5.01.32	Medical Cannabis for the Treatment of Pain and Spasticity		
Original Policy Date:	September 1, 2020	**Effective Date:**	August 1, 2023
Section:	5.0 Prescription Drug	**Page:**	Page 1 of 29

Policy Statement

I. Inhaled cannabis or extracted cannabinoids are considered **investigational** for **any** of the following:
   A. Treatment of chronic non-cancer pain
   B. Treatment of cancer pain
   C. Acute post-operative pain
   D. Treatment of spasticity associated with multiple sclerosis
   E. All other conditions that have not received approval from the U.S. Food and Drug Administration

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding
There is no specific HCPCS code for this medication. It would likely be reported using the following HCPCS code:

- **J3490**: Unclassified drugs

Description

Cannabis describes organic products (e.g., cannabinoids, marijuana, hemp) that are derived from the Cannabis sativa plant. There is a wide variety of proposed benefits of cannabis, and some pharmaceutical cannabis products have received approval from the U.S. Food and Drug Administration for very specific medical indications. Most studies on medical cannabis have been conducted with pharmaceutical formulations, which can provide indirect evidence for cannabis preparations that are available through medical marijuana programs in some states. This evidence review focuses on some of the strongest evidence of medical cannabis in the treatment of chronic non-cancer pain, cancer pain, acute post-operative pain, and spasticity associated with multiple sclerosis (MS).

Related Policies

- Drug Testing in Pain Management and Substance Use Disorder Treatment

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Three synthetic THC products and a plant-based pharmaceutical product have received approval by the FDA for non-pain indications. Another plant-based pharmaceutical product (Sativex) is approved for use outside of the U.S. and is considered an investigational drug by the FDA. Studies with these cannabinoids may provide indirect evidence of the effects of products sold at dispensaries.

- Dronabinol (Marinol®, ThePharmaNetwork, LLC) oral solution and (Syndros®, Benuvia Therapeutics Inc.) oral capsule are indicated in adults for the treatment of: (1) anorexia associated with weight loss in patients with acquired immune deficiency syndrome (AIDS), and (2) nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.
- Nabilone (Cesamet®, Bausch Health), is a synthetic analog of THC in an oral capsule that is indicated for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.
- Cannabidiol (Epidiolex®, GW Pharmaceuticals) is an oral solution containing CBD that is concentrated from cannabis plants. It is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex.
- Nabiximols (Sativex®, GW Pharmaceuticals) is a pharmaceutical product extracted from the whole cannabis plant that contains THC and CBD in a 1:1 ratio along with minor cannabinoids. Sativex is considered an investigational drug by the FDA and has been studied in 3 Phase III trials for the treatment of cancer pain.

Dronabinol oral solution is a Schedule II controlled substanceand dronabinol oral capsules are a Schedule III controlled substance. Nabilone is a Schedule II controlled substance. Epidiolex is not regulated as a controlled substance. Non-Epidiolex CBD and THC remain a Schedule I drug prohibited for any use.

In April 2019, FDA announced steps for the agency's continued evaluation of potential regulatory pathways for the marketing of cannabis and cannabis-derived products under the FDA's existing authorities.[4,] As part of this effort, the FDA issued warning letters to companies marketing CBD products with "egregious and unfounded claims" that were aimed at vulnerable populations, including individuals with cancer, Alzheimer disease, fibromyalgia, and substance abuse disorders.

Rationale

Background

The terms “marijuana” and “cannabis” are often used interchangeably in the U.S. but are distinct. Cannabis is a broader term that describes a variety of organic products (e.g., cannabinoids, marijuana, hemp) that are derived from the *Cannabis sativa* plant and used for a number of different purposes (e.g., medical, industrial, recreational).[1,] The more-encompassing word “cannabis” has been adopted as the standard terminology within scientific and scholarly communities; medical cannabis refers to the use of cannabis to treat disease or alleviate symptoms.

Cannabis contains over 450 compounds, with at least 70 classified as phytocannabinoids.[2,] The 2 that are of most interest are delta 9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is associated with the psychoactive properties of cannabis (e.g., euphoria and reduction of anxiety and stress) and is being evaluated for its pain-relieving properties. CBD does not cause the intoxication or euphoria (the “high”) that is associated with THC. Furthermore, CBD has lower affinity for the cannabinoid receptors and has the potential to counteract the effects of THC on memory, mood, and cognition. CBD is also known to enhance adenosine receptor signaling and is being evaluated for its effect on pain modulation and inflammation.

Cannabis-derived products (buds, resin, and oil) may be consumed by smoking or inhaling from cigarettes (joints), pipes (bowls), water pipes (bongs, hookahs), and blunts (cigars filled with cannabis); eating or drinking food products and beverages; or vaporizing the product.[1,] Cannabinoids can also be absorbed through the skin and mucosal tissues with topical creams, patches, and sprays.

At the federal level, cannabis and all derivatives of the plant, with the exception of the U.S. Food and Drug Administration (FDA)-approved drugs, are classified as a Schedule I substance under the Controlled Substances Act. Schedule I substances are considered to have no currently accepted medical use and a high potential for abuse, making distribution of cannabis a federal offense. At the state level, legalization of cannabis for both medical and recreational use has been increasing over the past decade. As of February 3, 2022, 37 states plus the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands had established comprehensive medical cannabis programs.[3,]

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Chronic Non-Cancer Pain

Clinical Context and Therapy Purpose

Chronic pain is the most common condition cited by patients for the medical use of cannabis.[1,] For example, in March 2022, 61.23% of active patients in the Minnesota Medical Cannabis Program were certified as having chronic pain , while another 39% were certified as having intractable pain. [5,] There is evidence that some individuals are replacing the use of conventional pain medications (e.g., opiates) with cannabis. Analyses of prescription data from Medicare Part D enrollees in states with medical access to cannabis suggest a significant reduction in the prescription of conventional pain medications.[6,] Combined with the survey data suggesting that pain is one of the primary reasons for the use of medical cannabis, these recent reports suggest that a number of pain patients are replacing the use of opioids with cannabis. Cannabis may also be used as an adjunctive treatment to pain medications.

The question addressed in this evidence review is: Does cannabis improve the net health outcome in patients with chronic non-cancer pain?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with chronic non-cancer pain due to a variety of etiologies:

- Neuropathic pain - Neuropathic pain is usually evaluated according to the cause of nerve injury. Some common causes of neuropathic pain include diabetes (diabetic neuropathy), postherpetic neuralgia (shingles), amputation, neuropathic pain after surgery or trauma, spinal cord injury, trigeminal neuralgia, HIV infection, or an unknown cause.[2,] Neuropathic pain can also be divided into central (e.g., spinal cord injury) or peripheral (e.g., diabetic neuropathy) types.
- Other causes of chronic non-cancer pain include musculoskeletal pain, fibromyalgia, and inflammatory bowel disease.

Interventions
The therapy being considered is medical cannabis, inhaled or extracted from the cannabis plant and sold at cannabis dispensaries. Indirect evidence may be provided by the pharmaceutical products which are composed of synthetic tetrahydrocannabinol (THC) (e.g., dronabinol, nabilone) or a plant-derived oromucosal spray (e.g., nabiximols).

Different strains of the cannabis plant contain varying amounts of THC and cannabidiol (CBD) along with other cannabinoids. The route of administration (inhaled or ingested) may also contribute to variability in efficacy.

Medical cannabis is being investigated as an alternative to pain medications or in addition to pain medications such as opioids.

Comparators
The choice of an appropriate initial therapeutic strategy is dependent upon an accurate evaluation of the cause of the pain and the type of chronic pain syndrome. The following therapies are currently being used to treat chronic pain:

- Physical therapy
- Nonopioid analgesic agents (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], cyclooxgenase-2 [COX-2] inhibitors)
- Opioids
- Antidepressants
- Antiepileptic drugs (e.g., gabapentin and pregabalin)
- Muscle relaxants
- Topical analgesics.

Outcomes
The primary outcome is pain, typically measured with a 10 cm or 100 mm visual analog score (VAS) or a numerical rating scale (NRS), which assesses pain on a scale of 0 (no pain) to 10 (worst imaginable pain). Typically, a 30% decrease or 2 cm on the 10 cm VAS pain scale is considered clinically significant.

Additional measures may include the brief pain inventory-short form (BPI), neuropathic pain scale, and the global impression of change score.

Functional outcomes and quality of life may be measured with a variety of condition-specific questionnaires. The impact on chronic pain should be measured after at least 1 week of use. The benefits and harms of long-term use should be studied at 1 year or more.
A beneficial outcome would be a reduction in chronic pain and improvement in function and quality of life.

Cannabis is not known to have serious adverse health effects. Harmful outcomes in the short-term may include dizziness, nausea, insomnia, sleepiness, sedation, and lethargy, as well as impaired

driving. The effects of long-term use are unknown but some reports suggest possible effects on cognition.

Study Selection Criteria

Because multiple, recent systematic reviews of RCTs on cannabis for chronic non-cancer pain etiologies are available, the focus of the following section is on these systematic reviews. Additional RCTs published after the systematic reviews are discussed in detail only if they address limitations identified in the systematic reviews.

Review of Evidence

Systematic Reviews

The National Academies of Science, Engineering, and Medicine (NASEM, 2017) conducted a review of systematic reviews on the health effects of cannabis and cannabinoids.[1,] Based primarily on the systematic reviews of Whiting et al (2015)[7,] and Andreae et al (2015)[8,], NASEM concluded that there was evidence that adults with chronic pain treated with cannabis or cannabinoids are more likely to experience a clinically significant improvement in pain symptoms. The systematic reviews included in the NASEM report and more recent systematic reviews are described in more detail below and in Tables 1 to 3.

Whiting et al (2015) conducted a systematic review of 79 studies (N=6462) to evaluate the effect of medical cannabis for a variety of conditions (nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis (MS) or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, or Tourette syndrome).[7,] These indications were prespecified by the project funders, the Swiss Federal Office of Public Health. Twenty-eight studies on chronic pain were identified, and are shown in Table 1. The review included both cancer pain and non-cancer pain, and also included trials with acute (less than 1 day) treatment duration. The authors found that cannabinoids were associated with a greater proportion of patients showing a 30% reduction in neuropathic pain (6 trials) and in cancer pain (see next section). Nabiximols was associated with a greater average reduction in the NRS of pain (6 trials), BPI-short form (3 trials), neuropathic pain scale (5 trials), and the proportion of patients reporting improvement on a global impression of change score (odds ratio, 2.08, 6 trials) compared with placebo (Table 3). All but 2 of the studies on chronic pain were considered to be at uncertain or high-risk of bias.

Andreae et al (2015) conducted a patient-level Bayesian meta-analysis of 5 RCTs that evaluated inhaled cannabis for neuropathic pain.[8,] The primary outcome was the proportion of responders with more than 30% improvement in a patient-reported instrument such as the VAS. Inhaled cannabis increased the proportion of responders with an odds ratio of 3.2 and a Bayesian posterior probability of 99.7%. This analysis provides direct evidence of inhaled cannabis for neuropathic pain but is limited by the small population with multiple etiologies, and the variability in the duration of the studies (from hours to weeks).

Butler et al (2017) conducted a systematic review of cannabis use for treating chronic non-cancer pain for the Minnesota Department of Public Health Medical Cannabis program.[9,] Reviewers identified 21 studies of at least 2 weeks duration. The studies used broad categories of chronic pain, and nearly all used cannabis as an adjunctive treatment to other pain medications. The most commonly studied cannabis product was nabiximols. Low strength evidence favored nabiximols over placebo for peripheral neuropathic pain and suggested no difference between nabiximols and placebo in patients with MS or central neuropathic pain. There was insufficient evidence for other non-cancer chronic pain conditions. The review found that cannabinoids are associated with greater risk of any adverse events (AEs), serious AE, withdrawals due to AE, and other specified AE, as compared to placebo. Only 1 small study compared AEs between cannabinoids and opioids or other analgesics. Limitations of the body of evidence were that the botanical and synthetic treatments in the review provided only indirect evidence regarding the benefits and harms of whole plant medical

cannabis, and treatment durations in the studies were too short to address benefits and harms from long-term use.

A Cochrane review on medical cannabis for neuropathic pain was reported by Mucke et al (2018).[2,] The authors evaluated 16 double-blind controlled trials and conducted analyses for the various outcome measures, with subgroup analysis for the type of neuropathic pain and route of administration. Ten studies evaluated nabiximols, 4 studies evaluated synthetic THC, and 2 studies evaluated inhaled herbal cannabis. There was moderate evidence that cannabis-based medicines probably increase the number of people achieving pain relief of 30% or greater (39% vs. 33%), with a number needed to treat of 11. There was an increase in nervous system events (number needed to harm of 3), but the authors did not have sufficient evidence to identify serious adverse events. Patient global impression of pain was influenced by the types of neuropathic pain (p=.02) and with the oromucosal spray compared to placebo. No other associations between subgroups and outcomes were identified. There was evidence of publication bias, as there were studies with negative results that had not been published. Results posted on www.clinicaltrials.gov, but not published in peer-reviewed journals, were included in the meta-analysis.

Sainsbury et al (2021) included 17 RCTs (N=861) in another systematic review of cannabis-based medicines for the management of chronic neuropathic pain. [10,] Cannabinoids were administered via a variety of methods and in various dosage forms for numerous different neuropathic pain etiologies. The investigators concluded that there was moderate-to-low quality evidence that THC, THC plus CBD, and dronabinol significantly reduce pain intensity (-6.624, -8.681, and -6.0 units, respectively). THC and THC plus CBD also increased the likelihood of a 30% reduction in pain by 1.917 and 1.756 times, respectively.

Johal et al (2020) included 29 placebo-controlled trials in a systematic review of the effect of cannabinoids on pain with a search through 2018.[11,] The investigators concluded that there was low-quality evidence of a significant treatment effect favoring the use of cannabinoids over placebo (p<.001), and that the effect of oral formulations was superior to oromucosal and inhaled cannabis. Treatment effects were modest. For oral formulations, there was a -1.07 point difference on a 10 cm VAS scale compared to -0.43 for an oromucosal spray and -0.42 for smoked cannabis. Results were mostly consistent when the duration of treatment was between 1 and 14 days, 2 to 8 weeks, or 2 to 6 months.

The Agency for Healthcare and Research and Quality (AHRQ) maintains a living systematic review on cannabis and other plant-based treatments for chronic pain.[12,] Studies in this review are grouped based on their THC to CBD ratio using the following categories: high THC to CBD ratio, comparable THC to CBD ratio, and low THC to CBD ratio. As of March 2022, the current surveillance report for this review concluded that short-term data are available for THC and/or CBD to treat primarily neuropathic chronic pain. The strength of available evidence was rated as low-to-moderate quality. Evidence for other interventions, including kratom, was insufficient or not found.

Table 1. Studies Included in Systematic Reviews and Meta-analyses on Chronic Pain

Study	Pain Type	Preparation	N	Whiting (2015)[7,]	Andrea e (2015)[8,]	Butler et al (2017)[9,]	Mucke (2018) Cochrane[2,]	Johal et al (2020)[11,a]	Sainsbury et al (2021)[10,]	AHRQ (2022)[12,]
Frank et al (2008)[13,]	Neuropathic-mixed	nabilone vs. hydroxy codeine	96	●		●	●			
Serpell et al (2014)[14,]	Neuropathic - peripheral	nabiximols vs. placebo	246	●		●	●	●	●	●
Hoggart et al (2015)[15,]	Neuropathic - peripheral	nabiximols	230			●				

Study	Pain Type	Preparation	N	Whiting (2015)[7]	Andreae (2015)[8]	Butler et al (2017)[9]	Mucke (2018) Cochrane[2]	Johal et al (2020)[11] [a]	Sainsbury et al (2021)[10]	AHRQ (2022)[12]
Nurmikko et al (2007)[16]	Neuropathic-peripheral	nabiximols vs. placebo spray	125	●		●	●	●	●	●
Selvarajah et al (2010)[17]	Diabetic neuropathy	nabiximols vs. placebo spray	30	●		●	●	●	●	●
Toth et al (2012)[18]	Diabetic neuropathy	nabilone vs. placebo	26				●	●		
GW Pharma (2012) NCT00710424[19]	Diabetic neuropathy	nabiximols vs. placebo spray	297	●			●			
Wallace et al (2015)[20]	Diabetic neuropathy	THC spray vs. placebo	16	●					●	●
Blake et al (2006)[21]	Rheumatoid arthritis	nabiximols vs. placebo spray	58	●		●		●		●
Langford et al (2012)[22]	Pain related to MS	nabiximols vs. placebo spray	339	●		●	●	●		
Rog et al (2005)[23]	Neuropathic-central	nabiximols vs. placebo spray	66	●		●	●	●		●
Svendsen et al (2004)[24]	Pain related to MS	dronabinol capsule vs. placebo	24	●		●	●	●	●	
GW Pharma (2012) NCT01606176[25]	Pain related to MS	nabiximols vs. placebo spray	70	●			●			
Schimrigk (2017)[26]	Pain related to MS	dronabinol capsule vs. placebo	240				●	●		●
Turcotte et al (2015)[27]	Pain related to MS	nabilone capsule vs. placebo	15	●		●		●		●
van Amerongen et al (2018) [28]	Pain related to MS	oral ECP002A vs. placebo	24					●		
Ware et al (2010)[29]	Fibromyalgia	nabilone vs. amitriptyline	32	●		●		●	●	
Skrabek et al (2008)[30]	Fibromyalgia	nabilone vs. placebo	40	●		●		●		●
Pinsger (2006)[31]	Musculoskeletal pain	nabilone vs. placebo	30	●						
Malik et al (2017) [32]	Functional chest pain	dronabinol vs. placebo	13					●		
Abrams et al (2007)[33]	HIV-related neuropathy	inhaled cannabis vs. placebo	50	●	●			●	●	

Study	Pain Type	Preparation	N	Whiting (2015)[7]	Andrea e (2015)[8]	Butler et al (2017)[9]	Mucke (2018) Cochrane[2]	Johal et al (2020)[11] [a]	Sainsb ury et al (2021)[10]	AHRQ (2022)[12]
Ellis et al (2009)[34]	HIV-related neuropathy	inhaled cannabis vs. placebo	34	●	●		●	●	●	
Ware et al (2010)[35]	Trauma-related neuropathy	inhaled cannabis vs. placebo	23	●	●		●	●		
Wilsey et al (2008)[36]	SCI, DM, CRPS	inhaled cannabis vs. placebo	38	●	●				●	
Wilsey et al (2012)[37]	SCI, DM, CRPS	inhaled cannabis vs. placebo	39	●	●				●	
Berman et al (2007) NCT01606202[38]	SCI	nabiximols vs. placebo	116	●			●		●	
Lynch et al (2014)[39]	Chemotherapy-induced polyneuropathy	nabiximols	18	●			●			●
Bermann et al (2004)[40]	Plexus injury	Oromucosal spray	48	●			●	●		
Karst et al (2003)[41]	Neuropathic pain	CT3 capsules vs. placebo	21	●				●	●	
Almog et al (2020)[42]	Neuropathic pain	inhaled cannabis vs. placebo	27						●	
Elibach et al (2020)[43]	HIV-related neuropathy	cannabidivarin oil vs. placebo	32						●	●
Wade et al (2002)[44]	Neuropathic pain	THC plus CBD spray vs. placebo	20						●	
Wilsey et al (2016)[45]	SCI	THC spray vs. placebo	42						●	
Wilsey et al (2016)[46]	Neuropathic pain	THC spray vs. placebo	42						●	
Xu et al (2020)[47]	Neuropathic pain	topical CBD vs. placebo	29							●
Vela et al (2021)[48]	Hand osteoarthritis and psoriatic arthritis	CBD tablet vs. placebo	129							●
Narang et al (2008)[49]	Chronic non-cancer pain	dronabinol vs. placebo	30	●						
Johnson et al (2010)[50]	Cancer-related pain	nabiximols vs. placebo	177	●						
Noyes et al (2008)[51]	Cancer-related pain	THC capsules	10	●						
Portenoy (2012)[52]	Cancer-related pain	nabiximols vs. placebo	360	●						

AHRQ: Agency for Healthcare Research and Quality; CBD: cannabidiol; CRPS: complex regional pain syndrome; DM: diabetes mellitus; MS: multiple sclerosis; SCI: spinal cord injury; THC: tetrahydrocannabinol.
[a]Additional trials on spasticity were included.

Table 2. Systematic Review and Meta-analyses Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Treatment Duration
Whiting et al (2015)[7,]	up to 2015	28	Chronic pain	2454 (10 to 360)	RCTs and observational studies	Hours to weeks
Andreae et al (2015)[8,]	up to 2014	5	Chronic neuropathic pain	178 (23 to 50)	RCTs	Hours to 2 weeks
Butler et al (2017)[9,]	2003-2015	19	Chronic non-cancer pain	1309 (15 to 339)	RCTs and observational studies	At least 2 weeks
Mucke et al (2018)[2,] Cochrane	up to 2017	16	Chronic neuropathic pain	1750 (20 to 339)	RCTs	2 to 26 weeks
Johal et al (2020)[11,]	2002-2018	29[a]	Non-cancer pain	2345 (13 to 339)	RCTs	1 day to 6 months
Sainsbury et al (2021)[10,]	up to 2021	17	Chronic neuropathic pain	861 (16 to 246)	RCTs	Hours to 14 weeks
AHRQ (2022) [12,]	up to Jan 2022	28	Chronic pain	RCTs: 1912 Observational studies: 13,095	RCTs and observational studies	RCTs: 4 to 47 weeks Observational: 12 to 208 weeks

AHRQ: Agency for Healthcare Research and Quality; RCT: randomized controlled trial.
[a]Additional trials on spasticity were included.

Table 3. Systematic Review and Meta-analyses Results

Study	All Chronic Pain	Neuropathic Pain - Mixed	Neuropathic Pain - Peripheral	MS-related Pain	Rheumatoid Arthritis	Fibromyalgia	Serious Adverse Events
Whiting et al (2015) [7,]	Greater average reduction in the NRS of pain and BPI, and an increase in the proportion of patients reporting improvement on a global impression of change score	Cannabinoids were associated with greater average reductions in the NPS and a greater proportion of patients showing a 30% reduction in neuropathic pain					
Odds ratio (95% CI)	2.08 (1.21 to 3.59)	1.38 (0.93 to 2.03)					
Andreae et al (2015)[8,]			Inhaled cannabis resulted in a higher proportion of patients achieving a				

Study	All Chronic Pain	Neuropathic Pain - Mixed	Neuropathic Pain - Peripheral	MS-related Pain	Rheumatoid Arthritis	Fibromyalgia	Serious Adverse Events
			30% decrease in pain				
Odds ratio (95% CRI)			3.2 (1.59 to 7.24)				
NNT (95% CRI)			5.55 (3.35 to 13.7)				
Posterior probability			99.7%				
Butler et al (2017)[9,]							
Total N			735	al N=444	58	72	
			Low strength evidence from 3 studies that nabiximols reduces peripheral neuropathic pain	Evidence is insufficient - possibility of no difference for nabiximols vs. placebo	Evidence is insufficient to draw a conclusion	No difference between nabilone and amitriptyline for pain	Increase in AEs compared to placebo. Only 1 study compared AEs with other treatments
Mucke et al (2018)[2,]Cochrane			Moderate quality evidence that cannabis probably increases the number of patients achieving a 30% reduction in pain				
Cannabis			39%				
Placebo			33%				
Risk difference (95% CI)			0.05 (0.00 to 0.09)				0.01 (0.06 to 0.15)
Johal et al (2020) [11,]	Low quality evidence that there was a significant treatment effect favoring the use of cannabinoids over placebo						
Weighted mean differenc	-0.63 (-0.85 to -0.42)			-0.35 (-0.64 to -0.06)			

Study	All Chronic Pain	Neuropathic Pain - Mixed	Neuropathic Pain - Peripheral	MS-related Pain	Rheumatoid Arthritis	Fibromyalgia	Serious Adverse Events
e (95% CI)							
Sainsbury et al (2021)[10],		Moderate-to-low quality evidence that there was a significant treatment effect favoring the use of cannabinoids over placebo.					
Pain intensity change from baseline, difference in means (p-value)		THC vs placebo: -8.68 (.00) THC plus CBD vs. placebo: -6.624 (.00) Dronabinol vs. placebo: -6 (.044)					
Responders with a 30% reduction in pain intensity, risk ratio (p-value)		THC vs. placebo:1.917 (.00) THC plus CBD: 1.756 (.008)					
AHRQ (2022) [12],		Short-term data are available for THC and/or CBD to treat neuropathic chronic pain					
Pain severity, mean difference vs. placebo (95% CI)		Comparable THC to CBD ratios: -0.54 (-0.95 to -0.19) High THC ratios: -1.26 (-2.17 to -0.65) Dronabinol: -0.52 (-1.43 to 0.07) Nabilone: -1.59 (-2.49 to -0.82)					
Responders with a 30% reduction		1.18 (0.93 to 1.71)					

Study	All Chronic Pain	Neuropathic Pain - Mixed	Neuropathic Pain - Peripheral	MS-related Pain	Rheumatoid Arthritis	Fibromyalgia	Serious Adverse Events
in pain intensity, risk ratio (95% CI)							

AE: adverse events; AHRQ: Agency for Healthcare Research and Quality; BPI: brief pain inventory; CBD: cannabidiol; CI: confidence interval; CRI: Bayesian credible interval; MS: multiple sclerosis; NNT: number needed to treat; NPS: neuropathic pain scale; NRS: numerical rating scale; THC: tetrahydrocannabinol; VAS: visual analogs scale.

Section Summary: Chronic Non-Cancer Pain

Most trials on cannabis for chronic non-cancer pain are randomized crossover studies, with periods of active cannabinoid or placebo in a within-subject design. Also, most trials have used pharmaceutical products, either synthetic THC or a plant-derived THC/CBD product that is administered as an oromucosal spray. Studies with the pharmaceutical products, including ones that are available only outside of the U.S., provide only indirect evidence of the potential benefits of cannabis available at dispensaries. Five controlled trials were identified that evaluated inhaled cannabis, and no studies were identified with edible cannabis products. Systematic reviews of the available studies have concluded that there is low to moderate strength evidence that either inhaled cannabis or an oromucosal cannabis spray can reduce neuropathic pain. One systematic review that evaluated the evidence separately for different pain types concluded that the benefit was only for peripheral neuropathic pain (e.g., diabetic neuropathy), with insufficient evidence or insufficient support for other pain types (e.g., central neuropathic pain, fibromyalgia, rheumatoid arthritis). It is notable that 2 systematic reviews, in addition to a third AHRQ living systematic review, of studies on cannabinoids for neuropathic pain that included randomized and mostly double-blind trials found modest treatment effects favoring the use of cannabinoids over placebo for a reduction in pain intensity and the likelihood of a 30% reduction in pain. None of these reviews distinguishes among different types of neuropathic pain. Another systematic review found that oral formulations were more effective than either smoked or oromucosal spray. Many of the trials have fewer than 50 participants and there is evidence of publication bias. There are questions that need to be addressed to reach conclusions regarding the efficacy of medical cannabis for chronic non-cancer pain. Further study is needed to identify if there are specific chronic non-cancer pain types that can be effectively treated with medical cannabis, and to determine what doses and delivery modes are effective. Long-term use of at least 1 year needs to be evaluated.

Cancer Pain

Clinical Context and Therapy Purpose

The purpose of cannabis in patients who have cancer pain is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Users of marijuana frequently mention cancer pain as the reason for use. For example, data from the Minnesota Medical Cannabis Program from March 2022 indicated that 5.2% of patients in the program were certified for cancer as an indication.[5,]

The question addressed in this evidence review is: Does cannabis in patients with cancer pain improve the net health outcome?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with pain associated with cancer.

Interventions
The therapy being considered is medical cannabis, smoked or extracted from the cannabis plant and sold at cannabis dispensaries. Indirect evidence may be provided by the pharmaceutical products which are composed of synthetic THC (e.g., dronabinol, nabilone) or a plant-derived oromucosal spray (e.g., nabiximols).

Different strains of the cannabis plant contain varying amounts of THC and CBD along with other cannabinoids. The route of administration (inhaled or ingested) may also contribute to variability in efficacy.

Medical cannabis is being investigated as an alternative to opioids or in addition to opioids for patients with unalleviated pain.

Comparators
The following therapies are currently being used to make decisions about cancer pain management:

- Supportive care
- Opioid therapy is the first-line approach for moderate or severe chronic cancer pain.

Outcomes
The primary outcome in patients with cancer pain is pain symptoms, typically measured with VAS or NRS. Typically, a 30% decrease or 2 cm on the 10 cm VAS pain scale is considered clinically significant. Functional outcomes and quality of life may be measured with a variety of condition-specific questionnaires. Measures may include the BPI and the global impression of change score. The impact on chronic pain should be measured after at least 1 week of use. The benefits and harms of long-term use should be studied at 1 year or more.

Cannabis is not known to have serious adverse health effects. Harmful outcomes in the short-term may include dizziness, nausea, insomnia, sleepiness, sedation, and lethargy, as well as impaired driving. The effects of long-term use are unknown but some reports suggest impairments in cognition.

Study Selection Criteria
Because recent systematic reviews of RCTs on cannabis for cancer pain are available, the focus of the following section is on these systematic reviews. Additional RCTs published after the systematic reviews are discussed in detail only if they address limitations identified in the systematic reviews.

Review of Evidence
Systematic Reviews
The systematic review and meta-analysis by Whiting et al (2015) included both cancer pain and non-cancer pain, and also included trials with acute (less than 1 day) treatment duration.[7,] For patients with cancer pain, a meta-analysis of 2 trials (Johnson et al (2010)[50,], Portenoy et al (2012)[52,] found that cannabinoids were associated with a greater proportion of patients showing a reduction in pain (odds ratio, 1.41; 95% confidence interval [CI], 0.99 to 2.00).

Three, phase 3 double-blind RCTs on nabiximols (Sativex) for the treatment of cancer pain were published since the 2015 systematic review by Whiting et al (2015) described above. These trials were conducted for submission to the U.S. Food and Drug Administration (FDA) and have similar protocols. The first trial reported by Fallon et al (2017) enrolled 399 patients with a second withdrawal trial in 216 patients.[53,] The trial by Lichtman (2018) enrolled 397 patients.[54,] In all 3 studies, patients had advanced cancer with unalleviated pain (NRS ≥4 and ≤8) despite optimized opioid therapy. Patients were randomized to nabiximols or placebo, with self-titrated study medications over 10 to 14 days, followed by a treatment period. In the withdrawal study, a titration period was followed by randomization to either placebo or nabiximols for the next 35 days. The primary outcome of the percentage of improvement in NRS compared to placebo was not met. There was a treatment effect

in favor of nabiximols for quality of life, despite the lack of effect on NRS score. Somnolence was reported in 4% to 6% of the nabiximols groups.

Boland et al (2020) published a systematic review and meta-analysis of these RCTs.[55,]. They identified 6 RCTs (N=1460), and included 5 of the 6 trials (n=1442) in the meta-analysis. There was no significant difference between cannabinoids and placebo for the difference in the average NRS pain scores. Meta-analysis of the 3 phase 3 studies also showed no benefit of treatment (mean difference, -0.021; p=.80). Treatment with cannabinoids was associated with a higher risk of somnolence (odds ratio, 2.69; 95% CI, 1.54 to 4.71; p<.001) and dizziness (odds ratio, 1.58; 95% CI, 0.99 to 2.51; p=.05). Similar findings were reported by Hauser et al (2019), who evaluated the percentage of patients who reported at least 50% or 30% improvement in pain. [56,]

Section Summary: Chronic Cancer Pain

The evidence on cannabis for the treatment of cancer pain includes 3 double-blind placebo-controlled RCTs with over 1000 patients. These trials were conducted in patients with advanced cancer who had unalleviated pain despite optimized opioid therapy. The group that received an oromucosal spray of extracted cannabis did not have improved pain scores compared to placebo controls. There was a favorable effect on quality of life. An earlier meta-analysis of 2 trials found that cannabinoids were associated with a reduction in pain compared to placebo, but more recent meta-analyses found no benefit on cancer pain. Generalizability of results is limited since the studies included patients with cancer who had moderate to severe pain despite high-dose opioid therapy. Further study is needed.

Acute Post-Operative Pain

Clinical Context and Therapy Purpose

The purpose of cannabis in patients who have acute post-operative pain is to provide a treatment option that is an alternative to or an improvement on existing therapies. Survey data have suggested that many patients are interested in using cannabis for acute pain management after surgery if it was prescribed by their physician.[57,]

The question addressed in this evidence review is: Does cannabis improve the net health outcome in patients with acute post-operative pain?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with acute post-operative pain.

Interventions

The therapy being considered is medical cannabis, smoked or extracted from the cannabis plant and sold at cannabis dispensaries. Indirect evidence may be provided by the pharmaceutical products which are composed of synthetic THC (e.g., dronabinol, nabilone) or a plant-derived oromucosal spray (e.g., nabiximols).

Different strains of the cannabis plant contain varying amounts of THC and CBD along with other cannabinoids. The route of administration (inhaled or ingested) may also contribute to variability in efficacy.

Medical cannabis is being investigated as an alternative to opioids or in addition to opioids for patients with unalleviated pain.

Comparators

The choice of an appropriate initial therapeutic strategy is dependent upon an accurate evaluation of the cause of the pain. The following therapies are currently being used to treat acute post-surgical

pain: nonopioid analgesic agents (e.g., NSAIDs, COX-2 inhibitors, acetaminophen), opioids, topical analgesics, muscle relaxants, and ketamine. Additional strategies to reduce acute perioperative pain include local anesthesia, regional anesthesia, and patient-controlled analgesia.

Outcomes

The primary outcome in patients with acute post-operative pain is pain symptoms, typically measured with VAS or NRS. Typically, a 30% decrease or 2 cm on the 10 cm VAS pain scale is considered clinically significant.

Cannabis is not known to have serious adverse health effects. Harmful outcomes in the short-term may include dizziness, nausea, insomnia, sleepiness, sedation, and lethargy, as well as impaired driving.

Study Selection Criteria

Because recent systematic reviews of RCTs on cannabis for acute post-operative pain are available, the focus of the following section is on these systematic reviews. Additional RCTs published after the systematic reviews are discussed in detail only if they address limitations identified in the systematic reviews.

Review of Evidence

Systematic Reviews

Gazendam et al (2020) conducted a meta-analysis evaluating the efficacy of cannabis for acute post-operative pain using subjective pain scores.[58,] Six trials were identified, with 4 evaluating postoperative pain and 2 evaluating pain with tooth extraction. Five studies evaluated oral cannabis formulations (2 trials for nabilone and 1 trial each for THC, AZD1940 [CB1/CB2 receptor agonist], and GW842166 [CB2 receptor agonist); the sixth trial evaluated intramuscular levonantradol [synthetic CBD analog]. The analysis found low-quality evidence to support a small, but statistically significant reduction in pain scores. However, when results were stratified by route of administration, there was no significant treatment effect on pain scores for oral cannabis compared to placebo (5 studies [n=622]; mean difference, -0.21; 95% CI, -0.64 to 0.22). One study (n=56) evaluated intramuscular administration, which reported a statistically significant reduction in pain scores compared to placebo (mean difference, -2.98; 95% CI, -4.09 to -1.87).[59,] Dizziness and hypotension were more frequently reported with cannabis. The analysis was limited by the quality of available trials, which largely were small and underpowered, and significant heterogeneity was present based on the variation in cannabis type, dosing, and route of administration.

Stevens et al (2017) conducted a systematic review evaluating the efficacy of cannabinoids for managing acute post-operative pain.[60,] Seven randomized controlled trials were identified, evaluating postoperative pain or pain with tooth extraction. Five studies evaluated oral cannabis formulations (1 trial each for nabilone, dronabinol, THC, AZD1940, and GW842166); 2 trials evaluated intramuscular levonantradol. Only a qualitative analysis of analgesic efficacy and reported adverse events were presented. Cannabinoids performed equivalently to placebo in 5 trials; 1 trial found nabilone was associated with significantly worse pain scores compared to ketoprofen and placebo[61,] and 1 study with levonantradol reported superior efficacy compared to placebo.[59,] In 5 of the studies, certain adverse events (e.g., sedation, agitation, nausea) were more frequent with cannabinoid treatment than with placebo or active comparator. However, further analysis of the safety profile was precluded by differences in reporting and defining adverse events. The analysis was limited by the quality of available trials, significant heterogeneity, and lack of a quantitative analysis.

Table 4. Studies Included in Systematic Reviews and Meta-analyses on Acute Post-Operative Pain

Study	Pain Type	Preparation	N	Gazendam (2020)[58]	Stevens (2017)[60]
Beaulieu (2006)[61]	Postoperative pain	nabilone vs. ketoprofen vs. placebo	30	●	●
Buggy et al (2003)[62]	Postoperative pain	THC vs. placebo	40	●	●
Jain et al (1981)[59]	Postoperative pain	Levonantradol vs. placebo	56	●	●
Kalliomaki et al (2013)[63]	Tooth extraction	AZD1940 vs. naproxen vs. placebo	120	●	●
Levin et al (2017)[64]	Postoperative pain	nabilone vs. placebo	340	●	
Ostenfeld et al (2011)[65]	Tooth extraction	GW842166 vs. ibuprofen	92	●	●
Guillaud et al (1983)[66]	Postoperative pain	Levonantradol vs. pethidine vs. placebo	100		●
Seeling et al (2006)[67]	Postoperative pain	Dronabinol vs. placebo	100		●

THC: tetrahydrocannabinol.

Table 5. Systematic Review and Meta-analyses on Acute Post-Operative Pain Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Treatment Duration
Gazendam et al (2020)[58]	up to Jan 2019	6	Acute post-operative pain	678 (30 to 340)	RCTs	2 to 24 hours
Stevens et al (2017)[60]	up to Aug 2016	7	Acute post-operative pain	611 (30 to 120)	RCTs	2 to 24 hours

RCT: randomized controlled trial.

Table 6. Systematic Review and Meta-analyses on Acute Post-Operative Pain Results

Study	Acute Pain
Gazendam et al (2020)[58]	Low quality evidence that cannabis reduces acute pain scores compared to placebo
Mean difference (95% CI)	-0.90 (-1.69 to -0.10)

CI: confidence interval.

Section Summary: Acute Post-Operative Pain

The evidence on cannabinoids for the treatment of acute post-operative pain includes 2 systematic reviews. One meta-analysis that evaluated evidence with cannabis for acute post-operative pain found a small, but significant, reduction in pain scores compared to placebo, but this was driven primarily by 1 trial with intramuscular administration of levonantradol (not available in the U.S.). When results were stratified by route of administration, there was no significant treatment effect on pain scores for oral cannabis compared to placebo. The other systematic review only provided a qualitative analysis, but concluded that available RCTs do not demonstrate an overall benefit with cannabinoids on acute post-operative pain.

Multiple Sclerosis-Related Spasticity

Clinical Context and Therapy Purpose

Multiple sclerosis (MS) is an immune-mediated, inflammatory, neurodegenerative disease of the central nervous system. A range of symptomatic problems can occur in patients with MS, including cognitive dysfunction, fatigue, gait impairment, and spasticity. Spasticity results from lesions in the descending motor tracts of the brain and spinal cord and can cause functional disability by impairing ambulation, interfering with activities of daily living, and increasing fatigue. Spasticity can be

characterized by stiffness and difficulty with movement, or with involuntary jerks and spasms of the limbs. Spasms may be more pronounced when attempting to sleep.

The question addressed in this evidence review is: Does cannabis relieve spasticity and improve the net health outcome in patients with MS?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with MS-related spasticity.

A frequently reported use of cannabis is to relieve MS-related spasticity. For example, data from the Minnesota Medical Cannabis Program in March 2022 indicated that 7.6% of patients in the program were certified for Severe and Persistent Muscle Spasms.[5,]

Interventions
The therapy being considered is medical cannabis, smoked or extracted from the cannabis plant and sold at cannabis dispensaries. Indirect evidence may be provided by the pharmaceutical products which are composed of synthetic THC (e.g., dronabinol, nabilone) or a plant-derived oromucosal spray (e.g., nabiximols).

Different strains of the cannabis plant contain varying amounts of THC and CBD along with other cannabinoids. The route of administration (inhaled or ingested) may also contribute to variability in efficacy.

Medical cannabis is being investigated as an alternative to medications or in addition to anti-spasticity medications.

Comparators
Oral medications are considered first-line therapy for spasticity in patients with MS. The management of spasticity and gait problems in MS may also include physical therapy and the use of mobility aids. Additional treatments include intrathecal baclofen infusions and botulinum toxin injections.

Outcomes
The outcomes of interest may include the following measures after several weeks of treatment:

- NRS or VAS for spasticity (scale of 0 to 10)
- 30% or 50% reduction in spasticity symptoms on NRS
- Ashworth Spasticity Scale is a clinical measure of muscle spasticity based on an assessment of a patient's muscle tone in different muscle groups that ranges from grade 0, which indicates no increase in muscle tone, to grade 4, which indicates "lead pipe" rigidity
- Barthel Index of Activities of Daily Living assesses the amount of time and assistance a patient requires for a range of activities (e.g., cutting, spreading butter, bathing). A score of 0 is totally dependent and a score of 100 is fully independent.
- Walking speed as assessed by timing Global Impression
- Patient global impression of change.

A beneficial outcome of cannabis in patients with MS would be a reduction in spasticity and improvement in function and quality of life.

A harmful outcome of cannabis in patients with MS would be neurological and cognitive adverse effects.

The benefits and harms of long-term use should be studied at 1 year or more.

Study Selection Criteria

Because multiple, recent systematic reviews of RCTs on cannabis for MS associated spasticity are available, the focus of the following section is on these systematic reviews. Additional RCTs published after the systematic reviews are discussed in detail only if they address limitations identified in the systematic reviews.

Review of Evidence

Systematic Reviews

The meta-analysis by Whiting et al (2015) described above included 14 placebo-controlled studies on cannabis for spasticity; 11 of these (N=2138) were for patients with MS and 3 studies (N=142) were for patients with spinal cord injury.[7,] Studies assessed nabiximols (n=6), dronabinol (n=3), nabilone (n=1), THC/CBD (n=4, 2 of these also assessed dronabinol), and 1 each for ECP002A and smoked THC. Twelve of the 14 studies were either at unclear or high-risk of bias and studies conducted in patients with spinal cord injury did not provide sufficient data to allow summary estimates. In patients with MS, cannabinoids (nabilone and nabiximols) were associated with a greater average improvement in spasticity assessed using the NRS (mean difference, −0.76; 95% CI, −1.38 to −0.14; 3 trials), but the association of cannabinoids (nabiximols, dronabinol, and THC/CBD, 5 trials) with improvement on the Ashworth scale for spasticity did not reach statistical significance (weighted mean difference, −0.12; 95% CI, −0.24 to 0.01). Other measures of spasticity also suggested a greater benefit of cannabinoids but did not reach statistical significance. The average number of patients who reported an improvement on a global impression of change score was greater with nabiximols than placebo (odds ratio, 1.44; 95% CI, 1.07 to 1.94; 3 trials). Sensitivity analyses that included crossover trials showed results consistent with those based on parallel group trials alone. Based on the meta-analysis of Whiting et al (2015), the National Academies concluded that in adults with MS-related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms, but not physician-reported spasticity.[1,]

A 2014 systematic review for the American Academy of Neurology also concluded, based on 4, Class I studies, that oral cannabis extract, THC, and nabiximols are either established as effective or probably effective for reducing patient-reported spasticity scores, but are probably ineffective for reducing objective measures of spasticity at short-term.[68,] Based on Class II studies, the American Academy of Neurology concluded that cannabinoids are possibly effective for reducing objective measures of spasticity at 1 year.

Section Summary: Multiple Sclerosis-Related Spasticity

The evidence on cannabinoids for the treatment of spasticity in patients with MS includes 4 Class I RCTs with pharmaceutical products. Results indicate an improvement in patient-reported spasticity symptoms, with no improvement in objective measures of spasticity in the short-term. Evidence for a reduction of objective measures of spasticity with cannabis at 1 year is based on Class II studies, leading to a conclusion that cannabinoids are possibly effective. High-quality evidence that evaluates inhaled or extracted cannabinoids is needed to determine whether medical cannabis can improve spasticity in individuals with MS.

Summary of Evidence

For individuals who have chronic non-cancer pain who receive inhaled cannabis or extracted cannabinoids, the evidence includes RCTs and systematic reviews of those trials. Relevant outcomes are symptoms, functional outcomes, quality of life, medication use, and treatment-related morbidity. Most trials on cannabis for chronic non-cancer pain are randomized crossover studies, with periods of active cannabinoids or placebo in a within-subject design. Also, most trials have used pharmaceutical products, either synthetic THC (delta 9-tetrahydrocannabinol) or a plant-derived THC/CBD product that is administered as an oromucosal spray. Studies with the pharmaceutical products, including ones that are available only outside of the U.S., provide only indirect evidence of the potential

benefits of cannabis available at dispensaries. Five controlled trials were identified that evaluated inhaled cannabis, and no studies were identified with edible cannabis products. Systematic reviews of the available studies have concluded there is low to moderate strength evidence that either inhaled cannabis or an oromucosal cannabis spray can reduce neuropathic pain. One systematic review that evaluated the evidence separately for different pain types concluded that the benefit was only for peripheral neuropathic pain (e.g., diabetic neuropathy), with insufficient evidence or insufficient support for other pain types (e.g., central neuropathic pain, fibromyalgia, rheumatoid arthritis). It is notable that 2 systematic reviews, in addition to a third AHRQ living systematic review, of studies on cannabinoids for neuropathic pain that included randomized and mostly double-blind trials found modest treatment effects favoring the use of cannabinoids over placebo for a reduction in pain intensity and the likelihood of a 30% reduction in pain. None of these reviews distinguishes among different types of neuropathic pain. Another systematic review found that oral formulations were more effective than either smoked or oromucosal spray. Many of the trials have fewer than 50 participants and there is evidence of publication bias. Overall, there are important questions that need to be addressed to reach conclusions regarding the efficacy of medical cannabis for chronic non-cancer pain. Further study is needed to identify if there are specific chronic non-cancer pain types that can be effectively treated with medical cannabis, and to determine what doses and delivery modes are effective. Long-term use of at least 1 year needs to be studied to evaluate benefits and harms. Approval of specific formulations by the FDA is also needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have cancer pain who receive inhaled cannabis or extracted cannabinoids, the evidence includes RCTs and systematic reviews of those trials. Relevant outcomes are symptoms, functional outcomes, quality of life, medication use, and treatment-related morbidity. The evidence on cannabis for the treatment of cancer pain includes 3 double-blind placebo-controlled RCTs with over 1000 patients. These trials were conducted in patients with advanced cancer who had unalleviated pain despite optimized opioid therapy. The group that received an oromucosal spray of extracted cannabis did not have improved pain scores compared to placebo controls. There was a favorable effect on the quality of life. Meta-analyses found no benefit of cannabinoids on cancer pain. Generalizability of results is limited since the studies included patients with cancer who had moderate to severe pain despite high-dose opioid therapy. Further study is needed to determine whether specific subgroups of patients with cancer pain may benefit from cannabinoids, and what doses and delivery modes are effective. Approval of specific formulations by the FDA is also needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have acute post-operative pain who receive inhaled cannabis or extracted cannabinoids, the evidence includes RCTs and systematic reviews of those trials. Relevant outcomes are symptoms, functional outcomes, quality of life, medication use, and treatment-related morbidity. The evidence on cannabinoids for the treatment of acute post-operative pain includes 2 systematic reviews. One systematic review that evaluated evidence with cannabis for acute post-operative pain found a small, but significant, reduction in pain scores compared to placebo, but this was driven primarily by 1 trial with intramuscular administration of levonantradol (not available in the US). When results were stratified by route of administration, there was no significant treatment effect on pain scores for oral cannabis compared to placebo. The other systematic review only provided a qualitative analysis, but concluded that available RCTs do not demonstrate an overall benefit with cannabinoids on acute post-operative pain. Approval of specific formulations by the FDA is also needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have spasticity associated with MS who receive inhaled cannabis or extracted cannabinoids, the evidence includes RCTs and systematic reviews of those trials. Relevant outcomes are symptoms, functional outcomes, quality of life, medication use, and treatment-related morbidity. The evidence on cannabinoids for the treatment of spasticity in patients with MS includes 4, Class I

RCTs with pharmaceutical products. Results indicate an improvement in patient-reported spasticity symptoms, with no improvement in objective measures of spasticity in the short-term. Evidence for a reduction of objective measures of spasticity with cannabis at 1 year is based on Class II studies, leading to a conclusion that cannabinoids are possibly effective. High-quality evidence that evaluates inhaled or extracted cannabinoids is needed to determine whether medical cannabis can improve spasticity in individuals with MS. Approval of specific formulations by the FDA is also needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Neurology

The American Academy of Neurology (AAN) last updated their position statement on the use of medical marijuana for neurologic disorders in 2020 (first published in 2014).[69,] The AAN "does not support the use of, nor any assertion of therapeutic benefits of, cannabis products as medicines for neurologic disorders in the absence of sufficient scientific peer-reviewed research to determine their safety and specific efficacy. The Food and Drug Administration (FDA)-approved plant-based cannabidiol product is an example that has now proven to be sufficiently safe and effective for the treatment of seizures for certain epilepsy patients." Further, the position notes that "existing limited medical research does not support the present and proposed legislative policies across the country that promote cannabis-based products as treatment options for the majority of neurologic disorders." The AAN also supports conducting rigorous Institutional Review Board-approved research and "reclassification of cannabis used for medical purposes from its current Schedule I status to Schedule II to allow for medical research." Lastly, the AAN also "recommends that each product and formulation of cannabis used in treating medical conditions demonstrate safety and efficacy via scientific study similar to the process required by the FDA for the approval of any drug" and "it is not appropriate to extrapolate the results of trials of standardized preparations to other non-standardized, non-regulated medical cannabis products."

The AAN published an evidenced-based guideline in 2014 (reaffirmed in 2020) on complementary and alternative medicine in multiple sclerosis.[70,] For cannabinoids, the AAN evaluated the available literature based on the specific formulation. Table 7 provides the recommendations related to symptoms of spasticity and pain.

Table 7. Cannabinoid Recommendations for Use in Multiple Sclerosis.

Cannabinoid	Number and Class of Studies[a]	Outcome	Recommendation Level[b]
Oral cannabis extract	2 Class I, 1 Class II, and 1 Class III	Symptoms of spasticity, pain	A Effective
	1 Class I	Signs of spasticity (short-term), tremor (short-term)	B Ineffective
	1 Class II	Signs and symptoms of spasticity (long-term)	C Effective
Synthetic THC	1 Class I, 1 Class II	Symptoms of spasticity, pain	B Effective

Cannabinoid	Number and Class of Studies[a]	Outcome	Recommendation Level[b]
	1 Class I	Signs of spasticity (short-term), tremor (short-term)	B Ineffective
	1 Class II	Signs and symptoms of spasticity (long-term)	C Effective
Sativex oromucosal spray	3 Class I, 2 Class II, 3 Class III	Symptoms of spasticity, pain, urinary frequency	B Effective
Smoked cannabis	2 Class III	Spasticity, pain, balance and posture, cognition	U

[a]Studies graded Class I are judged to have a low risk of bias, studies graded Class II are judged to have a moderate risk of bias, studies graded Class III are judged to have a moderately high risk of bias.
[b]A=established as effective or ineffective; B=probably effective or ineffective; C=possibly effective or ineffective; U=insufficient evidence to determine effectiveness or ineffectiveness.

In 2022, the AAN updated its guideline for oral and topical treatments for painful diabetic polyneuropathy.[71,] The following recommendation was made regarding the use of nabilone in this setting:

> "Nabilone, a synthetic cannabinoid, is probably more likely than placebo to improve pain (standardized mean difference [SMD] 1.32; 95% confidence interval [CI], 0.52 to 2.13; large effect, moderate confidence; 1 Class I study)."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guideline on adult cancer pain (version 1.2022) does not provide recommendations for use of cannabinoids and medical marijuana/ cannabis.[72,] A summary of evidence is provided as the use of medical marijuana among cancer patients is common. The guideline notes that "data supporting the use of cannabinoids as adjuvant analgesics for treatment of cancer pain are extremely limited and the results from what little data exists are somewhat conflicting," based on 2 trials with positive results with nabiximols and another 2 trials that found no benefit with tetrahydrocannabinol (THC) extract alone and nabiximols, respectively.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 8.

Table 8. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02892591	A double-blind, placebo-controlled crossover study comparing the analgesic efficacy of cannabis versus oxycodone	100	June 2023
NCT03635593[a]	Cannabis Oil for Chronic Non-CancEr Pain Treatment [CONCEPT] - Alpha (α): A Randomized Controlled Trial	309	Jan 2021
NCT03734731	Clinical Trial Policy Study for the Objective Comparison of Cannabis Vs Opioids (CVO) Pain Management and Therapy Types for Circulatory and Chronic Pain Issues	1000	Jan 2025

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03215940	Treatment of Chronic Pain With Cannabidiol (CBD) and Delta-9-tetrahydrocannabinol (THC): Effectiveness, Side Effects and Neurobiological Changes	75	Mar 2023
NCT04308148	Does Medical Cannabis Reduce Opioid Use in Adults With Pain: An Observational Study	352	Oct 2023
NCT04729179	Cannabidiol for Fibromyalgia -The CANNFIB Trial Protocol for a Randomized, Double-blind, Placebo-controlled, Parallel-group, Single-center Trial	200	Feb 2023
NCT04360044	Efficacy of Inhaled Cannabis Versus Placebo for the Acute Treatment of Migraine: a Randomized, Double-blind, Placebo-controlled, Crossover Trial	120	Nov 2023
ALCTRN12618001220257	Oral Medicinal Cannabinoids to Relieve Symptom Burden in the Palliative Care of Patients With Advanced Cancer: A Double-Blind, Placebo Controlled, Randomised Clinical Trial of Efficacy and Safety of Cannabidiol (CBD)		
Unpublished			
NCT01595620	Cannabinoid modulation of pain	120	Apr 2012

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	None	
HCPCS	J3490	Unclassified drugs

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
09/01/2020	New policy.
08/01/2021	Annual review. Policy statement and literature review updated. Policy title changed from Medical Cannabis for the Treatment of Chronic Pain and Spasticity to current one.
08/01/2022	Annual review. No change to policy statement. Literature review updated.
08/01/2023	Annual review. No change to policy statement.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Medical Cannabis for the Treatment of Pain and Spasticity 5.01.32 **Policy Statement:** I. Inhaled cannabis or extracted cannabinoids are considered **investigational** for **any** of the following: A. Treatment of chronic non-cancer pain B. Treatment of cancer pain C. Acute post-operative pain D. Treatment of spasticity associated with multiple sclerosis E. All other conditions that have not received approval from the U.S. Food and Drug Administration	**Medical Cannabis for the Treatment of Pain and Spasticity 5.01.32** **Policy Statement:** I. Inhaled cannabis or extracted cannabinoids are considered **investigational** for **any** of the following: A. Treatment of chronic non-cancer pain B. Treatment of cancer pain C. Acute post-operative pain D. Treatment of spasticity associated with multiple sclerosis E. All other conditions that have not received approval from the U.S. Food and Drug Administration