Are Cannabinoids Effective for Orofacial Pain States?

Acute orofacial pains can generally be managed quite effectively by available therapeutic approaches, but most chronic orofacial pain conditions, especially those that are of a neuropathic nature, are still difficult to diagnose and treat. This is due in large part to the incomplete understanding of their underlying mechanisms and the limited efficacy or undesirable side effects of the drugs most frequently prescribed to relieve the pain. However, there is increasing attention being given in the media as well as in the biomedical sciences to the use as analgesic agents of the crude extracts of plants of the genus Cannabis (eg, marijuana) and their active ingredient delta 9-tetrahydrocannabinol (Δ9-THC). These cannabinoid compounds have been reported in the biomedical literature to be beneficial in the treatment of some types of neuropathic pain and other pain states. However, since some of the reports have significant experimental design limitations, the literature on this topic has been somewhat confusing and not always conclusive, and this has added to the current controversies around the legalization and use of cannabinoids for pain relief. Furthermore, the major focus of the research on cannabinoids as analgesic agents has been on their applicability for pain states outside the orofacial region. Therefore, the evidence base is quite limited for using cannabinoids for orofacial pain conditions.

A systematic review appearing in this issue of the *Journal of Oral & Facial Pain and Headache* (see Boychuk et al, pages 7–14) has assessed randomized placebo-controlled trials (RCTs) of cannabinoids used in different populations of chronic nonmalignant neuropathic pain patients. This review has found evidence indicating that they may be effective analgesic agents for neuropathic pain conditions refractory to other therapeutic approaches. Nonetheless, the review concludes that there is a need for more high-quality studies to evaluate the impact of the duration of drug treatment as well as to assess drug delivery approaches, such as oromucosal spray systems which are showing some promising results. There is also a need for RCTs that address specifically orofacial pain conditions.

The clinical findings pointing to the usefulness of the cannabinoids for pain relief are supported by a growing body of evidence from basic science investigations addressing the possible efficacy and mechanisms of action of the cannabinoids in animal models of acute or chronic pain. This research, which has largely been directed at animal models of pain conditions in parts of the body outside the orofacial region, has provided a preclinical underpinning for the possible clinical utility of cannabinoids in such conditions. These investigations have revealed the existence of two types of cannabinoid receptors: the cannabinoid receptor type 1 (CB1) and the cannabinoid receptor type 2 (CB2) (for review, see references 1–3). Both cannabinoid receptor types are found in peripheral tissues but are also expressed in several regions of the central nervous system (CNS) that are involved in the processing of pain and/or its modulation, suggesting that activation of these receptors can modulate nociceptive processes. Indeed, cannabinoid agonists (eg, Δ9-THC and WIN 55,212-2) have been shown to attenuate nociceptive behavior as well as nociceptive neurons in the CNS in animal models of acute or chronic pain, including neuropathic pain. There is also evidence that their effects may involve interactions with other endogenous chemical processes participating in pain or its modulation, such as those utilizing gamma-aminobutyric acid (GABA), transient receptor potential (TRP), and opioid or serotonin receptors (for review, see references 1–3). Although investigations using orofacial pain models in animals are few in number, application of a cannabinoid CB1 agonist has been reported to attenuate evoked activity in nociceptive neurons and to reduce nociceptive behavior in animal models of orofacial inflammatory pain as well as neuropathic pain and headache.[4–7]

These preclinical findings add to the growing evidence, including that from the RCTs outlined in the systematic review, that cannabinoid receptor agonists may be effective agents for the treatment of neuropathic pain and other types of pain. They also point to their possible clinical utility in acute or chronic orofacial pain conditions, and thereby suggest an affirmative answer applies to the question posed in the title of this editorial. But given the limited research on the cannabinoids for the relief specifically of orofacial pain, plus the controversies surrounding their use as analgesic compounds, more RCTs and preclinical studies of the cannabinoids are warranted that specifically focus on neuropathic pain and other chronic pain states occurring in the orofacial region.

Finally, on a different topic, I wish to point out that Dr Alain Woda is stepping down as associate sditor of the journal. He has served in this position for the past 10 years, and he has contributed greatly to the success of the journal through his editorial activities and advice. Merci beaucoup, Alain! Because of

doi: 10.11607/ofph.2015.1.e

his expertise both as a clinician and basic scientist, Dr Woda was able to handle the review of articles addressing either clinical or basic science topics; his place as associate editor will be taken by Dr Greg Murray, who also has expertise in both the clinical and basic sciences. Dr Murray is associated with the University of Sydney, and I am very pleased to have a member of the editorial board from the Australian and New Zealand Academy of Orofacial Pain. Welcome, Greg!

Barry J. Sessle
Editor-in-Chief

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