Research Article

Medical Cannabis for Patients Over Age 50: A Multi-site, Prospective Study of Patterns of Use and Health Outcomes

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ABSTRACT

Objective: Cannabis is being used as a therapeutic option by patients around the globe, and older patients represent a rapidly growing subset of this population. This study aims to assess the patterns of medical cannabis use in patients over 50 years of age and its effect on health outcomes such as pain, sleep, quality of life, and co-medication. **Method**: The Medical Cannabis in Older Patients Study (MCOPS) is a multi-site, prospective observational study examining the real-world impact of medical cannabis use on patients over age 50 under the guidance of a health care provider. The study included validated instruments, with treating physicians collecting detailed data on participant characteristics, medical cannabis and co-medication use, and associated impacts on pain, sleep, quality of life, as well as adverse events. **Results**: Inclusion criteria were met by 299 participants. Average age of participants was 66.7 years, and 66.2% of respondents identified as female. Approximately 90% of patients used medical cannabis to treat pain-related conditions such as chronic pain and arthritis. Almost all patients reported a preference for oral cannabis products (e.g., extracts, edibles) rather than inhalation products (e.g., flower, vapes), and most preferred oral formulations high in cannabidiol and low in tetrahydrocannabinol. Over the six-month study period, significant improvements were noted in pain, sleep, and quality of life measures, with 45% experiencing a clinically meaningful improvement in pain interference and in sleep quality scores. Additionally, nearly 50% of patients taking co-medications at baseline had reduced their use by the end of the study period, and quality of life improved significantly from baseline to M3 and from baseline to M6, with an incremental cost per quality-adjusted life-year (QALY) of $25,357.20. No serious adverse events (SAEs) were reported. **Conclusions**: In this cohort of older patients, most of whom suffered from pain-related conditions, medical cannabis seemed to be a safe and effective treatment. Most patients experienced clinically significant improvements in pain, sleep, and quality of life and reductions in co-medication. The cost per QALY was well below the standard for traditional pharmaceuticals, and no SAEs were reported, suggesting that cannabis is a relatively safe and cost-effective therapeutic option for adults dealing with age-related health conditions.

Key words: = cannabis; cannabidiol; tetrahydrocannabinol; pain; older persons; geriatric

In Canada, a growing number of adults aged 50 and older are turning to cannabis for treatment of age-related ailments (Ahamed et al., 2020; Brown et al., 2020; Lloyd & Striley, 2018). Older patients tend to present with potentially confounding factors, such as polypharmacy, pharmacokinetic changes, and complex medical profiles. The many health conditions for which

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older patients are using medical cannabis have been documented via patient surveys and cross-sectional studies. While a large online survey of cannabis consumers in Canada and the US stemming from Wave 1 of The International Cannabis Policy Study (ICPS) conducted in 2018 found a higher prevalence of self-reported medical use in respondents <56 years old, a focus in the treatment of chronic pain conditions was found across the age spectrum (Leung et al., 2022). However, a study of invoice data tracking dispensary purchases in New York State found that patients ≥65 older (n = 2991) were more likely to use cannabis for cancer and Parkinson's disease, to use sublingual tinctures, and to start treatment with lower THC/higher CBD products (Kaufmann et al., 2022.). Moreover, a large clinic-based study of older patients in Canada (n = 9766) that gathered data from 2014-2020 found chronic pain was the most cited primary indication, and that older patients had a preference for high CBD orally-ingested cannabis oil. The majority reported improvements in pain, sleep and mood ($p < 0.0001$), and 35.6% reduced their use of opioids, and 19.9% reduced the use of benzodiazepines. The study concludes by citing the need for additional research to better determine indications, dosages and associated patient outcomes (Tumati et al., 2022).

Comprehensive clinical evidence for the effectiveness of cannabis-based products is limited to a few indications, such as pediatric epilepsy (Bialer & Perucca, 2020), chronic pain (Häuser et al., 2018), spasticity associated with multiple sclerosis (The Health Effects of Cannabis and Cannabinoids, 2017), and chemotherapy-induced nausea and vomiting (Gottschling et al., 2020; Grimison et al., 2020; Maida & Daeninck, 2016; Sarris et al., 2020; Smith et al., 2015). Additionally, numerous observational studies have reported significant reductions in symptoms and high satisfaction levels with cannabis-based products (Cahill et al., 2021; Schilling et al., 2021; Sexton et al., 2016; Tumati et al., 2022; Yang et al., 2021). Furthermore, recent studies have hypothesized that cannabis can function as a substitute for many traditional pharmaceutical medications such as opioids, benzodiazepines, and anti-depressants (Corroon et al., 2017; Kvamme, Pedersen, Alagem-Iversen, et al., 2021; Lucas et al., 2021), which may prove especially pertinent for older patients, who are more likely to hold multiple prescriptions that include drugs with potentially serious adverse effects. Of particular relevance, patient surveys show that reduction of pharmaceutical medications is a motivating factor for initiating medical cannabis treatment (Adams et al., 2021; Lucas et al., 2021; Lucas & Walsh, 2017), and US states where cannabis has been legalised have seen reductions in the use of many pharmaceuticals (Raman & Bradford, 2022a), including opioids (Bradford et al., 2018; Shi et al., 2019).

In order to increase the state of knowledge regarding the use of cannabis-based products by older patients, we have conducted a multi-site, longitudinal, observational study to examine the real-world effects of medical cannabis on the health and well-being of patients over 50 years of age who are receiving cannabis treatment under the guidance of a physician in a naturalistic setting. The primary objectives of the Medical Cannabis in Older Patients Study (MCOPS) were to assess safety and patterns of use; to evaluate the impact of medical cannabis on health outcomes, with a focus on pain, sleep and quality of life; and to explore changes in co-medication use and the associated pharmacoeconomics of medical cannabis use in this older patient population.

METHODS

Recruitment

Medical clinics across Canada that were identified as having a high percentage of older patients were contacted about the study. All participating sites went through ethics review and approval by Advarra, an independent service provider, prior to launch (protocol #Pro00059863).

Lead physicians were required to provide proof of completion of Tri-Council Policy Statement 2 Course on Research Ethics training prior to ethics review and launch of the study site. Physicians were compensated for unbillable time and resources needed to administer the study at a rate of $50 for each completed set of surveys.

Inclusion criteria were patients who had a permanent fixed address, had no previous recommendation/prescription from a physician for the use of medical cannabis, were over 50 years old, had the capacity to consent for themselves, could read, write, and speak English, and had chosen to initiate the use of Tilray medical cannabis products in their course of treatment. Patients were offered a 15% discount on all cannabis products purchased

from Tilray for the duration of the study, as confirmed by follow-up visits and completion of survey measures at those time points.

Instruments

The survey included seven instruments, four of which were self-administered by patients: a demographic survey, the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), the EuroQol 5-dimension 5-levels questionnaire (EQ-5D-5L) (Herdman et al., 2011), and the Cannabis Use Survey (Baron et al., 2018; Lucas & Walsh, 2017). The other three instruments were administered by physicians: the Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994), the Medical Cannabis and Prescription Drug Questionnaire (MCPDQ), and the Adverse Events Survey (AES).

The MCPDQ and the AES were developed specifically for this study. The MCPDQ provides a detailed inventory of medical cannabis and prescription drug use at all timepoints via multiple choice options inquiring about the methods of use tried as well as preferred primary method of use (e.g,. joint, waterpipe/bong, oil/edible, vaporizer for flower, vape pen, topical); type of cannabis currently used (indica, sativa, hybrid); use of extracts (yes/no), and if yes, preferred type of extract (2:100 THC/CBD, 1:25 THC/CBD; 5:20 THC/CBD; 10:10 THC/CBD and 25:0 THC/CBD), along with associated average dosing for both flower (in grams per day), and/or extracts (times used per day). In addition, the MCPDQ gathered retrospective information on daily and nondaily prescription drug use in milligrams per dose and doses per day or week (where applicable) at each medical visit, and has an autofill function connected to the National Drug Data File (NDDF), a US-based national prescription drug database, to ensure that consistent generic prescription drug names were used in order to facilitate final longitudinal analysis.

The Adverse Event Survey was administered at each follow up visit, starting with the following question: "Have you experienced any adverse events since the previous study visit?" If the response was "yes", a drop-down menu of common AEs reported in other medical cannabis studies presented a series of options to chose from (confusion/disorientation, depression, dizziness/lightheaded/faint, drowsiness, feeling too high, nausea/vomiting). A catch-all of "other" enabled a textual response for AEs not listed in the drop-down menu. If an AE was reported, a severity scale of 1-10 was provided for each event, followed by a question assessing the relationship between the AE and medical cannabis use (*Did the event begin within 1 hour of medical cannabis use?*; *More than 1 hour before or after use?*; Or *cannot recall*). This was followed by a question regarding what action was taken by the patient and physician (*none*; *medical cannabis use was temporarily disrupted*; *medical cannabis use stopped until today*; *patient was hospitalized*), and finally, what was the outcome of the AE (*patient recovered*; *patient did not recover*).

Data was collected at three timepoints: baseline, 2–3 months post-baseline (M3), and 6 months post-baseline (M6). Baseline data was collected between 2018 and 2020, with a final cut-off of 15 August 2020 to allow time for follow-up to M6. The demographic survey was completed at baseline, the Adverse Events Survey at M3 and M6, and the remaining measures at all three time points, except for the BPI. Only patients that reported chronic pain or an associated pain disorder such as arthritis or headaches/migraines as a primary condition at baseline and subsequent timepoints completed the BPI at baseline and the ensuing timepoints.

Due to public health measures related to COVID-19, which encouraged social distancing and use of telemedicine, the majority of M3 and M6 surveys were conducted via telemedicine or telephone.

Statistical Analysis

Mixed effects linear regression modelling was used to assess differences between baseline versus M3 or M6 for BPI pain severity, BPI pain interference, PSQI, EuroQol-5D-5L utility score, and co-medication costs. Proportional analysis using the Chi-square test (for categorical variables with all expected cell counts ≥ 5) or Fischer's Exact test (for categorical variables with any expected cell count < 5) was employed to identify significant differences in medication use.

Based on thresholds identified in the literature, minimal clinically important difference (MCID) scores were estimated for the BPI and PSQI (Buysse et al., 2011; Mathias et al., 2011): BPI: a decrease of at least -2; PSQI: a decrease of at least -3.

Analysis of BPI and PSQI scores included all patients for whom data was available, irrespective

of the primary condition treated with medicinal cannabis. Analysis of co-medication use included all patients for whom data was available, with pain medications sub-categorized as opioid medications, non-opioid pain medications (e.g., NSAIDs, non-opioid analgesics), as well as "any pain medication" that also included anti-seizure medications often used to treat chronic pain.

For the pharmacoeconomic analyses, medication costs were acquired through searches of the BC and Ontario drug formularies as well as a national commercial pharmacy. Using this information and QALY results from the EQ-5D-5L, incremental cost-utility ratios were calculated for medical cannabis use. Due to the single-arm nature of the study, it was not possible to assess incremental cost-utility ratios against a comparable population that did not use medical cannabis. Accordingly, a counterfactual scenario was employed with the assumption that, in the absence of medical cannabis treatment, participant baseline values would remain constant over the six-month follow-up period.

RESULTS

Nine clinics in British Columbia and Ontario participated in the study, recruiting a total of 417 patients. Of these, 299 met the inclusion criteria, which included a baseline visit prior to August 15, 2020 and at least one follow-up visit at M3 or M6. Data was available for 299 patients at baseline, 240 patients at M3, and 225 patients at M6.

Participant characteristics and primary medical condition

Participant characteristics and primary medical condition are shown in Table 1. This population was mostly female (66.2%), with a mean age of 66.7 years old. Thirty-three point eight percent report having a college degree or higher, 25.1% report working full or part time, 62.5% were retired, and 10.4% were unable to work due to a disability. Annual household income was quite low, with 47.8% reporting annual household incomes of less than $40,000. In terms of ethnicity, we saw an over-representation of White participants (87.6%), and an under-representation of all other ethnicities. Self-reported knowledge and experience with cannabis at baseline was low, with a mean rating of 30.4 on a scale of 1 (no knowledge and experience) to 100 (very knowledgeable and experienced). Chronic pain (60.5%), arthritis (20.5%), and insomnia (11.9%) were the most common primary conditions cited by participants, with 1.6% citing use for anxiety disorder.

Table 1. *Participant characteristics and primary medical condition associated with medical cannabis use.*

Variable	Results for N= 299 (n, %)
Gender	
Male	101 (33.8%)
Female	198 (66.2%)
Age	
Mean (SD)	66.7 (9.5)
Median (Q1, Q3)	66.0 (59.0, 73.0)
Range	51.0 – 92.0
Highest degree completed	
High school or lower	198 (66.2%)
College or higher	101 (33.8%)
Employment Status	
Working full time	50 (16.7%)
Working part time	25 (8.4%)
Unemployed but not looking for work	6 (2.0%)
Retired	187 (62.5%)
Unable to work (disabled)	31 (10.4%)
Annual Household Income	
Less than $40,000	143 (47.8%)
$40,000 - $69,000	82 (27.4%)
$70,000 - $99,000	38 (12.7%)
$100,000 - $129,000	23 (7.7%)
$130,000 or more	13 (4.3%)
Ethnicity	
Caucasian (White)	262 (87.6%)
Hispanic (e.g., Mexican, Central American, South America, etc.)	9 (3.0%)
Asian (e.g., Chinese, Japanese, Korean, Vietnamese, etc.)	7 (2.3%)
South Asian (e.g., East Indian, Pakistani, Sri Lankan, etc.)	11 (3.7%)
Black (e.g., African, Caribbean, etc.)	5 (1.7%)
Aboriginal/First Nation	4 (1.3%)
Metis	1 (0.3%)
Other	4 (1.3%)
	Results for N= 185 (n, %)*
Primary Condition	
Chronic Pain	112 (60.5%)
Arthritis	38 (20.5%)
Insomnia	22 (11.9%)
Anxiety Disorder	3 (1.6%)
Others	10 (5.4%)

Note. *Since patients were cannabis-naïve at baseline, the data on primary condition for which they actually used medical cannabis was collected at M3.

Patterns of Use

At baseline, 27 patients (9.0%) reported they had used cannabis in the previous 4 weeks, and their primary methods of use included oral products (n = 11), vaporizers (n = 7), joints (n = 7), water bongs (n = 1), and topical products (n = 1). Of those 27 patients, 12 (44.4%) reported that their cannabis use was recreational, and 15 (55.6%) were self-medicating prior to gaining the support of their physician for medical use.

Of the 223 participants that remained in the study at M6, 100 reported not using medical cannabis in the past 4 weeks but continued to participate in the study nonetheless. Of the remaining 123 patients that did continue to use cannabis, 95.9% (n = 119) reported using orally administered products as their primary method of use, 4 (3.3%) reported using joints, and 1 (0.8%) reported using a vaporizer. During the treatment period, patients used cannabis twice a day on average (mean ± SD = 2.1 ± 1.0 and 1.8 ± 0.9 times per day at M3 and M6, respectively) and 7 days per week on average (mean ± SD = 6.8 ± 1.0 and 6.7 ± 1.2 days at M3 and M6, respectively).

Among patients who reported using inhalational products, all preferred formulations were high in 9-tetrahydrocannabinol (THC). Among patients who reported using orally administered products, most preferred formulations were cannabidiol (CBD) dominant (M3 = 78.9% and M6 = 72.6%), followed by balanced THC/CBD products (M3 = 20.6% and M6 = 21.6%) and THC dominant products (M3 = 0.6% and M6 = 6.0%).

Impact of Medical Cannabis on Pain

Of the patients that reported chronic pain or an associated pain disorder such as arthritis or headaches/migraines as a primary condition at baseline and subsequent timepoints and that used medical cannabis in the previous four weeks, BPI scores for pain severity and pain interference decreased significantly at both M3 and M6 compared to baseline. Baseline scores for pain severity were a mean of 5.89 and median of 5.75 (n = 179), decreasing to 4.92 and 5.0 respectively at M3 (n = 144) and 4.96 and 5.0 at M6 (n = 136). BPI scores for pain interference saw an even greater decline, from a mean of 5.81/median of 6.0 at baseline, to 4.03/3.79 at M3, and 3.87/3.64 at M6 (Table 2). Of the 131 participants with chronic pain for whom a difference between baseline and M6 could be calculated, 31% (n = 40) saw clinically meaningful improvements in pain severity, and 45% (n = 59) saw clinically meaningful improvements in pain interference.

Table 2. *Changes in BPI scores from baseline to M3 and M6.*

Characteristics	Baseline (N = 299)	M3 (N = 240)	M6 (N = 225)
BPI Severity Scale			
N	179	144	136
Mean (SD)	5.89 (1.82)	4.92 (2.08)	4.96 (2.19)
Median (Q1, Q3)	5.75 (4.75, 7.00)	5.00 (3.50, 6.31)	5.00 (3.25, 6.50)
Range	1.00 - 10.00	0.00 - 10.00	0.00 - 10.00
BPI Interference Scale			
N	179	144	136
Mean (SD)	5.81 (2.29)	4.03 (2.54)	3.87 (2.63)
Median (Q1, Q3)	6.00 (4.29, 7.64)	3.79 (1.86, 6.14)	3.64 (1.57, 5.86)
Range	0.00 - 10.00	0.00 - 10.00	0.00 - 10.00

Impact of Medical Cannabis on Sleep Quality

Sleep quality saw statistically significant improvements at both M3 and M6. Baseline PSQI mean/median scores were 10.86/11 respectively (n = 299), decreasing to 8.55/8.0 at M3 (n = 238), and 8.51/8.0 at 6 months (n = 224) (Table 3). Of the 224 participants for whom a difference between baseline and M6 could be calculated, 100 (45%) showed a clinically meaningful improvement in sleep quality.

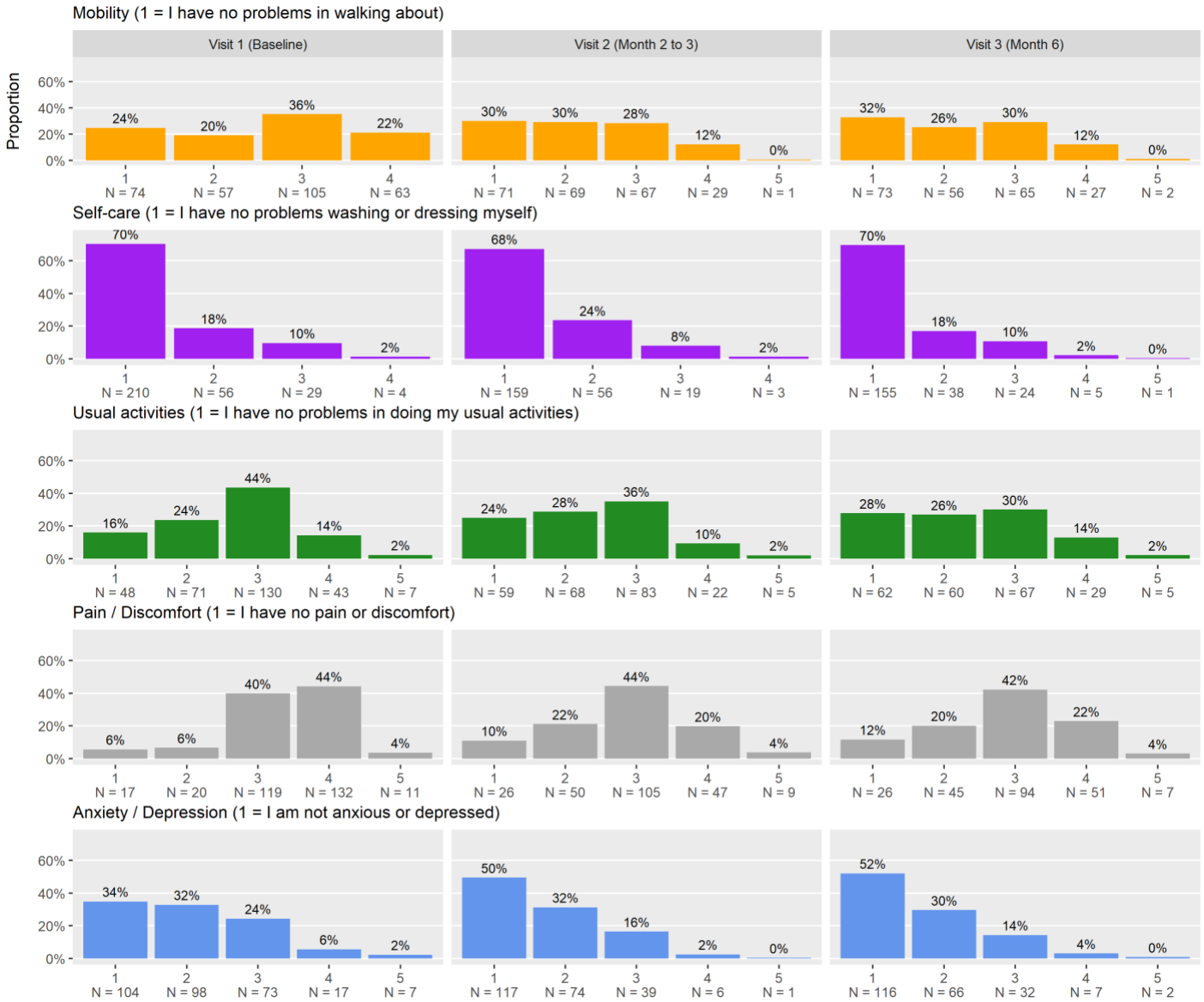
Table 3. *Changes in PSQI scores between baseline, M3 and M6.*

	Baseline (*N* = 299)	M3 (*N* = 240)	M6 (*N* = 225)
Global scale			
N	299	238	224
Mean (*SD*)	10.86 (4.39)	8.55 (3.91)	8.51 (4.01)
Median (Q1, Q3)	11.00 (7.50, 14.00)	8.00 (6.00, 12.00)	8.00 (6.00, 12.00)
Range	1.00 - 20.00	0.00 - 19.00	0.00 - 19.00

Impact of Medical Cannabis on Quality of Life

Figure 1 highlights improvements in quality of life. Results from EQ-5D-5L show statistically significant improvements in quality of life from baseline to M3 and M6. The most notable improvements over study visits were observed in the domains of ability to complete usual activities, pain/discomfort, and anxiety/depression over the course of the study, characterized by increasing proportions of individuals in the least severe category (level 1). Additionally, Visual Analogue Scale (VAS) scores increased from a mean of 61.81 at baseline, to 67.54 at M3, and 68.52 at M6.

Figure 1. *EQ-5D-5L categories over time, stratified by the five domains.*



Changes in Co-Medication Following Medical Cannabis Initiation

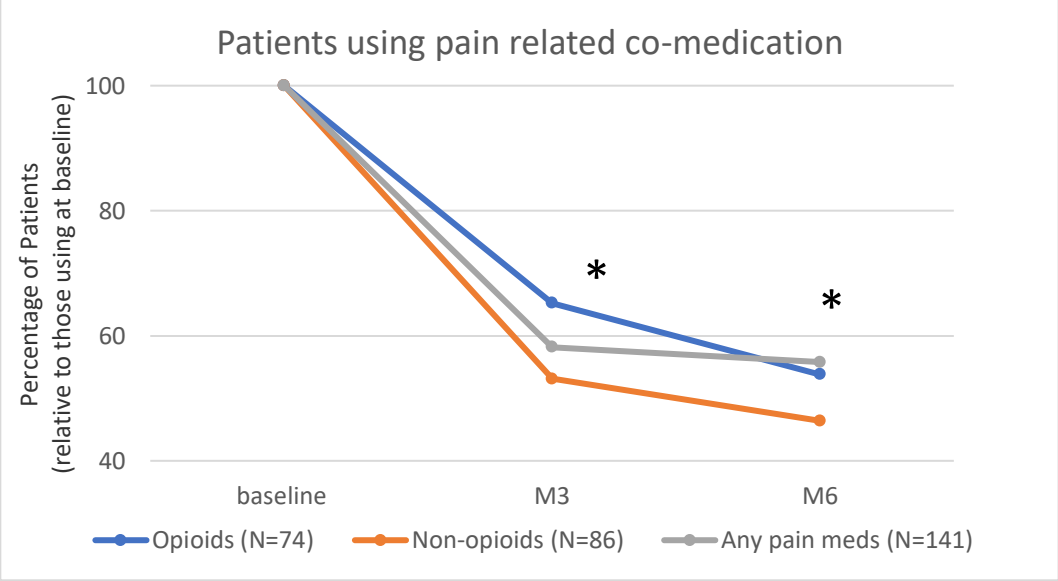
Table 4 shows changes in prescription drug use between baseline (pre-medical cannabis initiation), M3, and M6 by drug category. Percentages are based on the total number of patients with data at that time point (*n*). Almost half of all patients were using some kind of pain medication at baseline (47.2%; $n = 299$). For each medication category, the percentage of all patients using that type of medication decreased from baseline to M3, with further decreases at M6 for all medications except for benzodiazepines and antiseizure medications. When considering only patients who were using pain medications at baseline (47.2%; $n = 141$), the proportion of those still using pain medications decreased significantly at M3 and M6 ($p < 0.05$).

Table 4. *Changes in prescription drug use between baseline, M3 and M6.*

Medication Class	Baseline (*N* = 299)	M3 (*N* = 240)	M6 (*N* = 225)
Opioids	74 (24.7%)	46 (19.2%)	41 (18.2%)
Non-opioid pain/anti-inflammatory	86 (28.8%)	55 (22.9%)	48 (21.3%)
Stimulants	0 (%)	0 (%)	0 (%)
Benzodiazepines	10 (3.3%)	5 (2.1%)	7 (3.1%)
Muscle relaxants/Sleep aids	18 (6.0%)	1 (0.4%)	5 (2.2%)
Antidepressants	31 (10.4%)	13 (5.4%)	8 (3.6%)
Antiemetics	2 (0.7%)	0 (0.0%)	0 (0.0%)
Antipsychotics	1 (0.3%)	0 (0.0%)	0 (0.0%)
Antiseizure	40 (13.4%)	16 (6.7%)	16 (7.1%)
Diabetes medications	28 (9.4%)	14 (5.8%)	10 (4.4%)
Blood pressure medications	31 (10.4%)	10 (4.2%)	8 (3.6%)
Any pain-related medication	142 (47.5%)	84 (35.0%)	70 (31.1%)

Figure 2 highlights the percentage of patients at each time point who were still using opioids, non-opioids, or any type of pain medication relative to the number of patients at that timepoint who reported using pain medication at baseline. We saw statistically significant declines in all three pain medication categories, with most of the declines in use taking place between baseline and M3 ($p < 0.05$).

Figure 2. *Use of pain medication among patients using those medications at baseline.*



Note. * $p < 0.05$ (change compared to baseline).

Pharmacoeconomic Analysis

As shown in Table 5, there was a significant decrease in mean 30-day co-medication costs over time, both as a percentage of all patients and as a percentage of only those patients with co-medication costs at baseline. Among 'all patients' the decrease was from a mean of $42.60 per month at baseline (*SD* = $150.80) down to $17.90 (*SD* = $46.30) at M3, and $17.10 at M6 (*SD* = $53.80), representing a mean monthly savings of $25.50, and a 59.9% decline in monthly costs between baseline and M6.

Table 5. *30-day medication costs over time.*

	Baseline	M3	M6
Costs among all patients			
N	209	192	180
Mean (*SD*)	$42.6 (150.8)	$17.9 (46.3)*	$17.1 (53.8)*
Median (Q1, Q3)	5.0 (0.0, 35.4)	0.0 (0.0, 9.8)*	0.0 (0.0, 5.2)*
Costs among those with baseline costs			
N	120	76	75
Mean (*SD*)	$74.1 (193.3)	$26.1 (55.4)*	$28.7 (69.5)*
Median (Q1, Q3)	27.7 (7.6, 71.0)	0.0 (0.0, 19.0)*	0.0 (0.0, 14.9)*

Note. * $p < 0.05$ (change compared to baseline)

Among patients with medication costs at baseline, mean monthly medication costs dropped from $74.10 at baseline (*SD* = $193.30) down to $28.70 at M6 (*SD* = $69.50), representing a $45.40 mean monthly savings, and a 61.3% decline in prescription medication costs.

With respect to medical cannabis costs, the three most popular formulations for orally administered medical cannabis products were considered, based on percentage of patients at M6, their estimated cost per use (based on an average of 1.5 mL per use), and their estimated cost per month (based on mean self-reported cannabis use per day and 30.5 days per month).

Table 6 shows medical cannabis costs over the six-month study period, QALYs, and incremental cost-effectiveness ratios for all patients and for patients who were using prescription medications at baseline. For both populations, the incremental cost-utility ratio, which was $25,357 and $18,522 Canadian Dollars respectively, was well below the standard threshold of $50,000USD per QALY.

Table 6. *Incremental cost-utility analysis for medical cannabis treatment.*

	All patients			Patients with medication use at baseline		
	Observed	**Counter-factual**	**Difference**	**Observed**	**Counter-factual**	**Difference**
Medical cannabis costs	$1,174.80	$255.60	$919.20	$1,231.80	$444.60	$787.20
QALY	0.331	0.295	0.036	0.333	0.29	0.043
Incremental cost per QALY						
		$25,357.20			$18,522.30	

Adverse Events

As Table 7 illustrates, a total of 13 adverse events were reported during the study, none of which were considered serious adverse events (SAEs). Out of the 13 reports of adverse events, one patient reported such events at both M3 and M6, and four patients who reported adverse events during baseline-M3 did not experience any events during M3-M6. Additionally, two patients who did not report any events during baseline-M3 reported events during M3-M6.

Out of participants who reported adverse events at M3 follow up, the majority experienced dizziness, drowsiness, and nausea, typically within 1 hour of using medical cannabis. At both timeframes, most participants did not take any specific action related to the adverse event, and subsequently recovered. However, three participants stopped using medical cannabis following the adverse event they experienced.

Table 7. *Adverse event characteristics, context, and outcomes.*

	M3 (N = 240)	M6 (N = 225)
Describe the adverse event that you experienced		
Confusion/ disorientation	1 (0.4%)	0 (0.0%)
Depression	0 (0.0%)	1 (0.4%)
Dizziness/ lightheaded/ faint	2 (0.8%)	1 (0.4%)
Drowsiness	1 (0.4%)	0 (0.0%)
Feeling too high	2 (0.8%)	0 (0.0%)
Nausea and/or vomiting	4 (1.7%)	0 (0.0%)
Other	0 (0.0%)	1 (0.4%)
AMONGST INDIVIDUALS WITH ANY ADVERSE EVENT	N = 10	N = 3
Self-rated symptom severity on a scale of 1 to 10		
Mean (SD)	6.1 (1.9)	6.3 (4.0)
Median (Q1, Q3)	6.0 (4.2, 7.8)	7.0 (4.5, 8.5)
Range	4.0 - 9.0	2.0 - 10.0
What was the adverse events relationship to your medical cannabis use?		
Event began within 1 hour of medical cannabis use	7 (70.0%)	1 (33.3%)
Event began more than 1 hour before or after medical cannabis use	2 (20.0%)	0 (0.0%)
Cannot recall	1 (10.0%)	2 (66.7%)
What action did you take?		
None	5 (50.0%)	2 (66.7%)
Medical cannabis use interrupted temporarily	2 (20.0%)	1 (33.3%)
Medical cannabis use stopped completely (until today)	3 (30.0%)	0 (0.0%)
What was the outcome?		
Recovered	8 (80.0%)	2 (66.7%)

DISCUSSION

Adults over age 50 represent a rapidly growing segment of patients seeking cannabis-based products to treat a variety of health conditions, many of which are related to aging. In the present observational study, adults over 50 years of age (mean age 66.7) were treated with medical cannabis for six months under the guidance of a physician, and validated instruments for measuring pain, sleep, and quality of life were employed to evaluate patient outcomes.

Among study participants, the most common primary conditions for initiating medical cannabis treatment were chronic pain, arthritis, and insomnia, which is consistent with several previous studies (Cahill et al., 2021; Kvamme, Pedersen, Alagem-Iversen, et al., 2021; Leung et al., 2022; Lucas & Walsh, 2017), including those focusing on medical cannabis use by older patients (Brown et al., 2020; Kaufmann et al., 2022; Lum et al., 2019). MCOPS used a number of validated instruments to assess these health outcomes, and scores for pain severity/pain interference (BPI), and sleep quality (PSQI) saw statistically significant improvements over the 6 months of the study.

Reductions in the use of traditional prescription medications following the initiation of medical cannabis under guidance of a health care practitioner can also be viewed as further evidence of treatment tolerability and effectiveness. MCOPS saw a statistically significant reduction in the ratio of patients

taking any type of prescription medication, as well as pain medications, antidepressants, and sleep aids. These results are consistent with previous findings from past patient surveys (Corroon et al., 2017; Kvamme, Pedersen, Rømer Thomsen, et al., 2021; Lucas & Walsh, 2017; Takakuwa & Sulak, 2020), prospective studies (Lucas et al., 2021), and population-level studies monitoring prescription drug use following cannabis legalization in specific jurisdictions (Bradford et al., 2018; Bradford & Bradford, 2017; Liang et al., 2018; Raman & Bradford, 2022b; Shi et al., 2019). The substitution of traditional prescription pain medication with cannabis-based products – particularly opioids – may be an effective harm reduction strategy and result in public health benefits, especially in the context of the current opioid overdose crisis (Livingston et al., 2017).

Additionally, our results showed a significant improvement in quality-of-life scores during cannabis-based treatment, which is consistent with findings of several previous studies (Cahill et al., 2021; Doeve et al., 2020; Meng et al., 1903; Naftali et al., 2021; Peterson et al., 2021; Schlienz et al., 2021). Moreover, using EQ-5D-5L to track the impacts of medical cannabis on the quality of life of participants also presented an opportunity to assess the incremental cost per QALY for cannabis treatment (reported in Canadian Dollars). Our analysis suggests that the QALY costs associated with the medical use of cannabis, which ranged from $18-25,000CDN were well below the standard of $50,000USD (Neumann et al., 2014), suggesting that cannabis is a cost-effective treatment in this population of older medical cannabis users.

Finally, fewer than 5% of patients reported adverse effects, the most common of which were nausea/vomiting and feeling "too high", which is lower than those reported in most previous studies of medical cannabis in older populations. The lower rate of adverse events in the present study might reflect access to and use of quality-controlled cannabis products within the Canadian federally-regulated medical cannabis system, as well as the availability of standardized high CBD/low THC cannabis products preferred by this patient population, the latter of which are associated with fewer side-effects and adverse events than high THC/low CBD cannabis products.

This study has some limitations. While this is the largest longitudinal study of older medical cannabis patients that we're aware of, the participating clinics were from Ontario and BC, therefore the sample may not be representative of the broader population of older cannabis patients in Canada or otherwise. Furthermore, at baseline, 9% of patients reported they had used cannabis in the four weeks prior to joining the study, which may suggest they had already been benefitting from its use, resulting in a potential recruitment bias. Additionally, while the loss-to-follow-up (LTFU) rate at M6 was relatively low (13.29%) for a longitudinal study of this kind, a large ratio of patients (n=100 of 223) reported not using medical cannabis in the 4 weeks leading up to M6. The reasons for this discontinuation of use remain unknown, as there were no measures in the study that anticipated and/or assessed this particular outcome, and could have resulted in selection bias. In considering potential explanations, it seems unlikely the participants ceased use due to adverse events in light of the low rate of AEs reported in the study, which a subsequent sensitivity analysis did not associate with the population reporting no use in the 4 weeks prior to M6 (Lange et al., 2010; Lucas et al., 2021b). It is certainly possible that that some patients stopped using medical cannabis because of improvements in their overall condition (which is consistent with many of the outcomes reported in the study), or because they found it ineffective, or quite simply that their patterns of use were more occasional and did not coincide with the 4 weeks prior to M6. It may also be that the cost of medical cannabis – which is not covered by public payers, and which has been shown to be an obstacle to access in previous studies – also played a role (Lucas & Walsh, 2017; Lucas et al., 2021b). However, in light of the time period of this study, it may also be that their supply and subsequent patterns of use were interrupted by the COVID-19 pandemic, particularly closer to the end of the study (which would coincide with M6 for many participants) during the summer of 2020. To reduce any bias arising from these and other factors, all data was collected by physicians and clinic staff, and health outcomes were measured using validated instruments which were subsequently coded

and analyzed by a third-party health economics outcome research organization (Broadstreet HEOR, Vancouver BC). Additionally, the large sample size and prospective design of this study offsets some of these potential limitations.

Conclusion

To the best of our knowledge, the present report describes one of the largest longitudinal study of authorized older medical cannabis patients to date. Given current population trends suggesting significant growth in aging populations and longer lifespans overall, finding safe, efficacious, and cost-effective treatments for geriatric care is a priority. The results of this multi-site, prospective, longitudinal study of medical cannabis patients age 50 years and older indicate that cannabis may be a relatively safe and effective treatment for chronic pain, sleep disturbances, and other conditions associated with aging, leading to subsequent reductions in prescription drug use and healthcare costs, as well as significant improvements in quality of life. As the use of cannabis for medical purposes by older patients continues to increase in North America and around the globe, these findings suggest that further studies employing more robust methodological approaches, including clinical trials, are certainly justified.

REFERENCES

Adams, D., Ofei-Tenkorang, N. A., Connell, P., Owens, A., Gothard, A., Souza, D., & Narouze, S. (2021). Interests and concerns regarding medical marijuana among chronic pain patients in Ohio: an online survey. *Journal of Cannabis Research*, *3*(1). https://doi.org/10.1186/s42238-021-00092-y

Ahamed, A., Kullmann, K. C., Frasso, R., & Goldstein, J. N. (2020). Analysis of Unregulated Sale of Lifesaving Prescription Drugs Online in the United States. In *JAMA Internal Medicine* (Vol. 180, Issue 4, pp. 607–609). American Medical Association. https://doi.org/10.1001/jamainternmed.2019.7514

Baron, E. P., Lucas, P., Eades, J., & Hogue, O. (2018). Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. *Journal of Headache and Pain*, *19*(1). https://doi.org/10.1186/s10194-018-0862-2

Bialer, M., & Perucca, E. (2020). Does cannabidiol have antiseizure activity independent of its interactions with clobazam? An appraisal of the evidence from randomized controlled trials. *Epilepsia*, *61*(6), 1082–1089. https://doi.org/10.1111/epi.16542

Bradford, A. C., & Bradford, W. D. (2017). Medical Marijuana laws may be associated with a decline in the number of prescriptions for medicaid enrollees. *Health Affairs*, *36*(5), 945–951. https://doi.org/10.1377/hlthaff.2016.1135

Bradford, A. C., Bradford, W. D., Abraham, A., & Adams, G. B. (2018). Association between US state medical cannabis laws and opioid prescribing in the medicare part D population. *JAMA Internal Medicine*, *178*(5), 667–673. https://doi.org/10.1001/jamainternmed.2018.0266

Brown, J. D., Costales, B., van Boemmel-Wegmann, S., Goodin, A. J., Segal, R., & Winterstein, A. G. (2020). Characteristics of older adults who were early adopters of medical cannabis in the Florida medical Marijuana use registry. *Journal of Clinical Medicine*, *9*(4). https://doi.org/10.3390/jcm9041166

Buysse, D. J., Germain, A., Moul, D. E., Franzen, P. L., Brar, L. K., Fletcher, M. E., Begley, A., Houck, P. R., Mazumdar, S., Reynolds, C. F., & Monk, T. H. (2011). Efficacy of Brief Behavioral Treatment for Chronic Insomnia in Older Adults. *Archives of Internal Medicine*, *171*(10), 887. https://doi.org/10.1001/archinternmed.2010.535

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193–213. https://doi.org/10.1016/0165-1781(89)90047-4

Cahill, S. P., Lunn, S. E., Diaz, P., & Page, J. E. (2021). Evaluation of Patient Reported Safety and Efficacy of Cannabis From a Survey of Medical Cannabis Patients in Canada. *Frontiers in Public Health*, *9*. https://doi.org/10.3389/fpubh.2021.626853

Cleeland, C. S., & Ryan, K. M. (1994). Pain assessment: global use of the Brief Pain Inventory. *Annals of the Academy of Medicine, Singapore*, *23*(2), 129–138.

Corroon, J. M., Mischley, L. K., & Sexton, M. (2017). Cannabis as a substitute for prescription drugs - A cross-sectional study. *Journal of Pain Research*, *10*, 989–998. https://doi.org/10.2147/JPR.S134330

Doeve, B. H., van de Meeberg, M. M., van Schaik, F. D. M., & Fidder, H. H. (2020). A Systematic Review With Meta-Analysis of the Efficacy of Cannabis and Cannabinoids for Inflammatory Bowel Disease. *Journal of Clinical Gastroenterology*, *55*(9). https://doi.org/10.1097/MCG.0000000000001393

Gottschling, S., Ayonrinde, O., Bhaskar, A., Blockman, M., D'agnone, O., Schecter, D., Rodríguez, L. D. S., Yafai, S., & Cyr, C. (2020). Safety considerations in cannabinoid-based medicine. In *International Journal of General Medicine* (Vol. 13, pp. 1317–1333). Dove Medical Press Ltd. https://doi.org/10.2147/IJGM.S275049

Grimison, P., Mersiades, A., Kirby, A., Lintzeris, N., Morton, R., Haber, P., Olver, I., Walsh, A., McGregor, I., Cheung, Y., Tognela, A., Hahn, C., Briscoe, K., Aghmesheh, M., Fox, P., Abdi, E., Clarke, S., Della-Fiorentina, S., Shannon, J., … Stockler, M. (2020). Oral THC:CBD cannabis extract for refractory chemotherapy-induced nausea and vomiting: a randomised, placebo-controlled, phase II crossover trial. *Annals of Oncology*, *31*(11), 1553–1560. https://doi.org/10.1016/j.annonc.2020.07.020

Häuser, W., Finn, D. P., Kalso, E., Krcevski-Skvarc, N., Kress, H. G., Morlion, B., Perrot, S., Schäfer, M., Wells, C., & Brill, S. (2018). European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. In *European Journal of Pain (United Kingdom)* (Vol. 22, Issue 9, pp. 1547–1564). Blackwell Publishing Ltd. https://doi.org/10.1002/ejp.1297

Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., Bonsel, G., & Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research*, *20*(10), 1727–1736. https://doi.org/10.1007/s11136-011-9903-x

Kaufmann, C. N., Kim, A., Miyoshi, M., & Han, B. H. (2022). Patterns of Medical Cannabis Use Among Older Adults from a Cannabis Dispensary in New York State. *Cannabis and Cannabinoid Research*, *7*(2), 224–230. https://doi.org/10.1089/can.2020.0064

Kvamme, S. L., Pedersen, M. M., Alagem-Iversen, S., & Thylstrup, B. (2021). Beyond the high: Mapping patterns of use and motives for use of cannabis as medicine. *NAD Nordic Studies on Alcohol and Drugs*, *38*(3), 270–292. https://doi.org/10.1177/1455072520985967

Kvamme, S. L., Pedersen, M. M., Rømer Thomsen, K., & Thylstrup, B. (2021). Exploring the use of cannabis as a substitute for prescription drugs in a convenience sample. *Harm Reduction Journal*, *18*(1). https://doi.org/10.1186/s12954-021-00520-5

Leung, J., Chan, G., Stjepanović, D., Chung, J. Y. C., Hall, W., & Hammond, D. (2022). Prevalence and self-reported reasons of cannabis use for medical purposes in USA and Canada. *Psychopharmacology*, *239*(5), 1509–1519. https://doi.org/10.1007/s00213-021-06047-8

Liang, D., Bao, Y., Wallace, M., Grant, I., & Shi, Y. (2018). Medical cannabis legalization and opioid prescriptions: evidence on US Medicaid enrollees during 1993–2014. *Addiction*, *113*(11), 2060–2070. https://doi.org/10.1111/add.14382

Livingston, M. D., Barnett, T. E., Delcher, C., & Wagenaar, A. C. (2017). Recreational cannabis legalization and opioid-related deaths in Colorado, 2000-2015. *American Journal of Public Health*, *107*(11), 1827–1829. https://doi.org/10.2105/AJPH.2017.304059

Lloyd, S. L., & Striley, C. W. (2018). Marijuana Use Among Adults 50 Years or Older in the 21st Century. *Gerontology and Geriatric Medicine*, *4*, 233372141878166. https://doi.org/10.1177/2333721418781668

Lucas, P., Boyd, S., Milloy, M. J., & Walsh, Z. (2021). Cannabis Significantly Reduces the Use of Prescription Opioids and Improves Quality of Life in Authorized Patients: Results of a Large Prospective Study. *Pain Medicine (United States)*, *22*(3), 727–739. https://doi.org/10.1093/pm/pnaa396

Lucas, P., & Walsh, Z. (2017). Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. *International Journal of Drug Policy*, *42*, 30–35. https://doi.org/10.1016/j.drugpo.2017.01.011

Lum, H. D., Arora, K., Croker, J. A., Qualls, S. H., Schuchman, M., Bobitt, J., Milavetz, G., & Kaskie, B. (2019). Patterns of Marijuana Use and Health Impact: A Survey Among Older Coloradans. *Gerontology and Geriatric Medicine*, *5*, 233372141984370. https://doi.org/10.1177/2333721419843707

Maida, V., & Daeninck, P. J. (2016). A user's guide to cannabinoid therapies in oncology. In *Current Oncology* (Vol. 23, Issue 6, pp. 398–406). Multimed Inc. https://doi.org/10.3747/co.23.3487

Mathias, S. D., Crosby, R. D., Qian, Y., Jiang, Q., Dansey, R., & Chung, K. (2011). Estimating Minimally Important Differences for the Worst Pain Rating of the Brief Pain Inventory–Short Form. *The Journal of Supportive Oncology*, *9*(2), 72–78. https://doi.org/10.1016/j.suponc.2010.12.004

Meng, H., Gabrielle Page, M., Ajrawat Amol Deshpande, P., Bana Samman Mary Dominicis Karim Ladha, M. S., Fiorellino, J., Huang, A., Kotteeswaran, Y., McClaren-Blades, A., Kotra, L. P., Clarke, H., Meng, H., Page, M. G., Ajrawat Á Samman Á M Dominicis, P. B., Ladha, K. S., Fiorellino, J., Huang, A., & McClaren-Blades, Á. A. (1903). Patient-reported outcomes in those consuming medical cannabis: a prospective longitudinal observational study in chronic pain patients Résultats rapportés par les patients consommant du cannabis médical : une e ´tude observationnelle longitudinale prospective chez des patients souffrant de douleur chronique. *Canadian Journal of Anesthesia/Journal Canadien d'anesthésie*, *68*, 633–644. https://doi.org/10.1007/s12630

Naftali, T., Schleider, L. B. L., Benjaminov, F. S., Konikoff, F. M., Matalon, S. T., & Ringel, Y. (2021). Cannabis is associated with clinical but not endoscopic remission in ulcerative colitis: A randomized controlled trial. *PLoS ONE*, *16*(2 February). https://doi.org/10.1371/journal.pone.0246871

Neumann, P. J., Cohen, J. T., & Weinstein, M. C. (2014). Updating Cost-Effectiveness — The Curious Resilience of the $50,000-per-QALY Threshold. *New England Journal of Medicine*, *371*(9), 796–797. https://doi.org/10.1056/NEJMp1405158

Peterson, A. M., Le, C., & Dautrich, T. (2021). Measuring the Change in Health-Related Quality of Life in Patients Using Marijuana for Pain Relief. *Medical Cannabis and Cannabinoids*, *4*(2), 114–120. https://doi.org/10.1159/000517857

Raman, S., & Bradford, A. C. (2022a). Recreational cannabis legalizations associated with reductions in prescription drug utilization among Medicaid enrollees. *Health Economics*, *31*(7), 1513–1521. https://doi.org/10.1002/hec.4519

Raman, S., & Bradford, A. C. (2022b). Recreational cannabis legalizations associated with reductions in prescription drug utilization among Medicaid enrollees. *Health Economics*, *31*(7), 1513–1521. https://doi.org/10.1002/hec.4519

Sarris, J., Sinclair, J., Karamacoska, D., Davidson, M., & Firth, J. (2020). Medicinal cannabis for psychiatric disorders: A clinically-focused systematic review. *BMC Psychiatry*, *20*(1). https://doi.org/10.1186/s12888-019-2409-8

Schilling, J. M., Hughes, C. G., Wallace, M. S., Sexton, M., Backonja, M., & Moeller-Bertram, T. (2021). Cannabidiol as a treatment for chronic pain: A survey of patients' perspectives and attitudes. *Journal of Pain Research*, *14*, 1241–1250. https://doi.org/10.2147/JPR.S278718

Schlienz, N. J., Scalsky, R., Martin, E. L., Jackson, H., Munson, J., Strickland, J. C., Bonn-Miller, M. O., Loflin, M., & Vandrey, R. (2021). A Cross-Sectional and Prospective Comparison of Medicinal Cannabis Users and Controls on Self-Reported Health. *Cannabis and Cannabinoid Research*, *6*(6), 548–558. https://doi.org/10.1089/can.2019.0096

Sexton, M., Cuttler, C., Finnell, J. S., & Mischley, L. K. (2016). A Cross-Sectional Survey of Medical Cannabis Users: Patterns of Use and Perceived Efficacy. *Cannabis and Cannabinoid Research*, *1*(1), 131–138. https://doi.org/10.1089/can.2016.0007

Shi, Y., Liang, D., Bao, Y., An, R., Wallace, M. S., & Grant, I. (2019). Recreational marijuana legalization and prescription opioids received by Medicaid enrollees. *Drug and Alcohol Dependence*, *194*, 13–19. https://doi.org/10.1016/j.drugalcdep.2018.09.016

Smith, L. A., Azariah, F., Lavender, V. T., Stoner, N. S., & Bettiol, S. (2015). Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. In *Cochrane Database of Systematic Reviews* (Vol. 2015, Issue 11). John Wiley and Sons Ltd. https://doi.org/10.1002/14651858.CD009464.pub2

Takakuwa, K. M., & Sulak, D. (2020). A Survey on the Effect That Medical Cannabis Has on Prescription Opioid Medication Usage for the Treatment of Chronic Pain at Three Medical Cannabis Practice Sites. *Cureus*. https://doi.org/10.7759/cureus.11848

The Health Effects of Cannabis and Cannabinoids. (2017). National Academies Press. https://doi.org/10.17226/24625

Tumati, S., Lanctôt, K. L., Wang, R. D., Li, A., Davis, A., & Herrmann, N. (2022). Medical Cannabis Use Among Older Adults in Canada: Self-Reported Data on Types and Amount Used, and Perceived Effects. *Drugs and Aging*, *39*(2), 153–163. https://doi.org/10.1007/s40266-021-00913-y

Yang, K. H., Kaufmann, C. N., Nafsu, R., Lifset, E. T., Nguyen, K., Sexton, M., Han, B. H., Kim, A., & Moore, A. A. (2021). Cannabis: An Emerging Treatment for Common Symptoms in Older Adults. *Journal of the American Geriatrics Society*, *69*(1), 91–97. https://doi.org/10.1111/jgs.16833

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