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ORIGINAL RESEARCH

Cost-Effectiveness of Medical Cannabis Versus Opioids for Chronic Noncancer Pain

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Abstract

Background: Chronic noncancer pain (CNCP) affects one in five adults and is commonly managed with long-term opioid therapy. Concerns regarding rare but catastrophic harms associated with opioids, including overdose and death, have generated interest in alternatives including cannabis; however, the comparative cost-effectiveness of these management options is uncertain.

Methods: We used findings from a network meta-analysis of 90 randomized trials to develop a 1-year microsimulation model to compare costs and quality-adjusted life years (QALY) between oral medical cannabis and opioids for CNCP. We used a publicly funded health care payer perspective for our analyses and obtained cost and utility data from publicly available sources. All costs are reported in 2023 Canadian dollars. All analyses were probabilistic, and we conducted sensitivity and scenario analyses to assess robustness.

Results: Total mean annual cost per patient was $1,980 for oral medical cannabis and $1,851 for opioids, a difference of $129 (95% confidence interval [CI]: −$723 to $525). Mean QALYs were 0.582 for both oral medical cannabis and opioids (95% CI: −0.007 to 0.015). Cost-effectiveness acceptability curves showed that oral medical cannabis was cost-effective in 31% of iterations at willingness-to-pay thresholds up to $50,000/QALY gained. Use of opioids is associated with nonfatal and fatal overdose, whereas medical cannabis is not.

Discussion: Our findings suggest that medical cannabis as an alternative to opioids for chronic pain may confer similar, but modest, benefits to patients, and reduce the risk of opioid overdose without substantially increasing costs.

Keywords: cost-effectiveness; medical cannabis; opioids; chronic noncancer pain

Introduction

Chronic noncancer pain (CNCP) impacts 20% of the global population and is associated with reduced quality of life and considerable socioeconomic burden.[1–4] Opioids are commonly used to manage chronic pain but are associated with important harms including addiction, overdose, and death.[5–7] Since 2016, more than 30,000 people have died from opioid-related causes in Canada, with an estimated one in three possessing an active opioid prescription at the time of death.[8,9] Efforts to reduce harms of opioids have led to interest in alternatives for chronic pain, including cannabis.[10] Medical use of cannabis is legal in Canada, as well as in 38 states and the District of Columbia in the United States[11]; chronic pain is the qualifying condition for 62% of medical cannabis license holders in the United States.[12]

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While some clinical practice guidelines and position statements recommend against medical cannabis and chronic pain,[13,14] others provide conditional recommendations in favor of noninhaled cannabis when standard care proves insufficient.[15–17] In a network meta-analysis (NMA) of 90 randomized controlled trials (RCTs) enrolling a total of 22,028 patients, moderate-to-low certainty evidence showed that medical cannabis was similarly effective and resulted in fewer discontinuations than opioids for the management of CNCP.[18] We evaluated the cost-effectiveness of medical cannabis versus opioids for the management of CNCP to determine if medical cannabis should be reimbursed by Canadian publicly funded drug plans.

Methods

Overview

We constructed a 1-year microsimulation model with three pain severity states (mild, moderate, or severe) to compare the incremental costs and quality-adjusted life years (QALYs) associated with medical cannabis and opioids for the management of CNCP from the perspective of a Canadian publicly funded drug program. We followed Canadian and international guidelines for economic evaluations.[19–21] Sensitivity and scenario analyses were conducted to evaluate changes in key inputs and assumptions. All analyses were probabilistic, and we developed our model using TreeAge Pro 2024, R2.0 (TreeAge Software, Inc, Williamstown, MA).

Model structure

Patients with moderate-to-severe chronic pain (i.e., a pain score ≥4 on a 10 cm visual analogue scale [VAS][22,23]) entered the model and received either medical cannabis or opioids. We chose a cycle length of 3 months as this corresponds to the median duration of trials used in the NMA comparing medical cannabis to opioids.[18] During each cycle, a proportion of patients experienced a fatal overdose (opioids arm only) or died from natural causes while the remaining patients could be adherent or nonadherent to treatment. Adherent patients could either continue treatment, discontinue treatment due to adverse events, or experience a nonfatal overdose. For patient's adherent to therapy, a pain score was calculated at the end of each cycle based on the effectiveness of each treatment (see below for more information) which determined the patient's pain severity level (<4 for mild, ≥4 to <7 for moderate, ≥7 for severe on a 10 cm VAS).

Patients with pain scores <4 at the end of the 3-month cycle were classified as experiencing adequate pain relief (transition to a mild pain state) and received the same treatment in the next cycle. Patients with pain scores ≥4 remained in moderate or severe pain and could discontinue treatment, rotate (i.e., switch to a different product), or increase/decrease their dose in the next cycle. Patients who transitioned to mild pain could experience a pain score increase in subsequent cycles and move to moderate or severe pain. Patients who experienced adverse events either discontinued treatment, rotated their drug, or reduced their dose and maintained their starting pain score. Nonadherent patients were considered unresponsive to therapy and did not receive treatment in subsequent cycles. Patients who discontinued treatment or experienced a nonfatal overdose were considered to have had inadequate pain relief (i.e., Fig. 1).

Model inputs

Baseline characteristics. In microsimulation models, patients with different baseline characteristics randomly drawn from distributions entered the model one at a time. Baseline model inputs and distributions are described in Table 1. Baseline age was randomly selected from a normal distribution based on the median of the mean age (58.2) of participants enrolled in the 90 trials contributing to the NMA of cannabis vs. opioids for chronic pain.[18] Starting pain scores were drawn using a program evaluation review technique distribution based on a minimum of 4, a most likely value of 6.05 (i.e., median of the mean), and a maximum of 7.83 (on a 10 cm VAS), derived from baseline pain scores from patients enrolled in RCTs included in the source NMA.[18] A uniform distribution was assigned for sex. The percentages of patients starting on low (<50 mg morphine milligram equivalent ([MME]), medium (50–89 mg MME), high (90–199 mg MME), and very high (≥200 mg MME) opioid dosages were based on Canadian Institute for Health Information (CIHI) prescription data from community pharmacies.[24] Consensus recommendations on medical cannabis for chronic pain recommend initiating most patients on a low cannabidiol (CBD) dose (5 mg twice daily) and titrating to 40 mg per day before adding

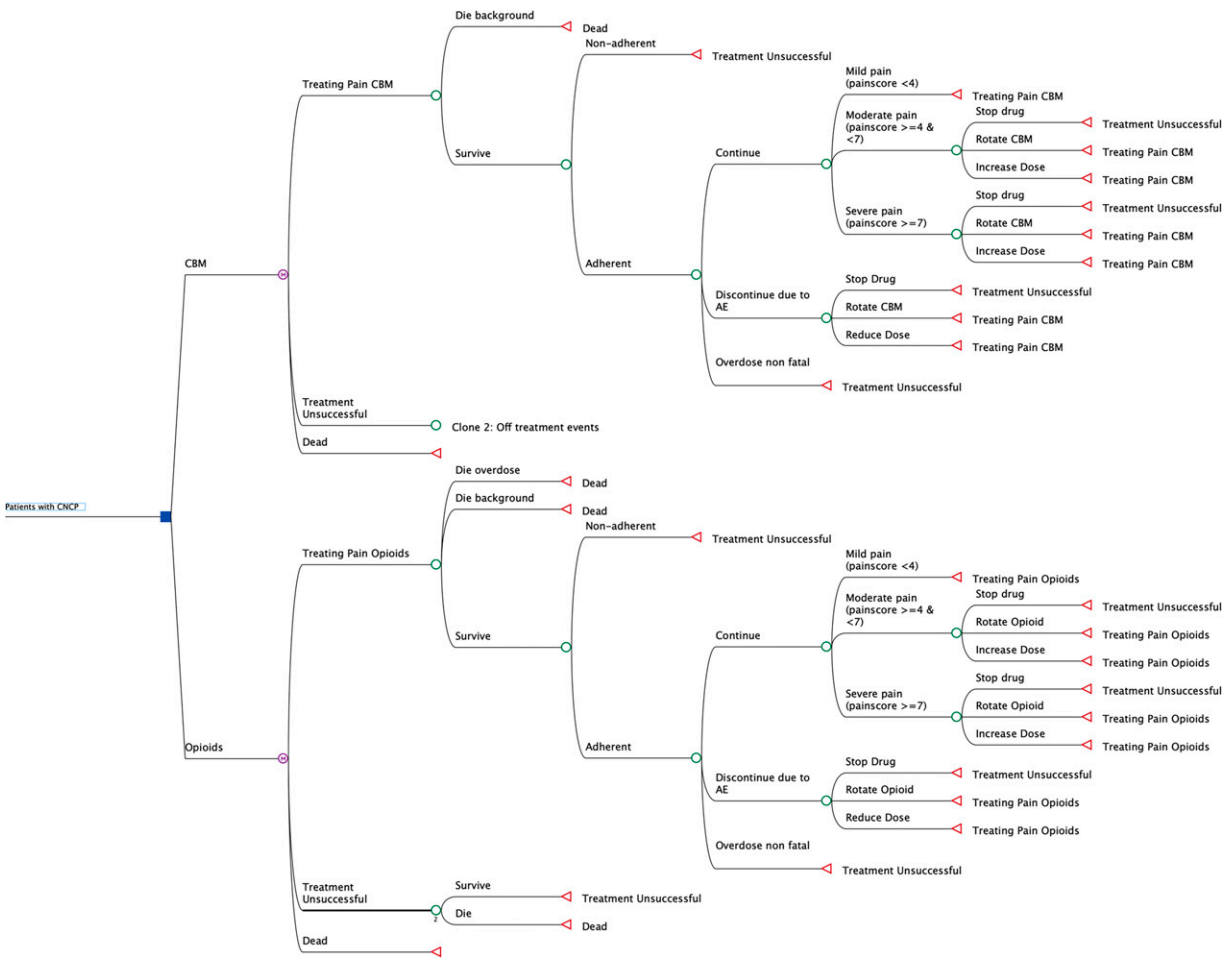

FIG. 1. Model structure (one out of four 3-month cycles). To deal with the uncertainty associated with the model inputs as recommended in Canada, all analyses are run probabilistically using the Monte Carlo method with 10,000 patients and 1000 samples.[19] For each intervention, the Monte Carlo simulation involves rerunning the model with random values drawn from probability distributions for each input parameter as per Table 1. Each input set and corresponding costs and outcomes are referred to as a sample or replication. When repeated 1000 times, costs and outcomes are estimated based on the mean values from all 1000 samples.

tetrahydrocannabinol (THC), and a rapid protocol initiating patients with more severe pain on a balanced THC:CBD regimen (2.5–5 mg) titrated up to 40 mg THC.[25] However, CBD alone may be less effective or ineffective versus cannabis products containing THC for chronic pain.[18,37] Our base-case analysis, therefore, followed the expedited protocol where patients initiated a cannabis product with balanced THC:CBD. Dirichlet distributions, the multivariate equivalent of the beta distribution,[38] were used for distributions of starting opioid and cannabis doses.

Clinical, utility, and cost data. We assumed 80% adherence to treatment based on studies evaluating pharmacologic management of CNCP.[26,27] Pain score reduction and discontinuation due to adverse events were derived from the NMA of opioids versus cannabis for chronic pain.[18] We assumed that patients achieved the maximum possible pain reduction by the end of two 3-month cycles and did not have additional pain, lowering reduction in subsequent cycles. Inputs for fatal and nonfatal overdose for each opioid MME dose were derived from a meta-analysis of

Table 1. Model Parameters and Inputs

Parameter	Mean	Probability distribution	Source
Baseline characteristics			
Age	58	Normal (mean 58.2; SD 10.6)	Jeddi et al.[18]
Sex	—	Uniform (min 1: max 2)	
Starting pain score	6.05	PERT[a] (min 4; likeliest 6.05; max 7.8)	Jeddi et al.[18]
Starting opioid MME dosages			
• Low (<50 MME) 75%	5–75%	Dirichlet (alpha 75%; 12; 8%; 5%)	CIHI[24]
• Medium (50–89 MME) 12%			
• High (90–199 MME) 8%			
• Very high (200+ MME) 5%			
Starting medical cannabis dosages			
• THC and CBD (≤40 mg/day THC and ≤40 mg/day CBD) 100% (base-case analysis)	0–100%	Dirichlet (alpha 100%; 0%; 0%)	Bhaskar et al.[25]
• Low CBD (<15 mg/day CBD) 0% (sensitivity analysis)			
• Usual CBD (≤40 mg/day CBD) 0% (sensitivity analysis)			
Adherence, probability	80%	Triangular (min 50%; likeliest; 80%; max 100%)	Bellows et al.[26,27]
Clinical data			
Pain score reduction			
Opioids	0.83	Normal (mean 0.83; SD 0.07)	Jeddi et al.[18]
Medical cannabis	0.60	Normal (mean 0.60; SD 0.14)	Jeddi et al.[18]
Discontinuations due to adverse events probability			
Opioids	24.60%	Beta (alpha 114; beta 349)	Jeddi et al.[18]
Medical cannabis	11.99%	Beta (alpha 126; beta 928)	Jeddi et al.[18]
Nonfatal overdose probability			
Low (<50 MME)	0.28%	Beta (alpha 782; beta 278,433)	Wang et al.[28]
Medium (50–89 MME)	0.54%	Beta (alpha 45; beta 8346)	Wang et al.[28]
High (90–199 MME)	0.99%	Beta (alpha 22; beta 2200)	Wang et al.[28]
Very high (200+ MME)	2.87%	Beta (alpha 7; beta 231)	Wang et al.[28]
Medical cannabis	0%		
Fatal overdose probability			
Low (<50 MME)	0.14%	Beta (alpha 196; beta 139,607)	Wang et al.[28]
Medium (50–89 MME)	0.27%	Beta (alpha 45; beta 16,783)	Wang et al.[28]
High (90–199 MME)	0.50%	Beta (alpha 21; beta 4090)	Wang et al.[28]
Very high (200+ MME)	1.44%	Beta (alpha 7; beta 479)	Wang et al.[28]
Medical cannabis	0%	—	
Utility data			
Mild pain	0.72	Beta (alpha 1451; beta 564)	Hogan et al.[29]
Moderate pain	0.59	Beta (alpha 1427; beta 991)	Hogan et al.[29]
Severe pain	0.35	Beta (alpha 796; beta 1478)	Hogan et al.[29]
Utility decrements, mean ± 20%			
Nonfatal overdose	0.12	Beta (alpha 127; beta 928)	Bellows et al.[26,30]
Cost data			
Opioid drug cost per month			
Low (<50 MME)	$47.87	Gamma (alpha 441; lambda 9)	Ontario Drug Benefit Formulary[31] and PMPRB[32]
Medium (50–89 MME)	$68.39	Gamma (alpha 440; lambda 3)	Ontario Drug Benefit Formulary[31] and PMPRB[32]
High (90–199 MME)	$141.61	Gamma (alpha 439; lambda 2)	Ontario Drug Benefit Formulary[31] and PMPRB[32]
Very high (200+ MME)	$195.37	Gamma (alpha 439; lambda 4)	Ontario Drug Benefit Formulary[31] and PMPRB[32]
Medical cannabis cost per month			
THC and CBD (≤40 mg/day THC and ≤40 mg/day CBD) (base-case analysis)	$123.90	Gamma (alpha 440; lambda 4)	Various[b]
Low CBD (<15 mg/day CBD) (sensitivity analysis)	$48.91	Gamma (alpha 441; lambda 9)	Various[b]
Usual CBD (≤40 mg/day CBD) (sensitivity analysis)	$60.14	Gamma (alpha 439; lambda 7)	Various[b]

(*continued*)

Table 1. Continued

Parameter	Mean	Probability distribution	Source
Physician office visit	$38.35	Gamma (alpha 439; lambda 11)	Physician fee schedule[33]
Mild pain cost/quarter	$182	Gamma (alpha 5; lambda 0.3)	Hogan et al.[34]
Moderate pain cost/quarter	$503	Gamma (alpha 154; lambda 0.3)	Hogan et al.[34]
Severe pain cost/quarter	$1,213	Gamma (alpha 112; lambda 0.09)	Hogan et al.[34]
Nonfatal overdose cost/event	$3,744	Gamma (alpha 439; lambda 0.12)	Cipriano and Zaric[35]
Fatal overdose cost/event	$9,492	Gamma (alpha 439; lambda 0.05)	Cipriano and Zaric[35]
Death due to natural cause	$14,905	Gamma (alpha 439; lambda 0.03)	Fassbender et al.[36]

[a]PERT distributions are special cases of beta distributions and useful when a variable can take on a minimum (4), most likely (6.05), and maximum (7.93) value as observed in the NMA.[18]

[b]Drug costs for medical cannabis were derived using average prices from three legal sources: (1) two popular storefront chains in Ontario (Spiritleaf [https://spiritleaf.ca/] and CANNA Cabana [https://cannacabana.com/]); (2) three licensed medical cannabis producers (e.g., AURORA™ [https://www.auroramedical.com], Emblem Cannabis [https://emblemcannabis.com], and Spectrum Therapeutics™ [https://www.spectrumtherapeutics.com]); and (3) the Ontario Cannabis Store (OCS; https://ocs.ca/) for online purchases.

CBD, cannabidiol, CIHI, Canadian Institute for Health Information; MME, morphine milligram equivalent; SD, standard deviation; THC, tetrahydrocannabinol.

observational studies.[28] We assumed a risk of zero for medical cannabis for fatal and nonfatal overdose based on a systematic review of 39 observational studies of 12,143 adult patients consuming cannabis for chronic pain that reported no occurrence of overdose.[39] Age- and sex-specific mortality rates were derived from Canadian life tables.[40] Utilities for each pain state were sourced from a Canadian study utilizing the Health Utilities Index Mark-3 instrument.[29] Patients experiencing a nonfatal overdose were assumed to have a utility decrement equivalent to a myocardial infarction.[26,30,41] Normal or beta distributions were assigned to clinical and utility model inputs, respectively (Table 1). Transition probabilities for patients stopping, rotating, or increasing/decreasing their initial treatment were based on input from four physicians with expertise in the use of cannabis and opioids for chronic pain (Table 2).

Drug costs for each opioid MME dose were based on prices from the Ontario Drug Benefit Formulary weighted by market shares of opioid brands.[31,32] The cost of 49 mg MME was used to represent the higher end of a low opioid dose (<50 MME), 70 mg to represent the midpoint of a medium dose (50–89 MME), 145 mg to represent the midpoint of a high dose (high 90–199 MME), and 200 mg to represent a very-high dose (≥200 mg MME). Drug costs for medical cannabis were derived using average prices from three legal sources: (1) two popular storefront chains in Ontario (Spiritleaf [https://spiritleaf.ca/] and CANNA Cabana [https://cannacabana.com/]); (2) three licensed medical cannabis producers (e.g., AURORA™ [https://www.auroramedical.com], Emblem Cannabis [https://emblemcannabis.com], and Spectrum Therapeutics™ [https://www.spectrumtherapeutics.com]); and (3) the Ontario Cannabis Store (OCS; https://ocs.ca/) for online purchases. Combined, these sources represent where medical cannabis is purchased by 73% of users.[42] For the base-case analysis, capsule formulations of cannabis were used because they are recommended over inhaled formulations due to their longer duration of action, dosing accuracy, and avoidance of pulmonary harms.[17] The cost of 20 mg THC and 20 mg CBD was used to represent the midpoint of THC:CBD products.

The cost for a physician visit was based on the cost of a reassessment from the Ontario Physician Fee Schedule.[33] Each patient was assumed to have a physician visit if they continued to experience moderate or severe pain, made a change to their treatment (e.g., rotate or change dose), or discontinued due to an adverse event. Costs for mild, moderate, and severe pain states were based on incremental direct medical costs borne by a government payer from a matched cohort study (i.e., 19,138 individuals with chronic pain matched with 19,138 individuals without pain) using health care administrative data from Ontario from 1999 to 2011.[34] Costs for nonfatal and fatal overdose were based on hospitalization and physician costs from a Canadian cost-effectiveness study of naloxone.[35] The cost of all-cause mortality was based on health care costs for sudden death from health care utilization data from Alberta.[36] Gamma distributions were assigned to unit costs (Table 2). When necessary (e.g., 2020 unit costs), the health care component of the Consumer Price Index was used to inflate costs to 2023 values.[43]

Base-case analyses. The base-case analysis was run probabilistically using the Monte Carlo method with

Table 2. Transition Probabilities for Stopping, Rotating, and Increasing or Decreasing Starting Dosages for Medical Cannabis and Opioids

	Medical cannabis dosages			Opioid MME dosages			
	THC and CBD (≤40 mg/day THC and ≤40 mg/day CBD) (base-case analysis)	Low CBD: <15mg/day CBD (sensitivity analysis)	Usual CBD: ≤40 mg/day CBD (sensitivity analysis)	Low: <50 MME/day	Medium: 50–89 MME/day	High: 90–199 MME/day	Very high: ≤200 MME/day
Probabilities for stopping, rotating, and decreasing starting dosages after discontinuing due to adverse events (informed by clinical experts)							
Stop product	31%	18%	20%	12%	16%	21%	43%
Rotate product[a]	43%	82%	69%	88%	55%	50%	34%
Reduce dose	26%	0%	11%	0%	29%	29%	23%
Probabilities for stopping, rotating, and increasing starting dosages for patients continuing treatment and experiencing moderate or severe pain (informed by clinical experts)							
Stop product[b]	25%	1%	9%	0%	20%	30%	54%
Rotate product[a]	75%	13%	20%	20%	40%	69%	46%
Increase dose	0%	86%	71%	80%	40%	2%	0%

All probabilities are based on mean percentages provided independently by four medical experts.
[a]Patients who rotate treatment were assumed to maintain their initial dose but switch to a different formulation/product (e.g., switch from a medium MME oxycodone dose to a medium tramadol dose).
[b]Stop product reflects the pathway where patients continue treatment, do not achieve mild pain, and discontinue treatment due to inadequate pain relief.
CBD, cannabidiol: MME, morphine milligram equivalent; SD, standard deviation; THC, tetrahydrocannabinol.

10,000 patients and 1000 samples to determine the 1-year expected costs and QALYs associated with medical cannabis compared with opioids. Other effectiveness measures included pain score reductions, time (i.e., cycles) spent in pain states, discontinuations due to adverse events, nonfatal overdoses, and deaths. Confidence intervals (CIs) for all outcomes were derived by ranking the 1000 samples from the probabilistic analyses and using the 25th and 975th values as boundaries of the 95% CI.[44] Parameter uncertainty was represented by cost-effectiveness acceptability curves showing the probability of medical cannabis being cost-effective at different willingness-to-pay thresholds.[45]

Sensitivity and scenario analyses. We used probabilistic one-way and scenario analyses to evaluate the impact of key model inputs and assumptions on our results. In one-way sensitivity analyses, the following parameter changes were evaluated: (1) 6-month and 2-year time horizons, (2) 90% and 100% treatment adherence, (3) varying the cost per month of opioids and cannabis by ±25%, (4) varying the source of cannabis purchases from licensed producers, (5) varying the type of cannabis purchased (e.g., flower and oils), (6) varying cost of death due to natural cause by ±25%, (7) changes to opioid dosages, (8) starting patients on CBD consistent with consensus recommendations for chronic pain,[25] (9) increasing risk of nonfatal overdose for cannabis to 50% of the modeled risks for opioids, and (10) no differences in transition probabilities for stopping, rotating, or increasing/decreasing initial treatments between medical cannabis and opioids. In scenario analyses, three opioid-sparing scenarios were evaluated: (1) patients on a medium MME dose switching to cannabis versus increasing to a high MME dose, (2) patients on a medium MME dose adding cannabis versus increasing to a high MME dose, and (3) patients on a high MME dose decreasing their opioid dose and adding cannabis versus increasing to a very-high MME dose. Due to the lack of effectiveness data, these scenario analyses only considered increased costs associated with the combinations and do not consider interactions between cannabis and opioids.

Results

Base-case cost-effectiveness analysis

Total mean annual cost per patient was $1,980 for medical cannabis and $1,851 for opioids, resulting in a nonstatistically significant difference of $129 (95% CI: −$723 to $525). Over a 1-year time horizon,

medical cannabis and opioids generated the same amount of QALYs (0.582 QALYs in each arm for a difference of 0.000, 95% CI: −0.007 to 0.015) (Table 3). There is a 29% probability that medical cannabis can provide an incremental benefit and savings compared with opioids (Fig. 2).

Sensitivity and scenario analyses

Sensitivity analyses were consistent with the base-case results, except when the starting cannabis dosage consisted of CBD, which represents less drug costs for cannabis compared with the base-case. In scenario analyses, switching to medical cannabis or adding medical cannabis to opioids was found to be cost-effective versus increasing the dose of opioids in >99% of iterations (Table 4).

Discussion

Compared with opioids, medical cannabis resulted in fewer nonfatal and fatal overdoses while generating similar QALYs at a slightly higher cost, although differences in costs were not statistically significant. A systematic review of economic evaluations of medical cannabis for refractory symptoms associated with chronic conditions identified eight cost-utility studies in multiple sclerosis (MS) and two in chronic pain.[47] Results of these studies showed that the incremental cost per QALY gained of medical cannabis compared with standard of care was less than $50,000/QALY gained in five studies, between $50,000/QALY and $100,000/QALY gained in three studies, and greater than $100,000/QALY gained in two studies.[47]

When compared with these evaluations, this microsimulation is the first economic evaluation comparing medical cannabis to opioids for the management of CNCP. A strength of our study is that most clinical inputs were informed by an NMA of 90 RCTs that pooled treatment effects across medical cannabis or cannabinoids and different opioids.[18] Pooled treatment effects were used because treatment effects for chronic pain have been shown to be similar across medical cannabis and different opioids.[37,48] In comparison, a cost-utility analysis comparing cannabis to various treatment options, including opioids, for chronic knee pain from a Canadian payer perspective over a 1-year time horizon reported that medical cannabis in capsules and oils was a dominant strategy.[49] That study used lower dosages for cannabis versus ours, and noncomparative clinical data. We also evaluated several outcomes beyond QALYs, including duration of pain severity states and dose-dependent opioid harms for nonfatal and fatal overdose, while permitting dosing changes. Further, our microsimulation approach is more reflective of real-world outcomes as patients with different baseline characteristics entered the model one at the time and were randomly transitioned through the model to generate individual outcomes as opposed to modeling a homogeneous cohort of individuals.[50]

Our study also has several limitations. First, trials included in the NMA of opioids versus cannabis for

Table 3. Base-Case Probabilistic Results

	Medical cannabis	Opioids	Difference
Outcomes	Mean (95% CI)	Mean (95% CI)	(Medical cannabis–opioids)
Direct costs, year			
Medication	$776 ($607; $971)	$600 $354; $972)	$176 (–$161; $368)
Physician services	$53 ($33; $76)	$50 ($30; $75)	$3 ($4; $32)
Nonfatal overdose	$0	$54 ($17; $172)	–$54 (–$172; –$17)
Death	$125 ($97; $156)	$209 ($145; $379)	-$84 (–$255; –$24)
Pain state (mild, moderate, severe)	$1,026 ($747; $1,316)	$938 ($506; $1,344)	$88 (–$590; –$32)
Total costs	$1,980 ($1,818; $2,166)	$1,851 ($1,407; $2,698)	$129 (–$723; 525)
QALYs	0.582 (0.564; 0.600)	0.582 (0.560; 0.603)	0.000 (–0.007; 0.015)
Pain score reduction	0.29 (0.08; 0.61)	0.41 (0.08; 0.99)	–0.12 (–0.41; 0.16)
Time in pain state (cycles)			
Mild pain	0.14 (0.06; 0.23)	0.26 (0.10; 0.48)	–0.12 (–0.27; –0.01)
Moderate pain	3.68 (3.61; 3.73)	3.54 (3.36; 3.66)	0.14 (0.07; 0.26)
Severe pain	0.17 (0.15; 0.20)	0.17 (0.13; 0.21)	0.00 (–0.03; 0.02)
Discontinuations due to adverse events	18.18% (10.39%; 27.7%)	37.66% (21.52%; 59.19%)	–19.48% (–34.57%; –7.29%)
Nonfatal overdoses	0	1.44% (0.46%; 4.56%)	–1.44% (–4.56%; –0.46%)
Deaths	0.84% (0.67%; 1.02%)	1.78% (1.14%; 3.66%)	–0.94% (–2.77%; –0.32%)
Probability cost-effective, $50,000/QALY willingness to pay[46]			31%

CI, confidence interval; QALY, quality-adjusted life years.

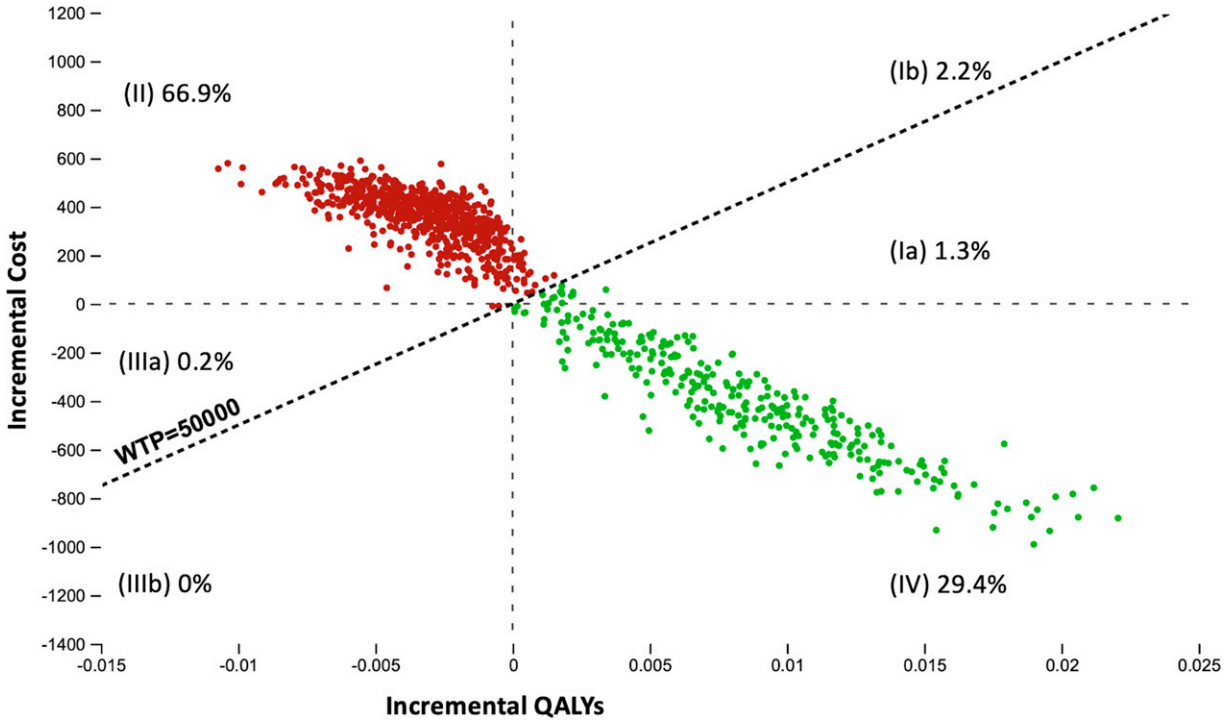

FIG. 2. Incremental cost-effectiveness scatterplot—medical cannabis versus opioids. Medical cannabis was more effective and less costly compared with opioids in 29.4% of iterations (quadrant IV). Medical cannabis was found to be more effective and more costly than opioids in 1.3% of iterations (Ia) based on a willingness to pay less than $50,000/QALY and in 2.2% of iterations based on a willingness to pay greater than $50,000/QALY (Ib). In 66.9% of iterations (quadrant II), medical cannabis was found to be less effective and more costly than opioids. In 0.2% of iterations (quadrant IIIa), medical cannabis was found to be less effective and less costly than opioids based on a willingness to pay less than $50,000/QALY. QALY, quality-adjusted life years.

chronic pain[18] from which we acquired several inputs for our model, sometimes allowed for continuation of pretrial analgesia (in both arms), or for limited use of nontrial analgesic, and less often prohibited additional analgesic therapy. As such, our results maybe confounded by trials that allowed the use of nontrial analgesia in both arms. Second, although the systematic review of cannabis for chronic pain[37] that we used to inform effect estimates found no systematic difference in treatment effects based on type of cannabis/cannabinoids, the small numbers of trials contributing to some subgroups may have obscured significant subgroup effects. Specifically, palmitoylethanolamide and CBD may be less effective than forms of medical cannabis that contain THC. Third, our base-case analysis evaluated a THC:CBD regimen, which is consistent with RCTs evaluating medical cannabis for CNCP, while consensus recommendations on dosing medical cannabis for chronic pain recommend initiating most patients on CBD.[25] Due to the lack of evidence around the therapeutic value of CBD-only regimens for CNCP, we did not model the consensus recommendations in our base-case analyses. Furthermore, a THC-only regimen, if used, may provide pain relief as observed in some RCTs and reduce medical cannabis costs. Fourth, we used a 1-year time horizon to reflect the available evidence (i.e., the median duration of trials used in the NMA[18] comparing medical cannabis to opioids was 3 months), while management of CNCP with either opioids or cannabis typically exceeds this timeframe. However, our 1-year time horizon is consistent with other economic evaluations

Table 4. Sensitivity and Scenario Analyses

Parameter	Total costs mean (95% CI)		Total QALYs mean (95% CI)		Probability cost-effective[a]
	Medical cannabis	Opioids	Medical cannabis	Opioids	
Base-case	$1,980 ($1,818; $2,166)	$1,851 ($1,407; $2,698)	0.582 (0.564; 0.600)	0.582 (0.560; 0.603)	31%
Sensitivity analysis					
(1a) Time horizon: 6 months (vs. 1 year in base-case analysis)	$918 ($854; $990)	$826 ($546; $1,499)	0.290 (0.280; 0.299)	0.288 (0.278; 0.298)	32%
(1b) Time horizon: 2 years[b] (vs. 1 year)	$4,198 ($3,781; $4,643)	$4,019 ($3,259; $5,054)	1.166 (1.125; 1206)	1.163 (1.111; 1216)	32%
(2a) Adherence: 60% (vs. 80%)	$2,000 ($1,828; $2,183)	$1,876 ($1,438; $2,671)	0.580 (0.558; 0.601)	0.581 (0.562; 0.599)	31%
(2b) Adherence: 100% (vs. 80%)	$1,957 ($1,797; $2,142)	$1,823 ($1,348; $2,736)	0.584 (0.560; 0.605)	0.584 (0.566; 0.602)	31%
(3a) 25% increase in cost per month of medical cannabis and no change to opioid drug costs: low CBD: $61.14 (vs. $48.91); usual CBD: $75.18 (vs. $60.14); THC and CBD: $154.88 (vs. $123.90)	$2,174 ($2,005; $2,345)	$1,850 ($1,407; $2,698)	0.582 (0.564; 0.600)	0.582 (0.560; 0.603)	28%
(3b) 25% decrease in cost per month of medical cannabis and no change to opioid drug costs: low CBD: $39.13 (vs. $48.91); usual CBD: $48.11 (vs. $60.14); THC and CBD: $99.12 (vs. $123.90)	$1,825 ($1,657; $2,024)	$1,850 ($1,407; $2,698)	0.582 (0.564; 0.600)	0.582 (0.560; 0.603)	33%
(3c) 25% increase in cost per month of opioids and no change to medical cannabis costs: low: $59.84 (vs. $47.87.); medium: $85.49 (vs. $68.39); high: $177.01 (vs. $141.61); very high: $244.21 (vs. 195.37)	$1,982 ($1,819; $2,168)	$1,960 ($1,547; $2,722)	0.582 (0.564; 0.600)	0.582 (0.559; 0.603)	34%
(3d) 25% decrease in cost per month of opioids and no change to medical cannabis costs: low: $38.30 (vs. $47.87.); medium: $54.71 (vs. $68.39); high: $113.29 (vs. $141.61); very high: $156.30 (vs. 195.37)	$1,982 ($1,814; $2,168)	$1,725 ($1,296; $2,502)	0.582 (0.564; 0.600)	0.582 (0.559; 0.603)	28%
(4) Medical cannabis prices from licensed producers Low CBD $56.50 (vs. $48.91); usual CBD: $94.22 (vs. $60.14); THC and CBD: $172.28 (vs. $123.90)	$2,284 ($2,115; $2,462)	$1,850 ($1,407; $2,698)	0.582 (0.564; 0.600)	0.582 (0.560; 0.603)	26%
(5a) Medical cannabis: flower prices[c] Low CBD $47.00 (vs. $48.91); usual CBD: $91.60 (vs. $60.14); THC and TBD: $140.99 (vs. $123.90)	$2,090 ($1,921; $2,267)	$1,851 ($1,407; $2,698)	0.582 (0.564; 0.600)	0.582 (0.560; 0.603)	29%
(5b) Medical cannabis: oil prices Low CBD: $21.66 (vs. $48.91); usual CBD: $36.11 (vs. $60.14); THC and TBD: $66.73 (vs. $123.90)	$1,623 ($1,434; $1,837)	$1,851 ($1,407; $2,698)	0.582 (0.564; 0.600)	0.582 (0.560; 0.603)	43%
(6a) Increased cost of death due to natural cause by 25% $18,631 (vs. $14,905)	$2,011 ($1,846; $2,197)	$1,882 ($1,437; $2,726)	0.582 (0.564; 0.600)	0.582 (0.560; 0.603)	31%
(6b) Decreased cost of death due to natural cause by 25% $11,924 (vs. $14,905)	$1,955 ($1,792; $2,142)	$1,826 ($1,380; $2,679)	0.582 (0.564; 0.600)	0.582 (0.560; 0.603)	31%
(7) Opioid starting doses Low (<50 MME): 85% (vs. 75%) Medium (50–89 MME): 8% (vs. 12%) High (90–199 MME): 5% (vs. 8%) Very high (200+ MME): 2% (vs. 5%)	$1,980 ($1,818; $2,166)	$1,721 ($1,384; $2,547)	0.582 (0.564; 0.600)	0.584 (0.561; 0.604)	18%

(*continued*)

Table 4. Continued

Parameter	Total costs mean (95% CI)		Total QALYs mean (95% CI)		Probability cost-effective[a]
	Medical cannabis	Opioids	Medical cannabis	Opioids	
(8a) Medical cannabis starting dose Low CBD: 100% (vs. 0%); usual CBD: 0% (vs. 0%); THC and CBD: 0% (vs. 100%)	$1,467 ($1,278; $1,688)	$1,851 ($1,407; $2,698)	0.586 (0.567; 0.604)	0.582 (0.560; 0.603)	90%
(8b) Medical cannabis starting dose Low CBD: 0% (vs. 0%); usual CBD: 100% (vs. 0%); THC and CBD: 0% (vs. 100%)	$1,686 ($1,541; $1,863)	$1,851 ($1,407; $2,698)	0.585 (0.566; 0.603)	0.582 (0.560; 0.603)	47%
(9) Nonfatal overdose probability for medical cannabis equal to 50% of modeled risks of nonfatal overdose for opioids: low: 0.14% (vs. 0%); usual: 0.27% (vs. 0%); high: 0.50% (vs. 0%)	$1,982 ($1,819; $2,169)	$1,851 ($1,407; $2,698)	0.581 (0.563; 0.603)	0.582 (0.560; 0.603)	31%
(10) Same transition probabilities between medical cannabis and opioids for stopping, rotating, or increasing/decreasing initial treatments[d]	$1,997 ($1,832; $2,181)	$1,851 ($1,407; $2,698)	0.582 (0.563; 0.599)	0.582 (0.559; 0.603)	30%
Scenario analyses					
(1) Switch medium opioid MME dose to medical cannabis vs. increasing to high opioid MME dose	$1,750 ($1,596; $1,933)	$1,809 ($1,660; $1,976)	0.583 (0.564; 0.601)	0.583 (0.564; 0.601)	100%
(2) Add medical cannabis to medium opioid MME dose vs. increasing to high opioid MME dose	$1,892 ($1,752; $2,044)	$1,809 ($1,660; $1,976)	0.583 (0.565; 0.602)	0.583 (0.564; 0.601)	4%
(3) High opioid MME dose decrease + cannabis vs. increasing opioid to a very-high MME dose	$2,221 ($2,058; $2,397)	$2,225 ($2,059; $2,400)	0.579 (0.561; 0.597)	0.579 (0.561; 0.597)	99%

All analyses run 10,000 patients and 1000 samples.

[a]Probability cost-effective, $50,000/QALY willingness to pay.

[b]1.5% discount rate applied to costs and QALYs incurred post 12 month.[19]

[c]Usual flower dose (23.6 g/month) based on average grams of dried flower/month purchased by cannabis users for medical use.[42] Low and high doses were assumed to represent −50/+50% of the usual dose.

[d]Transition probabilities for medical cannabis equal to transition probabilities for opioids. The cost of 15 mg CBD was used to represents the higher end of a low CBD dose, 25 mg CBD to represent the midpoint of the usual CBD dose, and 20 mg THC and 20 mg CBD was used to represent the midpoint of the THC + CBD dose.

CI, confidence interval; CBD, cannabidiol: MME, morphine milligram equivalent; QALY, quality-adjusted life years; THC, tetrahydrocannabinol.

in chronic pain as most evaluate a time horizon of 1 year or less.[51–53] Fifth, we were unable to find adherence data for opioids and medical cannabis for CNCP and therefore relied on treatment adherence data for pharmacologic management of CNCP conditions.[26,27] However, sensitivity analyses found that our results were not impacted by different adherence assumptions. Sixth, while we evaluated oral cannabis products, which are recommended in clinical guidelines[17] and commonly used for medical purposes,[42,54] our findings may not be generalizable to people with CNCP who use inhaled formulations because pulmonary harms were not considered. Seventh, opioids and cannabis can both result in use disorders, including withdrawal effects, which were not modeled due to uncertainty regarding the prevalence of cannabis use disorder among people with chronic pain who use medical cannabis.[55,56] While there is moderate certainty evidence supporting a 5.5% prevalence of opioid-use disorder following prescription for CNCP,[57] the prevalence of cannabis use disorder when used to manage chronic pain has been reported to range from 1.11% to 33%.[58–60] Eighth, outcomes associated with subsequent overdose risk from opioids were not modeled and our results may underestimate harms as the risk of a second overdose has been found to be higher after an initial overdose.[61] Ninth, results may underestimate costs associated with opioids because we did not consider a societal perspective (i.e., lost productivity) associated with fatal and nonfatal opioid overdoses. Tenth, we utilized clinician input for probabilities associated with stopping and switching treatments due to a lack of data from published literature. Lastly, while we evaluated opioid-sparring strategies due to the harms and risks associated with opioids, we did not consider interactions between cannabis and opioids or scenarios involving patients switching from medical cannabis to opioids. To test the impact of varying key assumptions on the results, we performed several probabilistic sensitivity and scenario analyses, which confirmed the robustness of our findings.

Except for synthetic formulations and nabiximols, medical cannabis is not reimbursed by provincial public drug plans in Canada, and out-of-pocket costs have been reported as an important barrier to access by people living with chronic pain.[62–64] Our findings suggest little-to-no difference in 1-year costs and QALYs between medical cannabis and opioids for chronic pain. However, medical cannabis does not cause fatal overdoses like opioids, suggesting it may be an appropriate alternative for CNCP, and is considered for funding by public drug plans aligning with Health Canada recommendations.[65] Future research informing long-term benefits and infrequent harms for both medical cannabis and opioids for CNCP (e.g., overdose, addiction, use disorder) and the effectiveness of CBD-only regimens are needed to evaluate long-term cost-effectiveness of medical cannabis versus opioids for managing CNCP.

Conclusions

Reimbursing medical cannabis as an alternative to opioids for chronic pain may confer similar, but modest, benefits to patients and reduce the risk of opioid overdose without significantly increasing costs to Canadian drug plans.

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Authors' Contributions

H.M.J., J.W.B., B.S., M.L., and J.-E.T. conceived and designed the study. H.M.J., C.M., L.W., and R.J.C. acquired the data. H.M.J., J.W.B., B.S., M.L., and J.-E.T. contributed to the analyses. All authors interpreted the data and could access data included in the study. H.M.J., J.W.B., and J.-E.T. drafted the article. All authors made critical revisions to the article for important intellectual content and gave approval for the article.

Data Availability

Data are available upon reasonable request.

Author Disclosure Statement

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Abbreviations Used

CBD = cannabidiol
CEAC = cost-effectiveness acceptability curve
CIHI = Canadian Institute for Health Information
CIs = confidence intervals
CNCP = chronic noncancer pain
MME = morphine milligram equivalent
MS = multiple sclerosis
NMA = network meta-analysis
OCS = Ontario Cannabis Store
PEA = palmitoylethanolamide
PERT = program evaluation review technique
QALYs = quality-adjusted life years
RCTs = randomized controlled trials
THC = tetrahydrocannabinol
VAS = visual analogue scale
WTP = willingness-to-pay