Review of 17 trials shows small benefit for MS

Cannabinoids appear to have modest clinical benefits and are safe for the treatment of spasticity, pain, and bladder dysfunction in patients with multiple sclerosis (MS), according to a meta-analysis published recently in ***JAMA Network Open*** (2018; 1[6]:183485).

In this systematic review of 17 randomized, double-blind, placebo-controlled clinical trials including 3,161 patients, cannabinoids were associated with small but significant increases in efficacy for spasticity (as assessed subjectively by patients), pain, and bladder dysfunction compared with placebo.

Efficacy of cannabinoids compared with placebo (expressed as standardized mean difference [SMD]) was SMD=–0.25 SD (95%CI,–0.38 to –0.13 SD) for subjective spasticity; –0.17 SD (95%CI, –0.31 to –0.03 SD) for pain, and –0.11 SD (95%CI, –0.22 to –0.0008 SD) for bladder dysfunction.

In terms of tolerability, cannabinoids had a higher risk of adverse events (AE). Expressed as rate ratio [RR], where RR=1.72 patient-years (95%CI, 1.46–2.02 patient-years) and withdrawals due to AE (2.95 patient-years (95%CI, 2.14 to 4.07patient-years).

Four different cannabinoids were studied, including nabiximols, a mixture of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in an approximate ratio of 1:1; oral cannabis extract (CE) containing THC and CBD from the *Cannabis sativa* plant; dronabinol, an oral synthetic THC; and nabilone, an oral synthetic THC analogue.

None of the interventions demonstrated clear efficacy in the treatment of spasticity when evaluated objectively. However, active treatments of CE, nabiximols, and cannabinoids were associated with significant differences in subjective assessment of spasticity.

Authors noted that this contrasts with findings of the single largest (almost 500 patients), longest (up to three years), and non-corporate-sponsored CUPID study, which favoured placebo for spasticity [subjective], pain, and bladder dysfunction.

"One possible concern in clinical trial results is the impact of industry-funded studies," noted lead author Mari Carmen Torres-Moreno, PhD, Universitat Autònoma de Barcelona, Barcelona, Spain.

"In our meta-analysis, all the studies concerning cannabis extract and dronabinol were funded by independent grants. The study of nabilone and [the majority] of those concerning nabiximols were funded by pharmaceutical companies."

They can be considered safe drugs, the authors noted the risk of AEs with cannabinoids versus placebo did not reach statistical significance. However, cannabinoids were associated with a higher risk of dizziness or vertigo, dry mouth, fatigue, feeling drunk, impaired balance or ataxia, memory impairment, and somnolence.

Of 5,357 AEs analyzed, 325 events were serious AEs (death or threat to a patient's life or functioning) and a total of 260 withdrawals were due to AEs.

In an accompanying editorial (doi:*10.1001/jamanetworkopen.2018.3484*), Drs. Marissa Slaven and Oren Levine, both of McMaster University, Hamilton, noted that "THC has dose-limiting adverse effects occurring at a much lower range (15–30 mg) than CBD, which can be dosed up to several hundred milligrams without treatment withdrawal. While symptomatic benefits of THC have been highlighted, more research is needed, especially given newer information suggesting that higher doses of CBD may in fact be more important in realizing the potential of this category of therapy." —**Kate Kniesel**, *CJMC Correspondent*

Commentary **Anthony Feinstein, MD** Toronto

TRYING TO MAKE sense of cannabis use in people with multiple sclerosis can be challenging. Multiple variables are at play simultaneously: pharmacologically manufactured versus naturally grown; the ratio of tetrahydrocannabinol (THC) versus cannabidiol; and legal versus illegal are just three factors that can determine how the drug is used.

It's very important to make a distinction between the pharmacologically manufactured product assessed in the Torres-Moreno meta-analysis and the grown "street cannabis" now being sold in clinics. I am not particularly familiar with the manufactured preparations, but based on very limited data, they don't necessarily have strong behavioural side effects.

In the Torres-Moreno study and other individual studies, you don't get a prominent effect size, in part because you're dealing with symptoms like spasticity and pain that are difficult to treat. The use of subjectively versus objectively assessed effects further complicates interpretation of the findings.

The data here are very similar to the recent findings of an American Academy of Neurology task force paper, which found that pharmacologically manufactured cannabis was effective in reducing spasticity, pain and bladder dysfunction. There was no comparable evidence for smoked, vaporized or ingested cannabis.

My research has focused on the cognitive and behavioural effects of the non-pharmacologic cannabis that you smoke, vape or ingest. Patients with MS who smoke cannabis are more cognitively impaired than non-users. Cannabis further compromises cerebral compensatory mechanisms already faulty in MS.

The other concern is the enormous variability. Studies aren't reporting the THC-CBD ratio, the potency, or the concomitant use of drugs like nicotine that can also influence symptoms. This makes it almost impossible to compare [data] because you don't have some of the compounds that are being used. There is a world-wide trend—particularly well described in Ontario—that over time the THC component is becoming far more potent.

The major side effects that can occur with opioids can make cannabis seem relatively benign and that's one of the selling points of cannabinoid treatments. Nevertheless, they are clearly not benign substances. These drugs have to be used with caution and patients should be carefully monitored.

Dr. Feinstein (MPhil, PhD, MD, FRCP) is a professor, Department of Psychiatry, University of Toronto and Sunnybrook Health Sciences Centre, Toronto.

CBD supplementation may be helpful for fatigue, pain, spasticity, mobility in MS

As reported in
Frontiers in Neurology
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Cannabidiol (CBD) supplementation may be advisable for people with multiple sclerosis (PwMS) to reduce fatigue, pain, spasticity, and ultimately improve mobility, authors of a recent literature review concluded.

The article noted that these symptoms—along with inflammation and depression—often lead to reduced physical activity and have a negative impact on functional mobility and on the patient's quality of life.

Advances have been made, but "none of the current treatments halts or cures MS-related symptoms. Consequently, many PwMS look for alternative and complementary therapies such as cannabis . . . [a reported] 66% currently use cannabis for symptom treatment. And an increasing number of PwMS use cannabis to improve their mobility," wrote Thorsten Rudroff and Jacob Sosnoff. Lead author Rudroff, PhD, FACSM, is from the Department of Health and Human Physiology, University of Iowa.

Dr. Thorsten Rudroff

Despite limited empirical data regarding its impact on mobility in PwMS, evidence suggests CBD has anti-inflammatory potential, Dr. Rudroff told the CANADIAN JOURNAL OF MEDICAL CANNABIS. "However, we do not know the dosage, which route of delivery is best [smoking, edibles, etc.], or the best ratio of THC:CBD," he added.

"It is very important to distinguish between THC and CBD, and not to talk about cannabis in general," Dr. Rudroff cautioned. The authors explained that cannabis contains around 60 cannabinoids; of these, Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) occur in high concentrations.

"Some researchers believe that some amount of THC is required [for] CBD [to be] effective, said Dr. Rudroff, adding that THC content should not exceed the amount of CBD. Data indicate that cannabis, with 1:1 CBD:THC ratio, reduces muscle spasticity and pain in PwMS, the authors noted.

Mechanisms of anti-inflammatory effects unclear

"The exact mechanisms of the anti-inflammatory effects of CBD are unclear," Dr. Rudroff said: "Some studies have suggested that cannabinoids may exert positive effects . . . by decreasing inflammation and pain. Furthermore, inflammation plays an important role in the generation of MS-related fatigue. Specifically, chronic peripheral inflammation and a resulting overactivity of the vagus nerve."

Indirect evidence suggests that reductions in spasticity, pain, and fatigue may result in mobility improvements for PwMS, the authors wrote. Noting that depression also contributes to impaired mobility in PwMS, and that CBD showed a dose-dependent antidepressant-like effect in the animal model, they proposed that the impact of CBD on mobility be investigated.

A 2011 review of 132 original studies reported that CBD does not induce catalepsy or alter physiological (heart rate, blood pressure, and body temperature), psychomotor, and psychological function.

While CBD is considered a safe compound, it is not risk-free, as it has drug interaction and adverse event potential, the authors noted. Fatigue and minor gastrointestinal disturbances are commonly reported; serious events such as elevated liver function have been observed more rarely. Because CBD is an effective anticonvulsant therapy, the U.S. FDA is concerned that it might similarly cause suicidal ideation, Dr. Rudroff explained.

"Longer-term safety data are critically needed to appreciate CBD's balance of benefit to harm," he said.

"The problem is THC, the psychoactive component which activates cannabinoid receptor type 1 (CB1) and is hypothesized to be responsible for cardiovascular side effects," Dr. Rudroff said. He cited reports of cardiovascular emergencies in at least 35 persons who recently smoked cannabis preparations, and at least 13 deaths from a cardiovascular mechanism.

Differentiation between dependence and addiction is important, he added. THC is the addictive element, though it is less addictive than other compounds. Addiction statistics about cannabis are over a decade old and likely on the low side of things. About one in every nine adults and one in every six juveniles using cannabis will, at some point, meet the diagnostic criteria for THC addiction.

The majority of PwMS who experience pain, anxiety, spasticity or panic are prescribed opioids, benzodiazepines, and antidepressants, with potential side effects that range from dizziness and nausea, to anterograde amnesia, blurred vision, and anxiety.

A 2017 survey of over 1,500 medical cannabis dispensary members found that after starting to use cannabis, 77% reduced their frequent opioid use, 72% reduced their use of anti-anxiety medications, 67% reduced use of migraine medication, and 65% reduced use of sleep medication.

"Complete or part replacement of these drugs by specific cannabis products should definitely be the long-term goal," the authors said. However, given the increasing use of cannabis to treat pain, Dr. Rudroff cautioned, "we should not repeat the problems we now face with opioid prescribing."

CBD and other cannabinoids can potentially interact with many pharmaceuticals, although serious drug interactions have not been seen with CBD. Notably, cannabinoids have a dose-dependent effect on the activity of liver enzymes (e.g., cytochrome P450), which metabolize more than 60% of marketed pharmaceuticals.

Another concern is that many plant-based cannabis products are mislabelled, while pharmacologically manufactured products, Sativex and Nabilone, have the advantage of a 1:1 THC:CBD ratio, "a ratio we can trust," noted Dr. Rudroff: "The best [Class I] efficacy and safety studies are with Sativex."

"It is clear that more research is needed," according to the conclusion of Dr. Rudroff's paper. "However, because of the safety of CBD and if the concerns listed above are accounted [for], we . . . already have some good reasons to believe that CBD-enriched cannabis is useful to improve the mobility of PwMS."

Dr. Rudroff welcomes comments and correspondence at: thorsten-rudroff@uiowa.edu

—**Kate Kniesel**, *CJMC Correspondent*