

## Are Cannabis-Based Chemicals Helpful in Headache?

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**Key words:** intracranial hypertension, cannabis, cannabinoid receptors, marijuana, pain, nociception, anandamide  
(*Headache* 2004;44:726-727)

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Headaches, which are present in 75% or more of idiopathic cases of pseudotumor cerebri, can be severe and disabling. A patient reported a novel, highly effective treatment for her headaches.

### CLINICAL HISTORY

This 38-year-old woman has a 3-year history of pseudotumor cerebri with recurring headaches and bilateral disc edema. Treatment has included lumbar punctures and acetazolamide, currently 500 mg BID. She has not been able to lose weight. The headaches were less frequent for a while but increased in the last 6 months. The headaches were occurring three to four times weekly and lasted all day. She described a throbbing in the back and front of her head sometimes with nausea, which was dulled by naproxen sodium. There is no prior history of similar headaches or migraine.

During the last few months, she noticed that if she smoked a marijuana cigarette when the headache was severe, the headache resolved within 5 minutes without recurrence that day. She was using the marijuana about once a week when she was at home but was not able to on other days when at work.

On examination, she was 5'4" with a weight of 237 pounds. Neurological examination was normal except for mild disc edema, left more than right, with enlarged blind spots. On lumbar puncture, the opening pressure was 33 cm.

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### EXPERT OPINION

The case of this 38-year-old woman raises some interesting clinical questions. First, are single observations or anecdotal reports proof of evidence? Second, is there evidence that cannabinoids reduce intracranial pressure in patients with pseudotumor cerebri? Third, what is the evidence that cannabinoids work in pain and headache, and what is the underlying basis?

Cannabinoid receptors and endogenous cannabinoids (endocannabinoids such as anandamide) may play a significant role in modulation of nociception, as well as in psychomotor control, memory function, appetite regulation, emesis, and many other brain functions.<sup>1</sup> Thus far, two cannabinoid receptors have been characterized. The CB<sub>1</sub> receptor is the only cannabinoid receptor that is expressed in the brain whereas CB<sub>2</sub> is expressed in peripheral tissues including the immune system. Cannabinoid receptors are located on axons and nerve terminals of the neocortex, basal ganglia, hippocampus, and cerebellum. These receptors are sparse in the brainstem. The presynaptic location of cannabinoid receptors is in accord with their role in inhibiting neurotransmitter release (eg, glutamate,  $\gamma$ -aminobutyrate or GABA, acetylcholine, etc).

In response to the first question, I would argue that clinical observations should stimulate research that validates or disproves the observation. Therefore, the case of the 38-year-old woman whose headache consistently improved when smoking marijuana should be the impetus for further investigation of the potential role of cannabinoid derivatives in headache. It should be borne in mind that any benefit should be weighed against the risk of adverse events.

The answer to the second question remains to be fully elucidated. A recent study in severe head injury patients, suggests that cannabinoids may reduce intracranial pressure.<sup>2</sup> It should be mentioned, however, that cannabinoids are appetite stimulant, and therefore, may not be ideal in overweight patients who suffer from the ill effects of pseudotumor cerebri.

With respect to the last question, observations on cannabis use for pain relief including migraine date over 100 years.<sup>3</sup> In the absence of evidence to suggest that the underlying mechanisms of headache are fundamentally different from those of other painful forms, a discussion of cannabinoids in general pain will have relevance to headache and migraine.

Endogenous cannabinoids and cannabinoid receptors are distributed throughout the pain pathways, including peripheral sensory nerve endings, spinal, and supraspinal centers. In a variety of animal models of pain, it has been demonstrated that cannabinoid agonists and anandamide are antinociceptive and antihyperalgesic. Also, anandamide may exert some of its effects through its binding to the vanilloid receptor VR<sub>1</sub>. Finally, some data indicate that cannabinoid receptor activation synergizes the antinociceptive effects of morphine.

Despite substantial preclinical evidence supporting the role of cannabinoids in pain modulation, clinical data have been conflicting although a recent small trial was quite promising.<sup>4</sup> The authors of a meta-analysis of clinical trials of cannabinoid derivatives in painful conditions concluded that more research is needed before recommending these therapies in neu-

ropathic pain or spasticity.<sup>5</sup> They also stated that the widespread use of cannabinoids in clinical practice is not warranted in the absence of evidence for superiority over conventional therapies, and with prominent CNS depressant side effects.

In conclusion, the preclinical data supporting the antinociceptive role of cannabinoids, and some clinical data indicating their benefit in pain, indicate that further research is needed before cannabinoids are recommended clinically for pain or headache. Receptor-specific approach and targeting the uptake transporter are some strategies that need to be, and in some instances are, pursued to improve the therapeutic index of cannabinoids.

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