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Systematic Literature Review

Cost-Effectiveness of Medicinal Cannabis for Management of Refractory Symptoms Associated With Chronic Conditions: A Systematic Review of Economic Evaluations

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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 with illicit growth and supply. This article 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 Consolidated Health Economic Evaluation Reporting Standards 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 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 US$451 800 per quality-adjusted life-year 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 cost-utility analysis conducted in a US 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 the Consolidated Health Economic Evaluation Reporting Standards checklist criteria.

Conclusions: 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, cost-effectiveness, economic evaluation, medicinal cannabis.

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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 suggest 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 authorizations, 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 cannabidiol (CBD) with or without tetrahydrocannabinol (THC) in various concentrations and dosage forms and include drugs such as dronabinol (a synthetic version of THC), nabilone (a synthetic THC analog), and nabiximols (a cannabis plant extract containing a roughly 1:1 ratio of THC and CBD).

Although an increasing number of patients are interested in or are using cannabis for medical reasons, the additional cost and resource utilization associated with medicinal cannabinoids should first be justified against its overall benefit to the patient, providers, and health system before introducing these drugs into specialist and primary healthcare settings. This is particularly so because 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[8] 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. Nevertheless, several CEAs have since been published for various conditions including for pediatric drug-resistant epilepsies[9,10] and neuropathic pain.[11] Therefore, the aim of this review was 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 (eg, pediatric drug-resistant epilepsy, MS spasticity, chronic pain, anorexia-cachexia, cancer-related nausea, and intractable pain in patients with advanced cancer). The findings will serve to inform the subsequent development of a within-trial and modeled economic evaluation to determine costs and benefits of prescribed medicinal cannabis for symptom control in patients with advanced cancer in Australia.

Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses 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 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 National Health Service [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 2 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 Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.04.1276.

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 the cost-effectiveness of cannabis-based medicines (eg, CBD with or without THC and synthetic THC formulations nabilone and dronabinol) as an adjunct or complementary therapy with standard treatment (both pharmacologic and non-pharmacologic treatments) for the management of intractable symptoms associated with chronic conditions (eg, advanced cancer, dementia, or chronic conditions with an intractable symptoms such as pediatric drug-resistant epilepsy, MS-associated spasticity) were included. We excluded gray literature, methodology papers, literature reviews, studies published in languages other than English, and conference or dissertation abstracts without the full text available for retrieval. Before 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 (Veritas Health Innovation Ltd), and 2 independent reviewers (D.E. and S.S.) screened all titles, abstracts, and full texts based on the eligibility criteria. Any discrepancies 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 Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.04.1276.

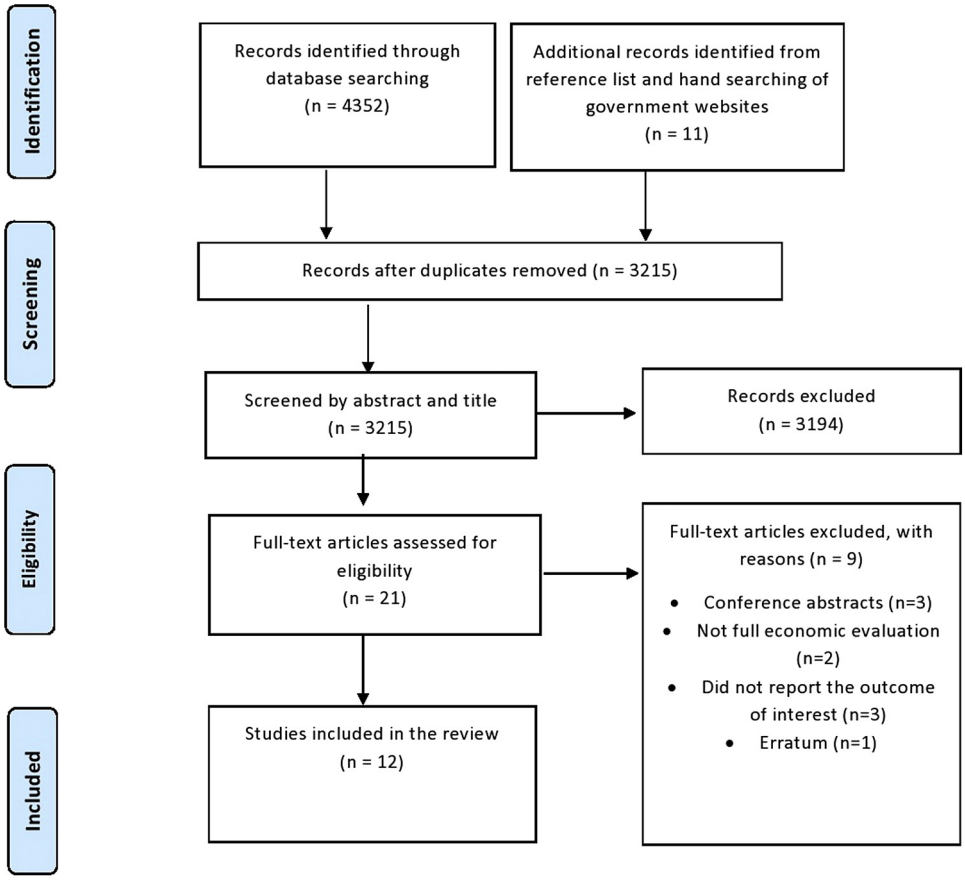
Reporting Quality of Studies

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 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 6 main categories: (1) title and abstract, (2) introduction, (3) methods, (4) results, (5) discussion, and (6) "other." Studies were scored independently by 2 of the authors (D.E. and S.S.) as having met the criteria in full (designated as "Yes" and given a score of 1), do not fulfill (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 (D.E. and S.S.) 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 2 main sections: (1) study characteristics (eg, publication details, country, study design, sample size, intervention/comparator, study perspective, analytical approach) and (2) study design and main outcomes (resource use, costs, effects, measurement, valuation methods, total and incremental quality-adjusted life-years [QALYs], incremental cost-effectiveness ratios [ICERs], uncertainty and sensitivity analyses, author's conclusions). Where possible, standardized ICER (cost estimates adjusted to US dollars in 2018) were calculated using a Cost Converter v.1.6, developed by the Campbell and Cochrane Economics Methods Group (CCEMG) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI Centre).[14] For model-based economic evaluations, details about the model structure (eg, health states, time horizon, and cycle length) and model inputs (eg, resource use and utility values) were extracted. For studies that reported probabilistic sensitivity analyses, we summarized the key model parameters reported the sensitivity analyses and their impact on the overall ICER estimate. The

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.



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 (Fig. 1). The studies were conducted between 2012 and 2020, and majority of them were from United Kingdom,[15-19] United States,[10,11] or Italy.[20,21] The characteristics of included studies are presented in Tables 1 and 2. MS-associated spasticity was the most common disease state for which cost-effectiveness of medicinal cannabis was 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 analyzed using a healthcare payer perspective. All except one studies included "standard of care (SoC)" in both intervention and comparator arms whereas the Mantovani et al[20] study 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 8 of the studies.[9-11,15-17,21,23] For the remaining studies, discounting was either not reported[22] or not applicable because the main analysis considered a time horizon of 6 months.[20]

Reporting of Costs and Effectiveness

Table 2 shows the costs included in the analyses and measurement and valuation of preference-based health outcomes. Although the types of costs included depended on the study setting and study perspectives, drug costs, direct medical costs (eg, laboratory tests and monitoring), and health system-related costs (eg, 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 (eg, 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 randomized 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]

Table 1. General characteristics of studies (N = 12).

Author, y	Country	Type of economic evaluation	Perspective	Disease or condition	Study population/ sample	Intervention	Comparators	Health outcomes	Time horizon	Funding
Ball et al,[15] 2015	United Kingdom	WTEE (CUA)	NHS and personal and social services	Progressive MS	493 adults aged 18-65 y	Oral Δ9-THC (maximum 28 mg/d) plus SoC	SoC alone	QALYs	3 y	National Institute for Health Research
NICE, 2019[18]	United Kingdom	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
Elliott et al,[9] 2020*	Canada	Markov model (CUA)	Canadian public healthcare system	Dravet syndrome	Children aged from 5 to 18 y	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 y	None
Flachenecker,[22] 2013	Germany	Markov model (CUA)	German healthcare system	MS spasticity	300 adults	Nabiximols plus SoC	SoC alone	QALYs	5 y	Laboratorios Almirall, SA
Gras and Broughton,[16] 2016	United Kingdom (Wales)	Markov model (CUA)	NHS in Wales and personal social services	MS spasticity	Not clearly stated	THC/CBD plus SoC	SoC alone	QALYs	30 y	Bayer plc.
Lu et al,[17] 2012	United Kingdom	Markov model (CUA)	United Kingdom 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 y	National Institute for Health Research
Mantovani et al,[20] 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 mo	Almirall S.p.A.
Neuberger et al,[10] 2020	United States	Markov decision analytic model (CUA)	US payer perspective	LGS	A probable LGS cohort of patients aged an average age of 13 y	CBD plus SoC	SoC alone	QALYs	Lifetime	Genentech
Slof and Gras,[23] 2012	Spain	Markov model (CUA)	German and Spanish healthcare payer perspective	MS spasticity	Not clearly reported	Nabiximols plus SoC	SoC alone	QALYs	5 y	Almirall
Slof et al,[21] 2015	Italy	Markov model (CUA)	Italian healthcare system	MS spasticity	Not clearly reported	Nabiximols plus SoC	SoC alone	QALYs	5 y	Almirall
NICE, 2019[19]	United Kingdom	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 y	NICE
Tyree et al,[11] 2019	United States	Markov model (CUA)	US healthcare sector perspective	Neuropathic pain	Microsimulation of 1 000 000 patients	Adjunctive smoked cannabis plus SoC	SoC alone	QALYs	1 y	National Institutes of Health

CBD indicates cannabidiol; CUA, cost-utility analysis; LGS, Lennox-Gastaut Syndrome; MS, multiple sclerosis; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-years; SoC, standard of care; THC, tetrahydrocannabinol; WTEE, within-trial economic evaluation.
*Doses of drugs included in the model: 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, y	Perspective	Resources and costs				Discount rate	Preference-based health outcomes	
		Types of cost data	Sources of cost data	Currency	Base year (conversion)		Type/ measurement	Valuation
Ball et al,[15] 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 United Kingdom No information on the type of EQ-5D used
NICE 2019[18]	NHS and personal and social services	Drug cost, adverse event costs, home care and community-based visits, outpatient clinic visits, hospital admissions	Drug Tariff; NHS reference costs; Reference costs; expert assumption	Pound sterling	Not reported	3.5%	QALYs	Used utility values from a utility study that included 2719 patients with chronic neuropathic pain
Elliott et al,[9] 2020	Canadian public healthcare system	Direct costs (eg, drug costs, healthcare 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 analog scale
Flachenecker[22] 2013[5]	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 and Broughton,[16] 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, United Kingdom 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 et al,[17] 2012	United Kingdom 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 et al,[20] 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 et al,[10] 2020	United States payer perspective	Drug costs, inpatient admissions, emergency department, outpatient visits, and antiepileptic prescription fills	Literature review, marketScan research databases	United States ($)	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)

continued on next page

Table 2. Continued

Author, y	Perspective	Resources and costs				Discount rate	Preference-based health outcomes	
		Types of cost data	Sources of cost data	Currency	Base year (conversion)		Type/ measurement	Valuation
Slof and Gras,[23] 2012	German and Spanish healthcare payer perspective	Drug costs, direct medical costs (eg, tests and monitoring) and health system-related costs (eg, 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 et al,[21] 2015	Italian healthcare system	Drug costs, direct medical costs (eg, tests and monitoring) and health system-related costs (eg, 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, 2019[19]	NHS and personal and social services	Drug acquisition costs; MS background management costs; costs of adverse events; home care visits	Literature review; NHS Drug tariff 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 et al,[11] 2019	United States healthcare sector perspective	Drug costs	Literature review	United States ($)	2017	3.0%	QALYs	Valuation not clearly stated. Health-state utilities were adopted from a published study

CBD indicates cannabidiol; EDSS, Expanded Disability Status Scale; LGS, Lennox-Gastaut Syndrome; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NRS, numeric rating scale; QALY, quality-adjusted life-year; QoL, quality of life; THC, tetrahydrocannabinol.
*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.[17–19,22,23]

In majority of the studies, health-state utilities were estimated from utility values provided in the literature (eg, 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]

Cost-Effectiveness Outcomes According to Disease Conditions and Drivers of ICER Estimates

Economic evaluation results are summarized in Table 3. Eleven studies reported 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 (ie, £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 because 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 US $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 6 studies conducted in Germany,[22,23] Italy,[20,21] Spain,[23] and United Kingdom[16,19] settings and not cost-effective in one study conducted in the United Kingdom setting.[17] All except one study (5 of 7 studies) that found nabiximols to be a cost-effective intervention were industry funded. The remaining 2 studies were funded by the United Kingdom government and reported conflicting conclusions (not cost-effective by Lu et al[17] study and cost-effective in a study commissioned by the United Kingdom's NICE[19]). An economic evaluation conducted alongside a clinical trial in the United Kingdom (Cannabinoid Use in Progressive inflammatory Brain Disease trial)[15] found that oral Δ9-THC (dronabinol) had significant additional costs with no improvement in health outcomes for patients with progressive MS (ie, dominated by usual care and thus not cost-effective).

Pediatric Drug-Resistant Epilepsy

A study conducted in United States[10] comparing CBD with the usual care for the management of LGS concluded that CBD is not a cost-effective option for this patient population at a WTP threshold of US $150 000/QALY (ICER $451 800 per QALY gained). On the other hand, a study from Canada (using a Canadian public healthcare 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 NICE in the United Kingdom 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 (ie, 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 United States 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] study reported the results of one-way sensitivity analyses, with some of them reporting probabilistic sensitivity analyses. Uncertainty in health-state utilities (eg, pain state utility, adverse events) was the largest contributor to uncertainty in the model outcomes in 5 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 hospitalizations.[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 RCTs 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 United Kingdom 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 Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.04.1276. 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. Although all model-based studies explicitly stated the modeling approach, none of them gave reasons for the specific type of decision-analytical model used. Among the modeling studies where the specified time horizon exceeded one year (n = 7), one study did not specify that costs and outcomes were discounted[22] whereas 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 of 10 articles.

Discussion

In this study, we sought to summarize 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 MS, DS, LGS, 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 6 of 7 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] Nevertheless, 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 United Kingdom setting found that THC/CBD spray plus SoC was £3836 more expensive and produced 0.35 more QALYs over a 30-year time horizon than SoC alone, making it cost-effective at the £20 000-£30 000 per QALY threshold. Nevertheless, the model has several limitations including (1) extrapolating short-term RCT Data from Novotna et al[4] (4 plus 12 weeks) to a 30-year model time horizon, (2) missing important parameters such as adverse events (thus favoring to the THC/CBD spray strategy), (3) relying on subjective estimates for resource use, (4) attributing all cost to spasticity alone while some of the costs might overlap with the management MS patients, and (5) 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 favor the cannabinoid strategy because 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 (1) treatment effects are likely overestimated owing to the design of the key clinical trial and (2) ICER was uncertain owing to "substantial structural issues and unrealistic assumptions" in the economic model.[25]

A study conducted in a US 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 United Kingdom 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 (eg, adverse event disutility), and lack of

Table 3. Cost-effectiveness outcomes (N = 12).

Author, y	Perspective	Condition	Intervention	WTP used	Analysis/main findings				Author's conclusion
					Cost	QALY	ICER (reported by authors) and standardized ICER*	Sensitivity analysis	
Ball et al,[15] 2015	NHS and Personal and Social Services	Progressive MS	Oral Δ9-THC (maximum 28 mg/d)	Not clearly stated	Incremental cost: £30 130	Incremental QALY: 0.066	ICER: Not mentioned as ICER	Not reported	Because intervention was not shown to be effective, a full cost-effectiveness analysis was not conducted. Overall, the intervention is not cost-effective.
NICE 2019[18]	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. Standardized 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
Elliott et al,[9] 2020	Canadian public healthcare 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. Standardized ICER: US$26 378.24 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[22] 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 Standardized 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 and Broughton[16] 2016	NHS in Wales and Personal Social Services	MS Spasticity	THC/CBD plus SoC	NICE (£30 000 per QALY)	Total cost: £102 337 Incremental cost: £3836	Total QALY: 11.00 Incremental QALY: 0.35	ICER: £10 891/QALY gained. Standardized ICER: US$16 966. 13 per QALY gained	Findings were robust to changes in parameters in sensitivity analyses, remaining cost-effective at a WTP of £30 000 per QALY.	The THC/CBD spray was found to be cost-effective for the treatment of MS spasticity, and dominant, if home carer costs were included.
Lu et al,[17] 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: £7627	Total QALY: 2.3716 Incremental QALY: 0.1548	ICER: £49 300 per QALY gained. Standardized ICER: US$82 221.24 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 et al,[20] 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. Standardized ICER: US$48 925.18 per QALY gained	There was little variability around the central estimate of ICER, and remained cost-effective at a WTP thresholds used.	Nabiximols is a cost-effective option for patients with MS-resistant spasticity.
Neuberger et al,[10] 2020	United States payer perspective	LGS	CBD plus SoC	$150 000/QALY	Total cost: US $331 400	Total QALY: 8.6	ICER: $451 800 per QALY gained. Standardized ICER: US $434 825.64 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 and Gras,[23] 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 Standardized ICER: US$17 897.16 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.

continued on next page

Table 3. Continued

Author, y	Perspective	Condition	Intervention	WTP used	Analysis/main findings				Author's conclusion
					Cost	QALY	ICER (reported by authors) and standardized ICER*	Sensitivity analysis	
Slof et al,[21] 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 Standardized ICER: US$7084.46 per QALY gained	In all scenarios analyzed 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, 2019[19]	NHS and Personal and Social Services	MS Spasticity	THC/CBD spray plus SoC	NICE (£30 000 per QALY)	Total cost: £32 210 Incremental cost: £1580	Total QALY: 1.367 Incremental QALY: 0.081	ICER: £19 512/QALY gained Standardized 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 ICER remained in the range normally	THC: CBD spray is a cost-effective option for patients with MS-related spasticity in the UK.
Tyree et al,[11] 2019	US healthcare sector perspective	Neuropathic pain	Adjunctive smoked cannabis	United States ($110 000 to $300 000 per QALY)	Total cost: US$7007 Incremental cost: US$610	Total QALY: 0.489 Incremental QALY: 0.013	ICER: $48 594 per QALY gained (second-line adjunctive cannabis) Standardized ICER: US$49 689.69 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

CBD indicates cannabidiol; ICER, incremental cost-effective ratio; MS, multiple sclerosis; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-year; SoC, standard of care; THC, tetrahydrocannabinol; WTP, willingness to pay.
*Cost estimates adjusted to US dollar in 2018

robust estimates of costs and resource use and reliance on expert opinion in the model have direct influence on the ICER estimate. Nevertheless, 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 article reported findings from a trial based CUA of THC/CBD spray plus SoC compared with 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. Nevertheless, it was difficult to critically examine the analysis because 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. Although 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 United States 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 United States (US$110 000-$300 000 per QALY) and Canada (CAD$50 000 per QALY gained). After the recent registration of Epidyolex, a CBD product, for use as adjunctive therapy of seizures associated with LGS or DS on the Australian Register of Therapeutic Goods as an orphan drug, it was listed on the Pharmaceutical Benefits Scheme (PBS) on 1 May 2021 for Dravet syndrome, making it the first medicinal cannabis product to be listed on the PBS.

The main shortcomings in publication quality as assessed by the CHEERS checklist were a lack of reasoning for the type of decision analytic model used and a 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 because 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.[27] Productivity losses in patients with MS can also be substantial because it predominantly affects adults of working age (diagnosed between the ages of 20 and 45 years).[28] Nevertheless, 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[29] with a direct implication on the validity of ICER estimate. Similarly, 4 of the 6 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 SoC. The inclusion criteria specified that patients had spasticity values ≥4

in the 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[16] calculated the transition probabilities from this RCT, nor was it 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.[30] In such situations where the evidence base is contentious and uncertain, using selected RCTs for deriving treatment effects 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[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 the United Kingdom's NICE[19] which have used 4 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 United Kingdom'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- or under-estimation of clinical benefits (ie, 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 trial with longer-term follow-up of participants to ascertain the role of medicinal cannabis in medical conditions where there is no or insufficient evidence. It is important that these clinical trials include measures of various utility-based health-related quality of life measures which are important to estimate benefit in terms of QALYs. In Australia, more than 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

Although we have employed rigorous and standard approaches to summarize 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 (eg, conference abstracts), which may have limited our study findings. The inherent subjectivity of assessing the quality of reporting of economic evaluations[31] 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. Because 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 has 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, DS, 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 to inform clinical practice and assist in resource allocation or public reimbursement decisions.

Supplemental Materials

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