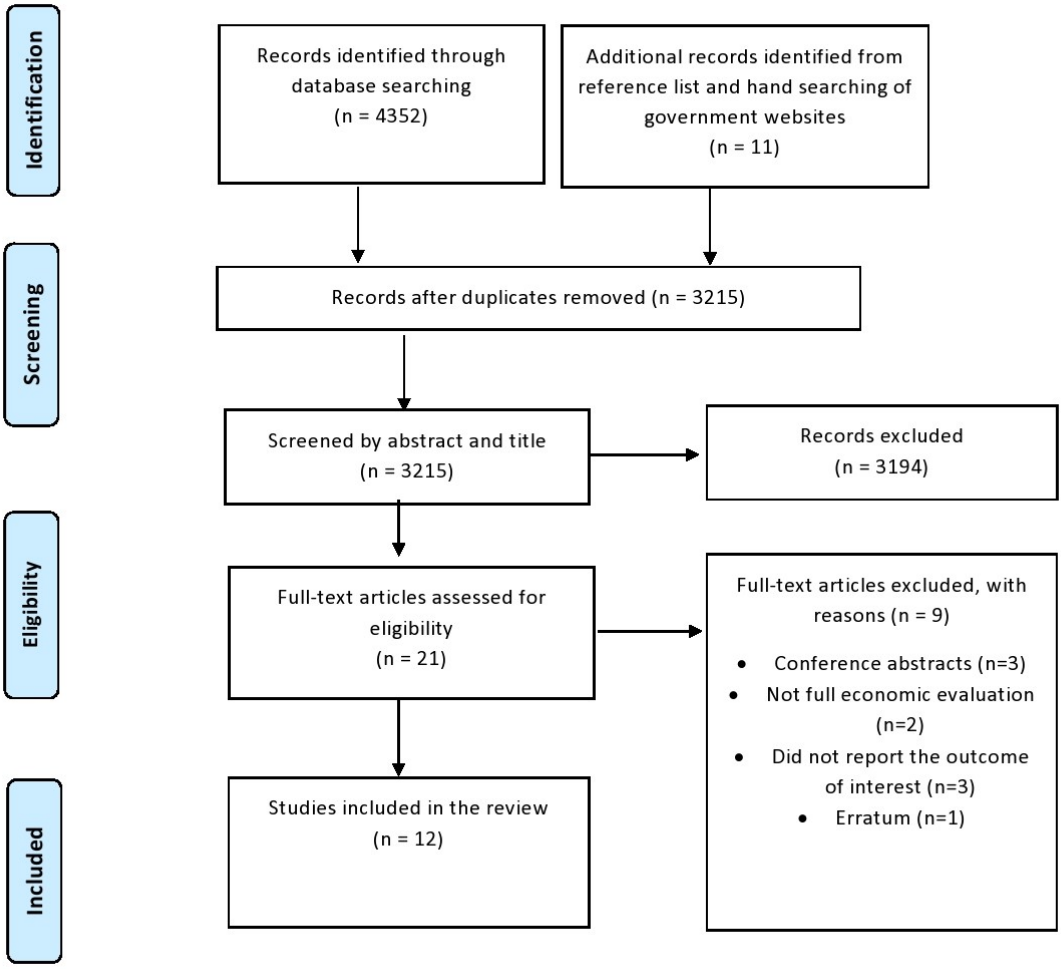

Figure 1. PRISMA flow diagram

Table 1. General characteristics of studies, N=12

Author, Year	Country	Type of economic evaluation	Perspective	Disease or condition	Study population/ sample	Intervention	Comparator(s)	Health outcome(s)	Time horizon	Funding
Bell S et al, 2015	UK	WTEE (CUA)	NHS and Personal and Social Services	Progressive Multiple Sclerosis (MS)	493 adults aged 18–65	Oral Δ9-THC (maximum 28 mg/day) plus SoC	SoC alone	QALYs	3 years	National Institute for Health Research
NICE [b], 2019	UK	Markov model (CUA)	NHS and Personal and Social Services	Chronic pain	Patients of any age with chronic pain	THC / CBD spray plus SoC	SoC alone	QALYs	Lifetime	NICE
Elliot et al, 2020*	Canada	Markov model (CUA)	Canadian public health care system	Dravet syndrome	Children aged from 5 to 18 years	Adjunctive cannabinoid oil (CanniMed 1:20 Oil) on a background of clobazam and valproate.	(1) Adjunctive stiripentol (on a background of clobazam and valproate); and (2) treatment with clobazam plus valproate alone.	QALYs	13 years	None
Flachenecker P, 2013	Germany	Markov model (CUA)	German healthcare system	MS spasticity	300 adults	Nabiximols plus SoC	SoC alone	QALYs	5 years	Laboratorios Almirall, SA
Gras A et al, 2016	UK (Wales)	Markov model (CUA)	NHS in Wales and Personal Social Services	MS spasticity	Not clearly stated	THC/CBD plus SoC	SoC alone	QALYs	30 years	Bayer plc.
Lu L et al, 2012	UK	Markov model (CUA)	UK NHS	MS spasticity	Adults with MS spasticity who did not respond adequately to oral anti-spasticity agents.	Nabiximols plus oral anti-spasticity agents	Oral anti-spasticity medicines alone	QALYs	5 years	National Institute for Health Research
Mantovani L et al, 2020	Italy	CUA based on real-world data	Italian NHS	MS spasticity	Adults patients with drug-resistant moderate-to-severe MS (n=1350)	Nabiximols treatment	No treatment	QALYs	6 months	Almirall S.p.A.

Neuberger E et al, 2020	USA	Markov decision analytic model (CUA)	US payer perspective	Lennox-Gastaut Syndrome (LGS)	A probable LGS cohort of patients aged an average age of 13 years	CBD plus SoC	SoC alone	QALYs	Lifetime	Genentech
Slof J et al, 2012	Spain	Markov model (CUA)	German and Spanish healthcare payer perspective	MS spasticity	Not clearly reported	Nabiximols plus SoC	SoC alone	QALYs	5 years	Almirall
Slof J et al, 2015	Italy	Markov model (CUA)	Italian healthcare system	MS spasticity	Not clearly reported	Nabiximols plus SoC	SoC alone	QALYs	5 years	Almirall
NICE [c], 2019	UK	Markov model (CUA)	NHS and Personal and Social Services	MS spasticity	Patients with MS spasticity who did not respond adequately to oral anti-spasticity agents.	THC / CBD spray plus SoC	SoC alone	QALYs	5 years	NICE
Tyree G et al, 2019	USA	Markov model (CUA)	U.S. health care sector perspective	Neuropathic pain	Microsimulation of 1,000,000 patients	Adjunctive smoked cannabis plus SoC	SoC alone	QALYs	1 year	National Institutes of Health

CUA: Cost Utility Analysis; NICE: National Institute for Health and Care Excellence; WTEE: Within Trial Economic Evaluation; *Doses of drugs included in the model: Cannabidiol (CBD): 12 mg/kg/day; clobazam: 12 mg/kg/day of 1 mg/ kg/day to a maximum of 40 mg/day; valproate: 60 mg/ kg/day; stiripentol: 50 mg/kg/day

Table 2. Reporting of costs and effectiveness, N=12

Author, year	Perspective	Resources and costs				Discount rate	Preference-based health outcome(s)	
		Types of cost data	Sources of cost data	Currency	Base year (conversion)		Type/measurement	Valuation
Bell S et al, 2015	NHS and Personal and Social Services	Drug cost, intervention costs (neurology consultations, management of adverse events), hospital admissions, primary and acute care services, personal care services	Case report form, expert opinion, and patient questionnaire.	Pound sterling	2010/11	3.5%	QALYs; calculated by applying an area under the curve method.	Using the EQ-5D valued based on the preferences of a community sample of people in the UK. No information on the type of EQ-5D used.
NICE [b] 2019	NHS and Personal and Social Services	Drug cost, adverse event costs, Home care and Community-based visits, Outpatient clinic visits, Hospital admissions	Drug Tarif; NHS Reference costs; Reference costs; expert assumption	Pound sterling	Not reported	3.5%	QALYs	Used utility values from a utility study that included 2,719 patients with chronic neuropathic pain
Elliot et al, 2020	Canadian public health care system	Direct costs (e.g. drug costs, health care resource use)	Provincial formularies, manufacturer's website and literature view	Canadian dollars	2019	1.5%	QALYs	Used utility values from Lennox–Gastaut syndrome, which were elicited from members of the general Canadian public by use of the EQ-5D-3L questionnaire, time trade-off, and visual analogue scale.
Flachenecker P, 2013	German healthcare system	Direct costs (drug costs, hospital visits, laboratory tests)	Literature review, Delphi panel, resource utilization study and public price tables	Not reported	Not reported	Not reported	QALYs	Utilities were derived from EQ-5D QoL data collected in nabiximols clinical trial. No information on valuation, and type of EQ-5D used.
Gras A et al, 2016	NHS in Wales and Personal Social Services	Drug cost (only for THC/CBD spray), consultation, hospital admissions, and home care costs	Survey of clinical experts, UK resource utilization study and published unit costs.	Pound sterling	2013	3.5%	QALYs	UK-weighted utility values obtained from data collected using EQ-5D questionnaire from a pivotal trial. No information on the type of EQ-5D used
Lu L et al, 2012	UK NHS	Costs associated with drugs, drug wastage, drug administration and clinical monitoring of patients.	Literature review, Expert opinions and only consisted of clinical visits. Costs were taken from NHS reference costs 2009,	Pound sterling	2009	3.5%	QALYs	Health-state utilities were estimated based on the EQ-5D utility values collected published in nabiximols clinical trial. No information on valuation, and type of EQ-5D used.
Mantovani L et al, 2020	Italian NHS	Drug costs (Nabiximols)	Ex-factory cost for a puff of Nabiximols	Euro (€)	2017	Not applied	QALYs	MS Spasticity NRS scores were transformed into utility value following the correlation between EQ-5D utility value and the NRS score based on published study.

Neuberger E et al, 2020	US payer perspective	Drug costs, inpatient admissions, emergency department, outpatient visits, and antiepileptic prescription fills	Literature review, marketScan® research databases	US dollar	2020	3.0%	QAYs	Time spent in health states were weighted by utilities based on a published utility elicitation study (a time-trade-off interviews among members of the UK general public,).
Slof J et al, 2012	German and Spanish healthcare payer perspective	Drug costs, direct medical costs (e.g. tests and monitoring) and health system-related costs (e.g., homecare workers, general practitioners).	Literature review, interviews, hospital and health insurance tariffs	Euro (€)	2010	3.5%	QALYs	Utilities for mild, moderate and severe MS spasticity were derived from data collected using the EQ-5D questionnaire in a clinical trial. No other information on valuation, and type of EQ-5D used.
Slof J et al, 2015	Italian healthcare system	Drug costs, direct medical costs (e.g. tests and monitoring) and health system-related costs (e.g., physiotherapy).	Literature review, databases, and official sources	Euro (€)	2013	3.0%	QALYs	Utilities for mild, moderate and severe MS spasticity were derived from data collected using the EQ-5D questionnaire in a clinical trial. No other information on valuation, and type of EQ-5D used.
NICE [c], 2019	NHS and Personal and Social Services	Drug acquisition costs; MS background management costs; costs of adverse events; home care visits	Literature review; NHS Drug Tarif and other and official sources	Pound sterling	Not reported	3.5%	QALYs	Health state utilities in the model were based on a published utility regression model of EQ-5D, spasticity NRS and EDSS
Tyree G et al, 2019	U.S. health care sector perspective	Drug costs	Literature review	US dollar	2017	3.0%	QALYs	Valuation not clearly stated. Health state utilities were adopted from a published study

Abbreviations: Cannabidiol, CBD; EQ-5D: EuroQoL-5 Dimension; NHS, National Health Service; NICE: National Institute for Health and Care Excellence; QALYs, Quality Adjusted Life Years; QoL: Quality of Life; THC, Tetrahydrocannabinol. **Note:** *In model-based studies, QALYs were calculated based on the utility value for each health state and the number of years spent in that health state
NRS: Numeric Rating Scale; EDSS

Table 3. Cost-effectiveness outcomes, N=12

Author, year	Perspective	Condition	Intervention	WTP used	Analysis/main findings				Author's conclusion
					Cost	QALY	ICER (reported by authors) & standardised ICER*	Sensitivity analysis	
Bell S et al, 2015	NHS and Personal and Social Services	Progressive MS	Oral Δ9-THC (maximum 28 mg/day)	Not clearly stated	Incremental cost: £30,130	Incremental QALY: 0.066	**ICER:** Not mentioned as ICER	Not reported	As intervention was not shown to be effective, a full cost-effectiveness analysis was not conducted. Overall, the intervention is not cost-effective.
NICE 2019	NHS and Personal and Social Services	Chronic pain	THC / CBD spray plus SoC	Not Reported (reference was made to NICE's WTP of £30,000	Total cost: £63,924 Incremental cost: £24,474	Total QALY: 10.606 Incremental QALY: 0.162	**ICER**: £151,431/QALY gained. **Standardised ICER:** Baseline currency year not reported	A probabilistic sensitivity analysis showed a 0% probability that THC / CBD are cost-effective even under extreme assumptions.	THC:CBD spray was found to be not cost-effective intervention for all treatment and condition specific subgroups
Elliot et al, 2020	Canadian public health care system	Dravet syndrome	Adjunctive cannabinoid oil (CanniMed 1:20 Oil) on a background of clobazam and valproate.	CAD $50,000 per QALY	Total cost: CAD $386,239	Total QALY: 15.12	**ICER**: CAD$32,399 per QALY gained. **Standardised ICER:** US$ 26378.24 per QALY gained.	When societal perspective was taken, cannabinoid oil was dominant over both stiripentol and clobazam and valproate. The interpretation of the results was insensitive to all model structural assumptions.	Adjunctive cannabinoid oil may be a cost-effective. Stiripentol was dominated by cannabinoid oil.
Flachenecker P, 2013	German healthcare system	MS Spasticity	Nabiximols plus Soc	Not Reported (reference was made to NICE's WTP of £30,000)	Incremental cost: €359,671	Incremental QALY: 32.53	**ICER**: €11,060 per QALY gained **Standardised ICER:** Baseline currency year not reported	Except for a ±20% change in the cost of Nabiximols and ±20% utility weights for mild, moderate or severe patients, ICER value was insensitive to all other variables.	Nabiximols is a cost-effective treatment option for patients with MS spasticity in Germany
Gras A et al, 2016	NHS in Wales and Personal	MS Spasticity	THC/CBD plus Soc	NICE (£30,000 per QALY)	Total cost: £102,337	Total QALY: 11.00	**ICER**: £10,891/ QALY gained.	Findings were robust to changes in parameters in sensitivity analyses, remaining cost-effective	The THC/CBD spray was found to be cost-effective for the treatment of MS

	Social Services				Incremental cost: £3,836	Incremental QALY: 0.35	**Standardised ICER:** US$ 16966.13 per QALY gained.	at a WTP of £30,000 per QALY.	spasticity, and dominant, if home carer costs were included.
Lu L et al, 2012	NHS and Personal and Social Services	MS Spasticity	Nabiximols plus oral anti-spasticity agents	NICE (£30,000 per QALY)	Total cost: £8925 Incremental cost: £7,627	Total QALY: 2.3716 Incremental QALY: 0.1548	**ICER**: £49,300 per QALY gained. **Standardised ICER:** US$ 82221.24 per QALY gained.	Findings were sensitive to the costs of Nabiximols and differences in utilities between responders and non-responders.	Nabiximols is not cost effective for MS spasticity at a WTP threshold of £30,000 per QALY.
Mantovani L et al, 2020	Italian NHS	MS Spasticity	Nabiximols treatment	NICE (£30,000 per QALY), and Italy (€60,000 per QALY)	Total cost: £1008.34 Incremental cost: 1008.34	Total QALY: 0.1744 Incremental QALY: 0.0284	**ICER**: €35,516 per QALY gained. **Standardised ICER:** US$ 48925.18 per QALY gained.	There was little variability around the central estimate of ICER, and remined cost-effective at a WTP thresholds used.	Nabiximols is a cost-effective option for patients with MS-resistant spasticity.
Neuberger E et al, 2020	US payer perspective	Lennox-Gastaut Syndrome (LGS)	CBD plus Soc	$150,000/QALY	Total cost: USD $331,400	Total QALY: 8.6	**ICER**: $451,800 per QALY gained. **Standardised ICER**: US $434825.64 per QALY gained.	Uncertainty in health state utilities was the largest contributor to uncertainty in the results.	Cannabidiol is not a cost-effective option in LGS patients at a WTP threshold of $150,000/QALY.
Slof J et al, 2012	German and Spanish healthcare payer perspective	MS Spasticity	Nabiximols plus Soc	Not reported (reference was made to NICE's WTP of £30,000)	Germany Incremental cost: €359,672	Incremental QALY: 32.07	**ICER**: €11,214 per QALY gained in Germany, and the dominant option in Spain **Standardised ICER:** US$ 17897.16 per QALY gained in Germany,	ICERs were found to be sensitive to utility data.	Nabiximols was shown to be a cost–effective for MS-related spasticity in Germany. Nabiximols may provide direct cost savings to the healthcare system in Spain.
Slof J et al, 2015	Italian healthcare system	MS Spasticity	Nabiximols plus Soc	Not reported (reference was made to NICE's WTP of £30,000)	Incremental cost: €2152	Incremental QALY: 0.433	**ICER**: €4968 per QALY gained. **Standardised ICER:** US$ 7084.46 per QALY gained.	In all scenarios analysed in the sensitivity analysis, the ICER remained below generally accepted WTP thresholds	Nabiximols is a cost–effective option for patients with MS-related spasticity in Italy.
NICE [c], 2019	NHS and Personal and Social Services	MS Spasticity	THC / CBD spray plus SoC	NICE (£30,000 per QALY)	Total cost: £32,210 Incremental cost: £1,580	Total QALY: 1.367 Incremental QALY: 0.081	**ICER:** £19,512/QALY gained **Standardised ICER:** Baseline currency year not reported	The model was sensitive to the assumptions related to treatment effects (odds ratios) and dosing of THC: CBD spray but in all scenarios analysed in the sensitivity analysis, the	THC: CBD spray is a cost–effective option for patients with MS-related spasticity in the UK.

								ICER remained in the range normally	
Tyree G et al, 2019	U.S. health care sector perspectiv e	Neuropath ic pain	Adjunctive smoked cannabis	USA ($110,000 to $300,000 per QALY)	Total cost: USD $7,007 Incremental cost: USD $610	Total QALY: 0.489 Incremental QALY: 0.013	**ICER**: $48,594 per QALY gained (second-line adjunctive cannabis). **Standardised ICER:** US$ 49689.69 per QALY gained (second-line adjunctive cannabis).	ICER was sensitive to changes in adherence threshold, mild pain state utility, and moderate-to-severe pain state utility	Cannabis appears cost-effective when augmenting second-line treatment for painful neuropathy

* Cost estimates adjusted to US$ in 2018;

Abbreviations: Cannabidiol, CBD; ICER: Incremental cost-effective ratio; MS, Multiple sclerosis; NHS, National Health Service; NICE, The National Institute for Health and Care Excellence; QALY: Quality Adjusted Life Year; SoC: standard of Care; WTP: Willingness to pay

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Supplement File:

Cost-effectiveness of medicinal cannabis for management of refractory symptoms associated with chronic conditions: A systematic review of economic evaluations

Contents

Appendix 1: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3-4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplimentary file
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3-4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5-6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Blinded title page

Appendix 2: Search strategy

Search history

Database: Ovid MEDLINE(R) <1946 to September Week 1 2020>

Search Strategy:

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1 exp Technology Assessment, Biomedical/ (11156)

2 (technology assessment* or HTA or HTAs).mp. (14197)

3 health technology assessment.jw. (1392)

4 exp "Costs and Cost Analysis"/ (238127)

5 exp Economics, Pharmaceutical/ or exp Economics, Medical/ or exp Economics, Hospital/ or exp Economics, Dental/ or exp Economics, Nursing/ (49069)

6 exp "Fees and Charges"/ (30378)

7 exp Budgets/ (13737)

8 (economic* or cost* or price* or pharmacoeconomic* or pharmaco-economic* or expenditure* or expense or financ*).ti,kf. (208870)

9 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. (133652)

10 (value adj2 (money or monetary)).ti,ab,kf. (1991)

11 exp Models, Economic/ (15137)

12 economic model*.ab,kf. (2759)

13 exp Markov Chains/ (14419)

14 markov.ti,ab,kf. (17500)

15 exp Monte Carlo Method/ (28464)

16 monte carlo.ti,ab,kf. (30607)

17 exp Decision Theory/ or exp Decision Trees/ (12104)

18 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. (19892)

19 ((healthcare or health care or resource?) adj3 (utili#ation? or utilise? or utilize? or utili#ing)).ti,ab,kf. (26924)

20 (resource? adj3 ("use" or used or uses or using)).ti,ab,kf. (24065)

21 ((utility or utili#ation) adj (study or studies)).ti,ab,kf. (1021)

22 (ICER or ICERs).ti,ab,kf. (3709)

23 exp "Value of Life"/ec [Economics] (251)

24 exp "Quality of Life"/ (196409)

25 quality of life.ti,kf. (70624)

26 exp Quality-Adjusted Life Years/ (12411)

27 quality adjusted life.ti,ab,kf. (11070)

28 disability adjusted life.ti,ab,kf. (2823)

29 (daly or dalys).ti,ab,kf. (2518)

30 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (761839)

31 marijuana smoking.mp. or exp Cannabis/tu [Therapeutic Use] (5113)

32 Cannabinoid.mp. or exp Cannabinoids/ (23677)

33 exp Cannabinoid Receptor Agonists/ (8005)

34 sativex.mp. (174)

35 nabiximols.mp. (224)

36 Dronabinol.mp. or exp Dronabinol/ (7134)

37 tetrahydrocannabinol.mp. (6419)

38 THC.mp. (6317)

39 CBD.mp. (5630)

40 nabilone.mp. (290)

41 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 (33956)

42 30 and 41 (562)

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Database: APA PsycInfo <1806 to September Week 1 2020>

Search Strategy:

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1 exp "Costs and Cost Analysis"/ (42632)

2 health technology assessment.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (352)

3 (technology assessment* or HTA or HTAs).mp. (1062)

4 economics/ or exp pharmacoeconomics/ or "costs and cost analysis"/ (38341)

5 (Fees and Charges).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (53)

6 Budgets.mp. or exp Budgets/ (3622)

7 (economic* or cost* or price* or pharmacoeconomic* or pharmaco-economic* or expenditure* or expense or financ*).mp. (297686)

8 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).mp. (37600)

9 (value adj2 (money or monetary)).mp. (1002)

10 exp Health Care Economics/ (894)

11 Markov Chains.mp. or exp Markov Chains/ (2214)

12 (decision* adj2 (tree* or analy* or model*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (13335)

13 ((healthcare or health care or resource?) adj3 (utili#ation? or utilise? or utilize? or utili#ing)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (21096)

14 (resource? adj3 ("use" or used or uses or using)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (9874)

15 ((utility or utili#ation) adj (study or studies)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (243)

16 (ICER or ICERs).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (344)

17 Quality of Life.mp. or exp "Quality of Life"/ (89333)

18 exp "Health Related Quality of Life"/ (4860)

19 (daly or dalys).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (762)

20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (421391)

21 exp Cannabis/ or exp Tetrahydrocannabinol/ (9646)

22 Cannabinoid.mp. or exp Cannabinoids/ (6484)

23 Cannabinoid Receptor Agonists.mp. (426)

24 sativex.mp. (71)

25 nabiximols.mp. (42)

26 Dronabinol.mp. (1650)

27 tetrahydrocannabinol.mp. (2521)

28 THC.mp. (2248)

29 CBD.mp. (931)

30 nabilone.mp. (84)

31 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 (14872)

32 20 and 31 (826)

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The full search key words for all databases is available upon request from the corresponding author.

Appendix 3: Included and excluded studies (full-text review)

Included studies

1. Ball S, Vickery J, Hobart J, Wright D, Green C, Shearer J, Nunn A, Cano MG, MacManus D, Miller D, Mallik S, Zajicek J. The Cannabinoid Use in Progressive Inflammatory brain Disease (CUPID) trial: a randomised double-blind placebo-controlled parallel-group multicentre trial and economic evaluation of cannabinoids to slow progression in multiple sclerosis. Health Technol Assess. 2015 Feb;19(12):vii-viii, xxv-xxxi, 1-187. doi: 10.3310/hta19120. PMID: 25676540; PMCID: PMC4781163.
2. Elliott J, McCoy B, Clifford T, Potter BK, Wells GA, Coyle D. Economic Evaluation of Cannabinoid Oil for Dravet Syndrome: A Cost-Utility Analysis. Pharmacoeconomics. 2020 Sep;38(9):971-980. doi: 10.1007/s40273-020-00923-5. PMID: 32406036.
3. Flachenecker P. A new multiple sclerosis spasticity treatment option: effect in everyday clinical practice and cost-effectiveness in Germany. Expert Rev Neurother. 2013 Feb;13(3 Suppl 1):15-9. doi: 10.1586/ern.13.1. PMID: 23369055.
4. Gras A, Broughton J. A cost-effectiveness model for the use of a cannabis-derived oromucosal spray for the treatment of spasticity in multiple sclerosis. Expert Rev Pharmacoecon Outcomes Res. 2016 Dec;16(6):771-779. doi: 10.1586/14737167.2016.1140574. Epub 2016 Feb 26. PMID: 26750641.
5. Lu L, Pearce H, Roome C, Shearer J, Lang IA, Stein K. Cost effectiveness of oromucosal cannabis-based medicine (Sativex®) for spasticity in multiple sclerosis. Pharmacoeconomics. 2012 Dec 1;30(12):1157-71. doi: 10.2165/11598470-000000000-00000. Erratum in: Pharmacoeconomics. 2015 Jun;33(6):611. PMID: 23072659.
6. Mantovani LG, Cozzolino P, Cortesi PA, Patti F; SA.FE. study group. Cost-Effectiveness Analysis of Cannabinoid Oromucosal Spray Use for the Management of Spasticity in Subjects with Multiple Sclerosis. Clin Drug Investig. 2020 Apr;40(4):319-326. doi: 10.1007/s40261-020-00895-6. PMID: 32130684.
7. Neuberger EE, Carlson JJ, Veenstra DL. Cost-Effectiveness of Cannabidiol Adjunct Therapy versus Usual Care for the Treatment of Seizures in Lennox-Gastaut Syndrome. Pharmacoeconomics. 2020 Nov;38(11):1237-1245. doi: 10.1007/s40273-020-00945-z. PMID: 32715412.
8. Slof J, Gras A. Sativex® in multiple sclerosis spasticity: a cost-effectiveness model. Expert Rev Pharmacoecon Outcomes Res. 2012 Aug;12(4):439-41. doi: 10.1586/erp.12.40. Epub 2012 Jun 8. PMID: 22681512.
9. Slof J, Ruiz L, Vila C. Cost-effectiveness of Sativex in multiple sclerosis spasticity: new data and application to Italy. Expert Rev Pharmacoecon Outcomes Res. 2015 Jun;15(3):379-91. doi: 10.1586/14737167.2015.1025759. Epub 2015 Mar 16. PMID: 25771713.
10. Tyree GA, Sarkar R, Bellows BK, et al. A Cost-Effectiveness Model for Adjunctive Smoked Cannabis in the Treatment of Chronic Neuropathic Pain. *Cannabis Cannabinoid Res*. 2019;4(1):62-72. Published 2019 Mar 13. doi:10.1089/can.2018.0027
11. NICE Guideline Updates Team (UK). Cannabis-based medicinal products: Evidence review for chronic pain. London: National Institute for Health and Care Excellence (UK); 2019 [NICE Guideline, No. 144. [B]]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK552240/.
12. NICE Guideline Updates Team (UK). Cannabis-based medicinal products: Evidence review for spasticity London: National Institute for Health and Care Excellence (UK); 2019 [NICE Guideline, No. 144.) [C]]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK552187/.

List of full text studies excluded with reason

Study	Reason for exclusion
Heather P McDonald, Nicole Mittmann and Pierre Isogai. Economic evaluation of sativex® for treatment of neuropathic pain in patients with multiple sclerosis (PND14). ISPOR 2008, Toronto, Ontario, Canada	Conference abstract
Oppe M, Ortín-Sulbarán D, Vila Silván 2, Estévez-Carrillo A, Quintero-González. Cost-utility analysis of delta-9-tetrahidrocannabinol and cannabidiol oromucosal spray. ISPOR Europe 2019, Copenhagen, Denmark	Conference abstract
Neuberger E, Veenstra DL. Cost-utility of cannabidiol in addition to background therapy versus background therapy alone in lennox-gastaut syndrome. ISPOR 2019, New Orleans, LA, USA	Conference abstract
Bellnier, T., Brown, G. W., & Ortega, T. R. (2018). Preliminary evaluation of the efficacy, safety, and costs associated with the treatment of chronic pain with medical cannabis. The mental health clinician, 8(3): 110–115.	Not full economic evaluation
Shepard KV. The cost of Marinol (dronabinol). JAMA. 1993 Dec 15;270(23):2810. PMID: 8155181.	Not full economic evaluation
Lu, L., Pearce, H., Roome, C., Shearer, J., Lang, I. A., Stein, K. (2015). Erratum to: cost effectiveness of Oromucosal cannabis-based medicine (Sativex(®)) for spasticity in multiple sclerosis. Pharmacoeconomics, 33(6):611.	Erratum
Wijnen, B., Armstrong, N., Ramaekers, B. *et al.* Cannabidiol for Adjuvant Treatment of Seizures Associated with Lennox–Gastaut Syndrome and Dravet Syndrome: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *PharmacoEconomics* **38,** 1043–1053 (2020). https://doi.org/10.1007/s40273-020-00932-4	Did not report outcome of interest
Riva N, Mora G, Sorarù G,. Safety and efficacy of nabiximols on spasticity symptoms in patients with motor neuron disease (CANALS): a multicentre, double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Neurol. 2019 Feb;18(2):155-164. doi: 10.1016/S1474-4422(18)30406-X. Epub 2018 Dec 13. PMID: 30554828.	Did not report outcome of interest
Sheridan Rains L, Marston L, Hinton M, et al. Clinical and cost-effectiveness of contingency management for cannabis use in early psychosis: the CIRCLE randomised clinical trial. BMC Med. 2019 Aug 15;17(1):161. doi: 10.1186/s12916-019-1395-5. PMID: 31412884; PMCID: PMC6694526.	Did not report outcome of interest

Appendix 4: Study-level quality assessment using the CHEERS checklist

Section	Item No	Recommendation	Lu et al 2012	Slof et al 2012	Flacheneckker et al 2013	Ball et al 2015	Slof et al 2015	Gras et al 2016	Tyree et al 2019	*NICE [b] 2019	**NICE [c] 2019	Elliott et al 2020	Neuberger et al 2020	Mantovani et al 2020
Title and abstract														
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Introduction														
Background and objectives		Provide an explicit statement of the broader context for the study.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	3	Present the study question and its relevance for health policy or practice decisions.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Methods														
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Measurement of effectiveness	11a	Single study -based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient	NA	NA	Yes	Yes	NA	NA	NA	Yes	Yes	NA	NA	Yes
	11b	Synthesis -based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Estimating resources and costs	13a	*Single study -based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to	NA	NA	NA	Yes	NA	NA	NA	NA	NA	NA	NA	Yes

		approximate to opportunity costs.												
	13b	*Model -based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
Currency, price date, and conversio n	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Choice of model	15	Describe and give reasons for the specific type of decision - analytical model used. Providing a figure to show model structure is strongly recommended.	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
Assumptio ns	16	Describe all structural or other assumptions underpinning the decision -analytical model.	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
Analytical method	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Results														

Study parameter	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost - effectiveness ratios.	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Characterising uncertainty	20a	*Single study -based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	NA	NA	NA	No	NA	NA	NA	NA	NA	NA	NA	Yes
	20b	*Model -based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost - effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	No	No	No	Yes	No	No	Yes	Yes	Yes	No	No	No
Discussion														

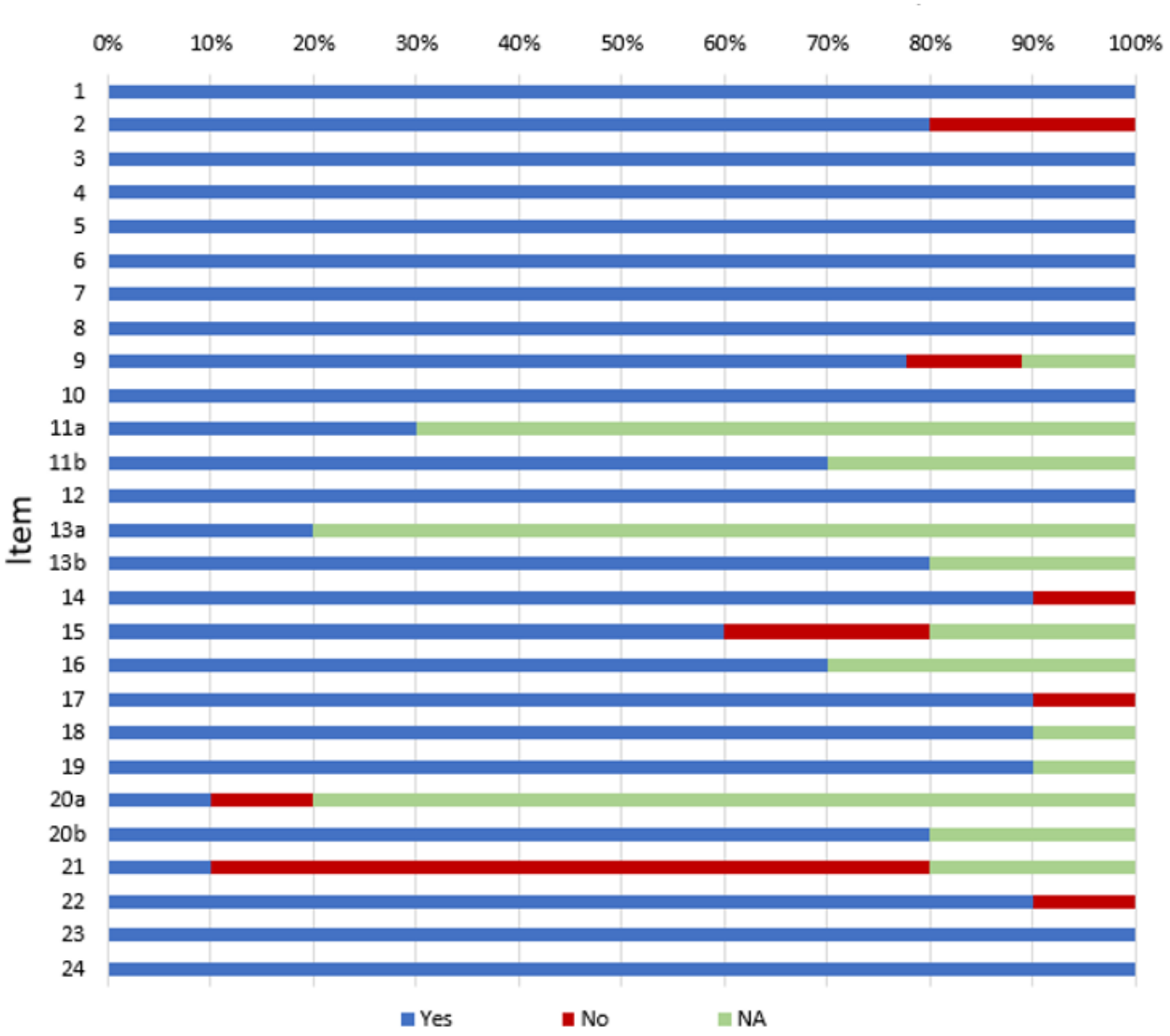
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Other														
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non - monetary sources of support	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Overall score % of reporting (Total score 24)			**95**	**94**	**70**	**94**	**90**	**95**	**100**	**95**	**95**	**95**	**96**	**95**

Note: The estimate of the score of reporting was calculated based on fulfilment of the reporting for each item. A score of 1 was given if fulfilled (Yes) and 0 if not fulfilled. The maximum possible score was 24.

Appendix 5: Quality of the included studies (figure)

Assessed by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (23 item): 1) Identified as an economic evaluation; 2) Structured abstract; 3) Clearly stated context; 4) Target population described; 5) Setting and location of decision described; 6) Perspective stated; 7) Comparators described; 8) Horizon described; 9) Discount rate stated for benefits and costs; 10) Health outcomes describe; 11) Source of effectiveness data described; 12) Measurement and valuation of preference-based outcomes described; 13) Resources and costs described; 14) Currency, price, and conversions reported; 15) Model described; 16) Assumptions described; 17) Analytical methods described; 18) Study parameters described; 19) Incremental costs and outcomes reported; 20) Uncertainty characterized; 21) Differences between subgroups described; 22) Findings, limitations, generalizability, and current knowledge described; 23) Sources of funding described; 24) Conflicts of interest stated.

Figure S1. Percent of studies that fulfilled the item criteria, N=12



Note: In this figure, “No” also included the option not “clear/can’t say”