EDITORIALS:
1. Editorial: The Indications for Medical Treatment Using Cannabis
2. Teaching notes to the January – June Edition

ARTICLES IN SUMMARY:
3. Smoked Cannabis for Spasticity in Multiple Sclerosis: CMAJ
184(10), 143-149
The treatment of a variety of medical conditions with inhaled cannabis continues to evolve. The paper by Bloom et al. *Smoked Cannabis for Spasticity in Multiple Sclerosis* (1) is one more paper giving solid evidence for a reduction in both spasticity and pain in MS patients. There is now clear medical evidence for the benefit of cannabis therapy in patients with MS provided that the “acute cognitive effects” are not disabling for the patient.

In a review article in the *Monthly News in Adolescent Medicine* Nov-Dec. 2001 the effect of cannabis on pain relief was reviewed (2). In a search of the literature using electronic databases, Campbell et al. (3) found nine randomized controlled studies involving a total of 222 patients receiving cannabis treatment for pain relief. In five trials involving cancer pain, a total of 128 patients were evaluated. Oral THC (5-20mg) was found to have an analgesic benefit compared to placebo in 10 patients with pain related to advanced cancer. The authors found that 10 mg of THC was equivalent to 60 mg of codeine, and that 20 mg of THC was equivalent to 120 mg of codeine (4).

Studies on non-malignant pain also show a beneficial effect from THC. In a patient with neuropathic pain and spasticity, 5 mg of THC was found to be equivalent to 50 mg of codeine (5).

Based on these reports, the utility of cannabis in the management of cancer pain and neuro-spasticity accompanied by pain seems clear. There is also evidence that cannabis can be useful in stimulating appetite in patients with cancer who suffer from anorexia. Because these studies have shown a quantitative pain relief equivalent to 50 mg of Codeine and 50 mg of Seconal, it would appear that cannabis should be useful in treating other kinds of pain (5).

Cannabis has other benefits. It stimulates appetite and treats nausea. Perhaps its most helpful characteristic is its ability to work synergistically with opiate-based pain medications (5), thus reducing the risk of opiate addiction.

In an article by Richardson (6), the risks to mental health from long-term opiate therapy for chronic pain are reviewed. The author concludes that when presenting with a new episode of chronic pain, youth with mental health disorders were at a greater than two-fold risk of becoming long-term opiate users compared with a control group. Because of the proven risk of addiction in opiate use, cannabis can be seen as a useful and less dangerous adjunct or alternative to chronic opiate administration.

Although the risk of addiction is less in cannabis than with opiates, there is also a risk of dependency, at least psychologically.
The following side-effect profile for cannabis use should be considered before treating patients with THC.

1. Mental clouding.
2. Ataxia
3. Disorientation and disconnected thoughts
4. Slurred speech.
5. Dry mouth and blurred vision
6. Impaired memory.
7. Tachycardia and lowered blood pressure.
8. Addiction potential.
10. May precipitate psychosis in predisposed individuals.

Patients involved in selling cannabis to others should be considered poor candidates for medically prescribed marijuana.

References:
(6) Richardson L *Mental Health Disorders and Long-Term Opioid use Among Adolescents and Young Adults with Chronic Pain*, J Adolescent Health 50 (2012), 553-558.
The article by Bloom et al. from the CMAJ repeats the rather consistent finding that cannabis reduces spasticity in MS patients and improves pain. The authors stress that the cognitive effects are significant, however. Nevertheless there is optimism that cannabis can assist with pain management, at least in selected cases, and decrease the risk of opiate addiction. See the article *Mental Health Disorders and long-term Opioid use Among Adolescents with chronic Pain* in this issue.

The realities of living in a community where suicide is common is illustrated in the article *Nunavut Youth Saturated in the Realities of Suicide*. Since Nunavut was created in 1999, nearly 400 Inuit have killed themselves through suicide. The statistics alone are horrific, but the article also demonstrates the causes: Sexual and physical abuse, substance and alcohol abuse, and impulsivity.

In my own work on the Wikemikong Reserve in Northern Ontario, the same set of circumstances was there. A point I did notice was that dropping out of school was an additional risk factor. This point is important, because communication between school officials and mental health personnel can take place when students are at the point of dropping out of school. This is a perfect time for preventive intervention; in our experience it worked quite well.

Opioid use is increasing in Canada and the United States. Among adults in the US, it is estimated that 3% of the population are now using opioid medication. In the paper *Mental Health Disorders and Long-term Opioid Use*, the incidence of mental health disorders in patients with long-term opioid use was double those of non-users. The authors suggest the importance of diagnosing and treating underlying mental health conditions before treating chronic pain with opioids.

**Smoked Cannabis for Spasticity in Multiple Sclerosis: A Randomized, Placebo-controlled Trial:**

Bloom C, CMAJ 184(10) 2012, 143-149

Spasticity is a common and disabling symptom that remains a substantial problem for many patients with multiple sclerosis. Some patients have adverse effects from conventional antispasticity medications; for others, spasticity persists despite treatment. A report from the Institute of Medicine in the United States concluded that the active compounds of cannabis (marijuana) are potentially effective in treating neurologic conditions and “should be tested rigorously in clinical trials.” There is evidence that the cannabinoid receptors CB-1 and CB-2 may be involved in the control of spasticity in multiple sclerosis and that the endogenous ligand of CB-1, anandamide, it itself an effective antispasticity agent. CB-1 receptors are primarily presynaptic; their activation inhibits calcium influx and glutamate release, ad reduces neuronal excitability by activating somatic and dendritic potassium channels.

Although many patients with multiple sclerosis endorse smoking cannabis as therapy, evidence that it relieves spasticity is largely anecdotal, as most trials focus on
orally administered cannabinoids. We sought to assess the safety and efficacy of smoked spasticity

**Methods: Participants**

We recruited participants from a regional multiple sclerosis clinic and by referral from specialists. Our eligibility criteria were spasticity and at least moderate increase in tone (score ≥3) points on the modified Ashworth scale at the elbow, hip or knee. Participants were allowed to continue other treatments for spasticity, with the exception of benzodiazepines, if they had been taking stable doses for three months or longer. Participants could continue disease-modifying therapy (e.g., interferon β-1a, interferon β-1b, glatiramer) if they had been on a stable regimen for at least six months. We prohibited any changes to medications that were expected to affect spasticity scores during the trial. Participants could be cannabis-exposed; if the participants had been previously exposed to cannabis, we asked that they refrain from smoking cannabis for one month before screening and during the trial.

We excluded patients with a history of major psychiatric disorder (other than depression) or substance abuse, substantial neurologic disease other than multiple sclerosis (e.g., epilepsy, head trauma) and severe or unstable medical illnesses, known pulmonary disorders (tuberculosis, asthma), patients who used benzodiazepines to control spasticity or high doses of narcotic medications for pain, and women who were pregnant or breastfeeding.

Our study was approved by the Human Research Protections Program at the University of California, San Diego, and Research Advisory Panel of California, the Drug Enforcement Administration, the US Food and Drug Administration and the National Institute on Drug Abuse. Our study was monitored by an independent data safety monitoring board through the University of California Center for Medical Cannabis Research.

**Study design**

We used a randomized, double-blind, placebo-controlled crossover design. We evaluated participants during eight visits over a period of two weeks. Visit 1 was a screening visit during which the participants gave their informed consent. At this time, we took medical/medication histories, screened participants for substance abuse (using urine toxicology) and psychiatric disorders, and determined spasticity using the modified Ashworth scale. Participants with a positive toxicological screening result (e.g., presence of delta-9 tetrahydrocannabinol, amphetamines, benzodiazepines, cocaine and/or benzoylecgonine) were excluded.

**Primary outcome**

Our primary outcome was change in spasticity as measured by patient score on the modified Ashworth scale. The modified Ashworth scale is an ordinal scale (0-5 points) ranking the intensity of muscle tone as follows: 0, no increase in muscle tone; 1, slight increase manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) flexed or extended; 2, slight increase manifested by a catch, followed by minimal resistance throughout the remaining (less
than half) range of motions; 3, more marked increase through most of the range of motion, but affected part(s) easily moved; 4, considerable increase in tone, and passive movement is difficult; 5, affected part(s) rigid in flexion and extension. We combined ratings for both elbows, hips and knees for a total possible score of 30 points. We assessed participants using the scale before and about 45 minutes after treatment (cannabis or placebo) at each visit.

Secondary outcomes
We assessed patients daily for pain (using a visual analogue scale), physical performance (using a timed walk) and cognitive function (the PASAT). We administered these tests before and about 45 minutes after treatment at each visit.

We assessed patients for symptoms using the Brief Symptom Inventory (BSI), for perceived deficits using the Perceived Deficits Questionnaire (PDQ) and for fatigue using the modified Fatigue Impact Scale (mFIS). We did these assessments before treatment on day 1 and after treatment on day 3.

In addition, at the end of each visit, we asked patients to access their feeling of "highness" after treatment, according to question 1 from the Subjective Ratings of High and Sedation Questionnaire (SRHS-R), and to guess which treatment they were receiving (placebo or cannabis). Detailed descriptions of these measures are available in Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.110827/-/DC1).

Study participants
We identified 196 patients for screening. Of these patients, 38 completed both screening visits, 37 were randomized, and 30 completed the study. (Seven patients withdrew before completion.)

Primary outcome
Smoking cannabis reduced patient scores on the modified Ashworth scale by an average of 2.74 points (95% bootstrap CI 2.20 to 3.14) more than placebo ($p<0.001$). The order of treatment (cannabis in phase 1 or phase 2) did not significantly affect the outcome ($p=0.8$).

Interpretation: Main findings
We saw a beneficial effect of smoked cannabis on treatment-resistant spasticity and pain associated with multiple sclerosis among our participants. Although generally well-tolerated by our participants, smoking cannabis was accompanied by acute cognitive effects.

We saw significant reduction in the pain felt by our participants. Although orally administered cannabinoids failed to improve pain in an uncontrolled study involving 20 patients with multiple sclerosis, two placebo-controlled studies did find a treatment effect. In a trial of sublingual spray containing delta-9 THC alone or combined with cannabidiol, Rog and colleagues reported a 41% reduction in pain, compared with a 22% reduction with placebo. Literature on cannabinoids for pain conditions other than multiple sclerosis is limited, although three recent randomized placebo-controlled trials of smoked cannabis found significant reduction in neuropathic pain. Our participants
began with relatively low levels of pain; future studies might focus on pain with more intense pain.