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Cannabis Has Low Risks, Small Benefits for All Types of Chronic Pain, Say New International Guidelines

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Patients who experience chronic pain that is not relieved with standard care—whether from cancer or other conditions—should be offered a trial of non-inhaled medical cannabis or cannabinoids, according to a recommendation characterized as “weak” by an expert panel for the Rapid Recommendations series in *BMJ* (2021;374:n2040. doi:10.1136/bmj.n2040).

“The recommendation is weak because of the close balance between benefits and harms of medical cannabis for chronic pain,” wrote the guideline authors, who were led by Jason W. Busse, DC, PhD, the associate director of the Michael G. DeGroot Centre for Medicinal Cannabis Research at McMaster University, in Hamilton, Ontario. “It reflects a high value placed on small to very small improvements in self-reported pain intensity, physical functioning and sleep quality, and willingness to accept a small to modest risk of mostly self-limited and transient harms.”

The guideline recommendations follow a concurrently published systematic review and meta-analysis by lead author Li Wang, PhD, an assistant professor in anesthesia at McMaster University, and colleagues, also published in *BMJ* (2021;373:n1034. doi:10.1136/bmj.n1034).

Their review of 32 trials with 5,174 adult patients, mainly with chronic noncancer pain (28/32 trials), included 29 placebo-controlled comparisons with medical cannabis or cannabinoids, with follow-up periods up to 5.5 months.



The researchers consider their review to be more comprehensive than those previously conducted, including the one that informed the United Kingdom's 2019 National Institute for Health and Care Excellence (NICE) guidelines. That review included only 12 of the trials in the present review, while also including eight trials that the current study authors had excluded for having insufficient periods of follow-up.

"Although the recent guidelines from NICE and the International Association for the Study of Pain [IASP] recommend against the use of medical cannabis for chronic pain, both NICE and IASP reviews stratified effects by type of cannabis or cannabinoid without subgroup analyses to confirm systematic differences in effects, which greatly limited their ability to conduct meta-analyses," Wang told *Pain Medicine News*.

Wang explained that when compared with placebo, non-inhaled medical cannabis probably results in a small increase in the proportion of patients who experience at least the minimally important difference of 1 cm on a 10-cm visual analog scale of pain relief, with a modified risk difference (RD) of 10% (95% CI, 5%-15%). Similarly, they determined that medical cannabis taken orally results in a very small improvement in physical functioning (RD, 4%; 95% CI, 0.1%-8%).

Wang and colleagues concluded that there was moderate- to high-certainty evidence of small to very small improvement in pain relief, physical functioning and sleep quality among patients with chronic pain compared with placebo, along with several transient adverse effects.

"Consultation with our patient partners, and our review of patients' values and preferences suggests that many people living with chronic pain would be interested in a 10% chance at achieving important pain relief," Wang said.

Of the adverse effects, they found evidence of moderate certainty for cognitive

impairment (RD, 2%; 95% CI, 0.1%-0.6%); vomiting (RD, 3%; 95% CI, 0.4%-6%), drowsiness (RD, 5%; 95% CI, 2%-8%), impaired attention (RD, 3%; 95% CI, 1%-8%) and nausea (RD, 5%; 95% CI, 2%-8%); and high-certainty evidence of increased risk for dizziness (RD, 9%; 95% CI, 5%-14%).

Guidelines Cover All Pain Types

In a *BMJ* editorial (2021;374:n1942. doi:10.1136/bmj.n1942) that accompanied the review and the guideline publications, Edeltraut Kröger, PhD, an adjunct professor of pharmacy in the Department of Family Medicine at McGill University, in Montreal, and a researcher at the Québec Centre of Aging at Hôpital Saint-Sacrement, and Clermont Dionne, PhD, a professor in the Department of Rehabilitation at Laval University School of Medicine and Hôpital Saint-Sacrement, in Québec City, emphasized the importance of the review finding no significant differences in the effects of medical cannabis on chronic pain—whether neuropathic, nociplastic or nociceptive.

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Noting that the review and the related guidelines recommend a trial of non-inhaled medical cannabis for all chronic pain regardless of origin, Kröger and Dionne suggested that “It may be time for more inclusive recommendations.”

They also offered several caveats, however, including the possibility that self-medication might lead to increased use of cannabis products with less favorable risk–benefit profiles. Although non-inhaled forms were recommended in the guidelines, they point out that patients may prefer inhaled products as they seek a faster and more powerful pharmacologic effect.

“Access to optimal pain treatment is often limited, which could lead to widespread and problematic use of cannabis,” they cautioned. “Other products available for self-medication have uncertain compositions that may often vary between batches, making accurate dosing challenging.”

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In addition, Kröger and Dionne indicated that the distinction between recreational and medical use of cannabis and cannabinoids is not always clear. This can lead some patients—particularly adolescents and younger adults, they noted—to self-medicate with recreational cannabis under the assumption that it is a safe, “medically recommended” substance.

Kröger and Dionne acknowledged that the reviewers found no evidence linking psychosis

to the use of medical cannabis, but they indicated that knowledge of the effects of cannabis products on the young brain is just emerging. “Researchers have observed, for example, that simultaneous use of recreational cannabis and alcohol increases the potential for addiction,” they wrote.

Busse discussed the concerns raised in the editorial with *Pain Medicine News*. “I would agree that clinicians that engage patients in a trial of medical cannabis should monitor response, and that cannabis should be discontinued if patients experience problematic side effects that outweigh benefits, a maximum dose is achieved without important benefits, or patients are diverting cannabis or develop a cannabis use disorder,” he said.

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The guidelines developed by Busse et al offer several recommendations to increase the benefit over risk, including the following:

- Start the therapeutic trial with low-dose, non-inhaled CBD products, gradually increasing the dose and THC level depending on clinical response and tolerability.
- Consider prior cannabis experience, and monitor for adverse events.
- CBD-predominant preparations are preferred for younger or adolescent patients because of uncertain effects of THC on neurocognitive development.

Although the opioid-sparing effects of medical cannabis for chronic pain remain uncertain—with evidence rated as very low certainty—the guideline authors nevertheless consider this a potential strategy. “Clinicians may, however, consider medical cannabis as part of an approach to help facilitate opioid tapering among consenting patients,” they wrote.

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Elaborating on their published recommendations, Busse commented on the benefits of applying effective, and likely multidisciplinary, treatment early in the course of chronic pain, including a possible early trial with cannabis.

“Ideally a successful approach can be identified as early as possible, as chronic pain can have devastating consequences for patients in whom their symptoms greatly reduce their level of functioning. ... As such, it would seem desirable to try and identify treatment options that facilitated functioning sooner rather than later, including medical cannabis,” Busse recommended.

—Kenneth Bender

Two meta-analysis authors reported financial relationships with Evergreen Pacific Insurance Corp., Monk-E Psychedelics, Northern Green Canada, Northern Green Science, Spectrum Therapeutics and Tilray Inc.