The evolving role of cannabinoids in supportive oncology

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HOT SPOT

- Three pharmaceutical cannabinoids currently available in Canada. THC: CBD buccal spray (Sativex®) recently approved by Health Canada for opioid non-responsive pain in adult cancer patients. Nabilone (Cesamet®) and Dronabinol (Marinol®) indicated for chemotherapy-induced nausea and vomiting
- Cannabinoids possess broad spectrum of activity and may be effective in the management of other symptoms such as pain, spasms, anorexia, anxiety, and depression

Chemotherapy-induced nausea and vomiting (CINV)

- The cannabinoids, nabilone and dronabinol, reduce the frequency of vomiting and lessen the severity of nausea in cancer patients with persistent CINV
- 5HT3 antagonists exert incomplete control of acute and delayed CINV. Adjuvant use of cannabinoids may improve the overall CINV control
- Anticipatory CINV remains a significant issue as it affects 10% to 29% of patients. A recent animal model of anticipatory CINV has demonstrated that THC is effective, while 5-HT3 receptor antagonists were ineffective for its prevention

Analgesia

- Cannabinoids possess robust analgesic properties mediated through anti-nociceptive, anti-hyperalgesic, anti-allodynia, and anti-inflammatory mechanisms
- Synergistic sensory analgesia when combining opioids and cannabinoids may permit prescribing opioids at lower doses, thereby translating into reduced risk for opioid-related side effects
- Two recent meta-analyses examining the use of cannabinoid therapies conclude that they are highly effective in the management of central and peripheral neuropathic pain. A European phase III study, in patients with opioid-non-responsive cancer pain, demonstrated that patients receiving Sativex® experienced a significant reduction in pain, as measured by a numeric rating scale, versus placebo (P=0.014). In addition, 43% of subjects demonstrated more than 30% reduction in pain

Spasmolysis

- Cannabinoids have long been known to possess spasmolytic properties with respect to both skeletal and visceral muscle
- Cannabinoids are highly effective for muscle spasms as well as spasm-induced pain

Orexigenic

- The synthetic cannabinoid dronabinol is indicated for the treatment of anorexia in AIDS patients. Long-term use in this patient population has been shown to be effective and safe. Clinical evidence for the use of cannabinoids in cancer and palliative care patients with CACS is limited

Keys to clinical application

- Cannabinoids have a favourable safety profile. There are no reported deaths in the setting of overdose. The most commonly reported side effects of cannabinoid therapy are dizziness, drowsiness, dry mouth, ataxia, and euphoria. Side effects are generally mild to moderate in intensity and are of short duration
- While Sativex® is administered as a buccal spray, nabilone and dronabinol are given orally. The buccal spray route of administration for Sativex® provides a pathway that can significantly bypass the "first-pass" effect that cannabinoids are known to undergo if taken orally. The duration of action of nabilone is longer than that of dronabinol, which translates into less-frequent dosing. Nabilone is typically given once or twice daily, while dronabinol may be given as many as six times daily. In contrast, the dosing regimen for Sativex® is self-titrating allowing individualized dosing
- The cannabinoids are metabolized principally via the cytochrome P450 (CYP450) 2C9 isoenzyme. Neither nabilone, dronabinol nor the THC component of Sativex® induces CYP450 isoenzymes. However, dronabinol and the CBD component of Sativex® inhibits the CYP450 3A4 isoenzyme. The lack of inhibition associated with nabilone suggests a low potential for drug-drug interactions, particularly with those medications metabolized via the CYP450 3A4 pathway. This is an important aspect in cancer patients who often are receiving several different medications, many of which are metabolized via the CYP450 3A4 isoenzyme
- Similar to many medications, judicious dosing enables the practitioner to attain maximum benefit of cannabinoids while avoiding intolerable side effects. The starting dose of either nabilone or dronabinol should be the lowest recommended, that is, 0.5 mg for nabilone and 2.5 mg for dronabinol. The dosage can then be gradually increased, with patient monitoring during titration. The maximum daily dosage of nabilone is 6 mg. For dronabinol, the maximum daily dosage is 20 mg. Beginning nabilone or dronabinol therapy at the lowest dose at bedtime may reduce the emergence of unwanted side effects and improve sleep. Sativex® should be started at a maximum

rate of one spray every four hours on the first day, up to a maximum of four sprays on the first day. On subsequent days, the patient may gradually increase the total number of sprays as needed and tolerated. The majority of patients require 12 sprays or less, however, some patients may require and tolerate a higher number of sprays. For all agents, once the point at which benefits are maximized and side effects are minimized has been reached, the patient can be maintained on that dose

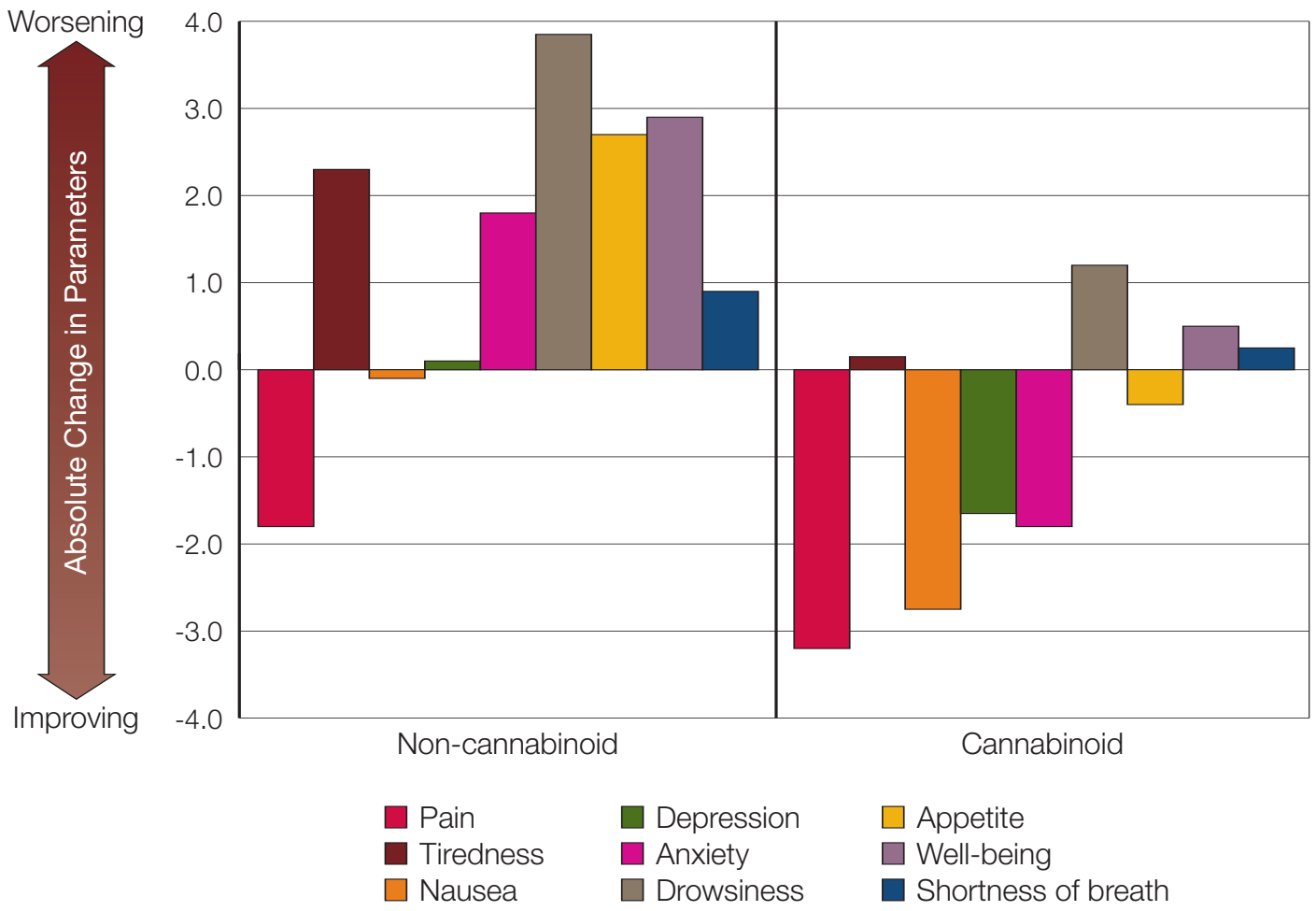

Figure One. Cannabinoids significantly reduce multiple symptoms in cancer patients
Maida, V., et al., San Antonio Breast Cancer Symposium 2006, Abstract 3145

Cannabinoids as "broad-spectrum optimizers"

- An observational cohort study involving advanced cancer patients has demonstrated the potential of nabilone to improve the pain and polysymptom management. Sixty-five cancer patients were prescribed nabilone in the setting of severe pain and polysymptom burden (Figure One)
- The nabilone-treated group demonstrated significant improvements in pain, nausea, appetite, anxiety, and depression as reflected through serial Edmonton Symptom Assessment System (ESAS) evaluations. The nabilone-treated patients were prescribed an average daily dose of 1.8 mg. In addition, the nabilone-treated group demonstrated lower utilization of other drugs, such as opioids, NSAIDs, corticosteroids, and tricyclic

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