INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Medical Cannabis***

-January 2024-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of medical cannabis and select cannabis-based medicines. There are no cannabis-based medicines which are FDA-approved, except for rare indications. Nevertheless, a U.S.-based survey in 2017 among people reporting cannabis use (9005 participants, 55% response rate) found that the vast majority use medical cannabis for mood disorders, insomnia, and pain.[1] For these indications, the NPTC analyzed all available medical literature of usable quality. Currently, the evidence does not support the use of medical cannabis for any indication. As a result of the review, the NPTC made **no modifications** to the National Core Formulary.

Discussion:

Cannabidiol (CBD) is a non-psychoactive ingredient of the cannabis plant and, as a prescription drug (i.e., Epidiolex®), is currently FDA approved for specific, rare seizure disorders including seizures associated with Lennox-Gastaut or Dravet syndromes and seizures associated with tuberous sclerosis complex. Dronabinol (Marinol®, Syndros®), a synthetic but chemically identical form of delta-9-tetrahydrocannabinol (THC), is FDA approved for anorexia associated with weight loss in patients with AIDS, and nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

Nabiximols (Sativex®) is an oromucosal spray with a 1:1 ratio of CBD to THC and is approved in Canada for spasticity associated with multiple sclerosis, while nabilone (Cesamet®) is a synthetic cannabinoid approved in Canada for chemotherapy-associated nausea and vomiting. While neither product is approved in the U.S., both are prescribed in other countries and most higher quality research findings are derived from these formulations.

Studies of medical cannabis to treat mood, sleep, and pain usually observe clinically significant placebo responses. Furthermore, cannabis use is fraught with confounders not easily amenable to statistical adjustment including but not limited to political and religious views, use of alcohol and other psychoactive substances, and trust in institutions. For these reasons, this review focuses solely on findings derived from randomized, controlled trials (RCT).

The Cochrane Library workgroup has previously evaluated cannabis for cancer pain and neuropathic pain. While the evidence did not show benefit for cancer pain,[2] authors did note moderate quality evidence for a small increase in the number of patients experiencing a 30% reduction in neuropathic pain vs placebo (39% vs. 33%; Risk Difference [RD] 0.09 {95% CI: 0.03 to 0.15}); NNTB 11 (95% CI: 7 to 33). However, harms may outweigh benefits. There were increases in nervous system adverse events vs. placebo (61% vs 29%; RD 0.38 [95% CI: 0.18 to 0.58]); NNTH 3 (95% CI: 2 to 6); psychiatric disorders vs. placebo (17% vs. 5%; RD 0.10 [95% CI: 0.06 to 0.15]); NNTH 10 (95% CI: 7 to 16); and withdrawals from the studies due to adverse events vs. placebo (10% vs 5%; RD 0.04 (95% CI: 0.02 to 0.07); NNTH 25 (95% CI: 16 to 50).[3]

The Oregon Health Sciences University, in collaboration with the Department of Veterans Affairs and the Agency for Healthcare Research and Quality, publishes an updated systematic review every quarter on cannabis-based medicines for chronic pain. Currently, there is only one benefit for which there is at least moderate quality evidence; that nabiximols has a small effect on pain severity and function which may be outweighed by large adverse effects of dizziness and sedation.[4] Conversely, a review by Bell et al., concluded that "we recommend the use of [cannabis-based medicine] as monotherapy, replacement, or adjunct treatment, in people living with chronic pain, for the management of chronic pain including central and/or peripheral neuropathic pain to improve pain outcomes" [Strong Recommendation, Moderate-Quality Evidence].[5] In light of these conflicting views, the NPTC separately analyzed every RCT included in the above reviews. Furthermore, the NPTC also analyzed every RCT found by PubMed on medical cannabis for anxiety, depression, post-traumatic stress disorder (PTSD), pain, and sleep. For search algorithm details and the full reference list, please contact the NPTC.

For all mood disorders, including anxiety, depression, and PTSD, the NPTC found only one study of at least low quality: a double-blind, cross-over RCT of smoked cannabis that included 80 U.S. military veterans with DSM-5 diagnosed PTSD with a CAPS-5 score ≥ 25. Each veteran spent 3 weeks in each of 4 treatment arms: (1) 12% THC, (2) 11% CBD, (3) 8% THC and CBD, and (4) cannabis with THC and CBD removed (placebo). All participants (100% of THC groups) correctly guessed that they had been assigned to active treatment. Despite this complete failure of blinding, there was no significant difference between any of the treatment arms.[6]

In the review of medical cannabis for pain, the NPTC reviewed 38 RCTs. There was broad consensus among the NPTC that the most positive trials were of generally low to very low quality, and that the higher quality trials had mostly negative findings. Listed below are the highest quality trial findings of medical cannabis for pain reviewed:

Neuropathic pain: (highest quality positive data was reported in non-diabetic causes of neuropathic pain with allodynia)

- 246 adults treated with nabiximols or placebo for 15 weeks. Blinding was not confirmed. While there was no significant difference in mean pain severity, a significantly higher number of people in the nabiximols group achieved a 30% reduction in pain (28% Sativex® vs. 16% placebo; *p*=0.034). There was also sleep improvement of borderline clinical significance (-0.83 on a 0-10 visual analog scale (VAS), *p*=0.007).[7]
- 115 adults with neuropathic pain were treated for 8 weeks and randomized to 1 of 4 groups: CBD 50mg/day, THC 25mg/day, both, or placebo. CBD was statistically but not clinically significantly worse than placebo for pain and sleep. No other significant findings for pain or sleep were noted.[8]
- 297 adults with diabetic neuropathic pain treated with nabiximols or placebo for 14 weeks. No significant differences in pain or sleep.[9]

Abdominal pain:

- 62 patients with chronic abdominal pain due to surgery or chronic pancreatitis treated with THC 24mg/day or placebo for 7 weeks. No significant differences in pain or sleep.[10]

Cancer pain:

- 397 patients with pain due to advanced cancer treated with nabiximols or placebo for 5 weeks. No significant difference for pain. Decreased sleep disruption reported of doubtful clinical significance (-0.38 on a 0-10 VAS, p=0.026).[11]

Multiple sclerosis (MS) pain:

- 238 adults with MS neuropathic pain treated with dronabinol 15mg/day or placebo for 16 weeks. No significant difference for pain or quality of life.[12]
- 630 adults with MS and "problematic spasticity" treated with THC 25mg/day, THC/CBD 25mg/12.5mg/day, or placebo for 14 weeks. As one of many secondary outcomes, participants were asked at the end of the study whether pain and sleep was "improved". Reportedly, pain "improved" 46% on THC, 50% on THC/CBD, and 30% of those receiving placebo (*p*=0.002). Sleep "improved": 47% on THC, 50% on THC/CBD, and 36% in those receiving placebo (*p*=0.025). Unable to ascertain the clinical significance of this binary outcome.[13]
- 339 adults with MS neuropathic pain treated with nabiximols or placebo for 15 weeks. No significant differences in pain or sleep.[14]
- 335 adults with MS neuropathic pain treated with nabiximols or placebo for 15 weeks. No significant differences in pain or sleep.[15]

Musculoskeletal pain:

- 136 adults with hand osteoarthritis or psoriatic arthritis treated with CBD 30mg/day or placebo for 12 weeks. No significant differences for pain or sleep.[16]
- 58 patients with rheumatoid arthritis treated with nabiximols or placebo for 5 weeks. On a 0-10 VAS, pain improved vs. placebo -0.95 (*p*=0.044), and sleep improved -1.17 (*p*=0.027).[17]

Notably, current practice guidelines from the National Institute of Health and Care Excellence (U.K.) and the College of Family Physicians of Canada both recommend against all cannabis-based medications for all pain indications.[18,19]

For sleep, the NPTC analyzed 6 RCTs with improvement in sleep as the primary outcome. The quality of these trials was uniformly low to very low. Much of the limited evidence for efficacy of cannabis-based medicines for sleep is derived from secondary outcomes in pain or spasticity trials, such as those listed above.

Findings:

Mood Disorders: Despite this indication serving as the most popular intended medicinal use for cannabinoids, it has gone largely unstudied.
Pain: Most higher quality data suggests no effect. Positive trials have found an effect of borderline clinical significance.
Sleep: Data is conflicting. Cannabinoids may provide short-term sleep improvements of borderline clinical significance.

There is a strong need for additional research based on the following supporting statements; (1) currently available evidence is strong enough to justify investment in higher quality research on products commonly used in the U.S.; (2) even the longest published RCTs to date are only 14-16 weeks in duration; (3) longer studies are needed to determine long term effectiveness and side effects, such as hyperalgesia; and (4) larger studies will improve safety data on uncommon but severe side effects, such as psychosis.

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