5.01.32 Medical Cannabis for the Treatment of Chronic Pain and Spasticity

Original Policy Date: September 1, 2020
Effective Date: September 1, 2020
Section: 5.0 Prescription Drug
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Policy Statement

Inhaled cannabis or extracted cannabinoids are considered investigational for any of the following:

- Treatment of chronic non-cancer pain
- Treatment of cancer pain
- Treatment of spasticity associated with multiple sclerosis
- All other conditions that have not received approval from the U.S. Food and Drug Administration

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, 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 U.S. Food and Drug Administration (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(R) oral solution and Syndros(R) 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®), 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(R) GW Pharmaceuticals) is an oral solution containing CBD that is concentrated from cannabis plants. It is indicated for the treatment of seizures associated with 2 rare and severe forms of epilepsy, Lennox-Gastaut syndrome, and Dravet syndrome. Epidiolex received FDA approval in 2018.
- 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.

Following the FDA approval of Epidiolex, the Drug Enforcement Administration announced that Epidiolex would be placed in Schedule V, the least restrictive class. Non-Epidiolex CBD remains 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. 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). 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. 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. 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. 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-approved drug Epidiolex) 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 March 10, 2020, 33 states plus the District of Columbia, Guam, Puerto Rico and the U.S. Virgin Islands had established comprehensive medical cannabis programs.

**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 a 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. RCTs 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. For example, in April 2020, 65% of active patients in the Minnesota Medical Cannabis Program were certified as having intractable pain. 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. 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.

**Patients**

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. 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], 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
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 (6462 participants) 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), brief pain inventory-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 (see 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 by 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 (AE), 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=0.02) 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.

Johal et al (2020) included 29 placebo controlled trials in a systematic review of the effect of cannabinoids on pain with a search through 2018.10. 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.

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

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</thead>
<tbody>
<tr>
<td>Serpell et al (2014)</td>
<td>Neuropathic - peripheral</td>
<td>nabiximols vs placebo</td>
<td>246</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<tr>
<td>Numikko et al (2007)</td>
<td>Neuropathic - peripheral</td>
<td>nabiximols vs placebo spray</td>
<td>125</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Toth et al (2012)</td>
<td>Diabetic neuropathy</td>
<td>nabilone vs placebo</td>
<td>26</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<tr>
<td>GW Pharma (2012) NCT00710424</td>
<td>Diabetic neuropathy</td>
<td>nabiximols vs placebo spray</td>
<td>297</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Blake et al (2006)</td>
<td>Rheumatoid arthritis</td>
<td>nabiximols vs placebo spray</td>
<td>58</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<td>●</td>
</tr>
<tr>
<td>GW Pharma (2012) NCT01606176</td>
<td>Pain related to MS</td>
<td>nabiximols vs placebo spray</td>
<td>70</td>
<td>●</td>
<td>●</td>
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<tr>
<td>Schimrigk (2017)</td>
<td>Pain related to MS</td>
<td>dronabinol capsule vs placebo</td>
<td>240</td>
<td>●</td>
<td>●</td>
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<td></td>
<td>●</td>
</tr>
</tbody>
</table>
Table 2. Systematic Review and Meta-analyses Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Pain Type</th>
<th>Preparation</th>
<th>N (Range)</th>
<th>Design</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whiting et al (2015)2</td>
<td>Chronic pain</td>
<td>nabimols vs placebo</td>
<td>2454 (10 to 360)</td>
<td>RCTs and observational studies</td>
<td>Hours to weeks</td>
</tr>
<tr>
<td>Andreae et al (2015)3</td>
<td>Chronic neuropathic pain</td>
<td>nabimols vs placebo</td>
<td>178 (23-50)</td>
<td>RCTs</td>
<td>Hours to 2 weeks</td>
</tr>
</tbody>
</table>

CRPS: complex regional pain syndrome; DM: diabetes mellitus; MS: multiple sclerosis; SCI: spinal cord injury

Additional trials on spasticity were included.
<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butler et al (2017)</td>
<td>2003-2015</td>
<td>19</td>
<td>Chronic non-cancer pain</td>
<td>1309 (15 to 339)</td>
<td>RCTs and observational studies</td>
<td>At least 2 weeks</td>
</tr>
<tr>
<td>Mucke et al (2018)</td>
<td>up to 2017</td>
<td>16</td>
<td>Chronic neuropathic pain</td>
<td>1750 (20-339)</td>
<td>RCTs</td>
<td>2 to 26 weeks</td>
</tr>
<tr>
<td>Johal et al (2020)</td>
<td>2002-2018</td>
<td>29a</td>
<td>Non-cancer pain</td>
<td>2345 (13-339)</td>
<td>RCTs</td>
<td>1 day to 6 months</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial.

aAdditional trials on spasticity were included.

### Table 3. Systematic Review and Meta-analyses Results

<table>
<thead>
<tr>
<th>Study</th>
<th>All Chronic Pain</th>
<th>Neuropathic Pain - Mixed</th>
<th>Neuropathic Pain - Peripheral</th>
<th>MS-related Pain</th>
<th>Rheumatoid Arthritis</th>
<th>Fibromyalgia</th>
<th>Serious Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whiting et al (2015)²</td>
<td>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</td>
<td>Cannabinoids were associated with greater average reductions in the NPS and a greater proportion of patients showing a 30% reduction in neuropathic pain</td>
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<tr>
<td>Odds ratio (95% CI)</td>
<td>2.08 (1.21 to 3.59)</td>
<td>1.38 (0.93 to 2.03)</td>
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<tr>
<td>Andreae et al (2015)²</td>
<td>Inhaled cannabis resulted in a higher proportion of patients achieving a 30% decrease in pain.</td>
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<tr>
<td>Odds ratio (CRI95%)</td>
<td>3.2 (1.59 to 7.24)</td>
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<td>NNT (CRI95%)</td>
<td>5.55 (3.35 to 13.7)</td>
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<tr>
<td>Posterior probability</td>
<td>99.7%</td>
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</table>

Butler et al (2017)³³³ Total N N=735 Low strength evidence from 3 studies that nabiximols reduces peripheral neuropathic pain Total N=444 Evidence is insufficient - possibility of no difference for nabiximols vs placebo Total N=58 Evidence is insufficient to draw a conclusion No difference between nabilone and amitriptyline for pain Total N=72 Increase in adverse events compared to placebo. Only one study compared AEs with
<table>
<thead>
<tr>
<th>Study</th>
<th>All Chronic Pain</th>
<th>Neuropathic Pain - Mixed</th>
<th>Neuropathic Pain - Peripheral</th>
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<th>Rheumatoid Arthritis</th>
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<th>Serious Adverse Events</th>
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<tbody>
<tr>
<td><strong>Mucke et al</strong> (2018)</td>
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<tr>
<td>Cochrane</td>
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<td>Other treatments</td>
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<td><strong>Cannabis</strong></td>
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<td>Placebo</td>
<td>39%</td>
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<tr>
<td>Risk difference</td>
<td><strong>0.05 (0.00 to 0.09)</strong></td>
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<td>(95% CI)</td>
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<td><strong>Johal et al</strong> (2020)</td>
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| AE: adverse events; BPI: brief pain inventory; CI: confidence interval; CRI: Bayesian credible interval; MS: multiple sclerosis; NNT: number needed to treat; NPS: neuropathic pain scale; NRS: numerical rating 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 a meta-analysis of studies on cannabis for neuropathic pain that included only double-blind controlled trials found a modest difference between the active and control conditions in the number of patients achieving a 30% reduction in pain (39% vs 33%, respectively), but did not distinguish 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 2019 indicated that 9% 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.

**Patients**

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 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**
The systematic review and meta-analysis by Whiting et al (2015) included both cancer pain and non-cancer pain, and also included trials with a acute (less than 1 day) treatment duration. For patients with cancer pain, a meta-analysis of 2 trials (Johnson et al (2010), Portenoy (2012)) found that cannabinoids were associated with a greater proportion of patients showing a reduction in pain (OR, 1.41 [95% CI, 0.99-2.00]).

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 and have similar protocols. The first trial reported by Fallon et al (2017) enrolled 399 patients with a second withdrawal trial in 216 patients. The trial by Lichtman (2018) enrolled 397 patients. 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. They identified 6 RCTs (total 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 numeric rating scale pain scores. Meta-analysis of the 3 phase 3 studies also showed no benefit of treatment (mean difference -0.021, p=0.80). Treatment with cannabinoids was associated with a higher risk of somnolence (odds ratio 2.69, 95% CI 1.54 to 4.71, p<0.001) and dizziness (odds ratio 1.58, 95% CI 0.99 to 2.51, p=0.05). 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.

**Section Summary: Chronic Non-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.

**Multiple Sclerosis-Related Spasticity**

**Clinical Context and Therapy Purpose**
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.

**Patients**
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 in March 2019 indicated that 12% 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 which 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
The meta-analysis by Whiting et al (2015) described above included 14 placebo-controlled studies on cannabis for spasticity; 11 of these (2138 participants) were for patients with MS and 3 studies (142 participants) were for patients with spinal cord injury. 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.

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. 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 randomized controlled trials (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 cannabis 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 (cannabidiol) 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 a meta-analysis of studies on cannabis for neuropathic pain that included only double-blind controlled trials found a modest difference.
between the active and control conditions in the number of patients achieving a 30% reduction in pain (39% vs 33%, respectively), but this systematic review did not distinguish 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 U.S. Food and Drug Administration (FDA) is also needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

**Supplemental Information**

**Practice Guidelines and Position Statements**

**American Academy of Neurology**

In 2018, the American Academy of Neurology (AAN) published a position statement on the use of medical marijuana for neurologic disorders. The AAN "supports scientific research of medical marijuana and rescheduling from Schedule I to Schedule II to encourage more scientists to investigate the safety and potential benefits. The AAN does not support the legalization or prescribing of medical marijuana for use in neurologic disorders." In addition, the AAN "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 U.S. Food and Drug Administration (FDA) for the approval of any drug."
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 unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

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<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>NCT03693833</td>
<td>CBD Treatment in Hand Osteoarthritis and Psoriatic Arthritis: A Randomized,</td>
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<td></td>
<td>Double-blind Placebo Controlled Study</td>
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<td>NCT01595620</td>
<td>Cannabinoid modulation of pain</td>
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<td>Jun 2020</td>
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<td>NCT02892591</td>
<td>A double-blind, placebo-controlled crossover study comparing the analgesic</td>
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<td>Dec 2020</td>
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<td>efficacy of cannabis versus oxycodone</td>
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<td>NCT03635593a</td>
<td>Cannabis Oil for Chronic Non-Cancer Pain Treatment [CONCEPT] - Alpha (α):</td>
<td>309</td>
<td>Jan 2021</td>
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<td></td>
<td>A Randomized Controlled Trial</td>
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<td>NCT03734731</td>
<td>Clinical Trial Policy Study for the Objective Comparison of Cannabis Vs</td>
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<td>Opioids (CVO) Pain Management and Therapy Types for Circulatory and Chronic</td>
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<td>Pain Issues</td>
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<td>Oral Medicinal Cannabinoids to Relieve Symptom</td>
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<td>Burden in the Palliative Care of Patients With Advanced Cancer: A Double-</td>
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<tr>
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<td>Blind, Placebo Controlled, Randomised Clinical Trial of Efficacy and Safety</td>
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<tr>
<td></td>
<td>of Cannabidiol (CBD)</td>
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</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

References


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. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE

The following services may be considered investigational.

<table>
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<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tr>
<td>CPT®</td>
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<tr>
<td>HCPCS</td>
<td>J3490</td>
<td>Unclassified drugs</td>
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Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>09/01/2020</td>
<td>New policy.</td>
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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.

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.