

Comment

In humans, ajulemic acid has a more favorable side-effect profile than THC for the treatment of chronic neuropathic pain

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Abstract

This is a comment on a report by Vann et al. (2006) on the pharmacological effects of ajulemic acid compared to CB1 receptor agonists. Their data, which were obtained using animal models, suggested an unfavorable therapeutic index as an analgesic. However, the available clinical data do not support such conclusions and indicate a deficiency in some of their models.

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Literally hundreds of cannabinoid analogs have been synthesized over the years with the goal of separating psychotropic activity from therapeutic properties. Only a handful have advanced beyond the preclinical stage of which ajulemic acid (AJA) is one example [1]. AJA is currently undergoing development as a possible treatment for interstitial cystitis, a chronic bladder inflammatory condition for which no effective treatment is known. A recurring question concerning AJA is whether its preclinical literature can predict its possible psychotropic activity in humans. The numerous reports from a number of independent laboratories have yielded occasionally conflicting conclusions [11]. The modest affinity of AJA for the CB1 receptor appears to be the inspiration for conclusions predicting cannabinomimetic actions in humans. However, the available clinical data thus far does not support such conclusions [6,9].

Vann et al. (2006) in a recent paper, have attempted to shed light on this long-standing debate concerning the therapeutic index of AJA [10]. In their report they refer to the ratio of an analgesic effect to the response in a drug discrimination assay where they found no separation of activities. The authors claim that their findings predict certain adverse effects for AJA when given to human subjects. Thus far, in both Phase 1 and Phase 2 trials [6], these effects have not been seen suggesting

limitations for the models used by Vann et al. While the authors acknowledge this problem for the tetrad assay, they feel that the drug discrimination test is highly accurate.

An example of a divergent finding is evidenced in a recent study by Dyson et al. (2005) [5]. Using a different set of models, they obtained a therapeutic index of 5-10 in comparing psychotropic action with analgesia in contrast to the conclusion reached by Vann et al. In a recent review, Pacher et al. (2006) stated that "Pre-clinical studies (Burstein et al., 1998; Burstein, 2000; Burstein and Zurier, 2004; Dyson et al., 2005; Mitchell et al., 2005) and a recent clinical trial of 24 patients with neuropathic pain of varying etiologies demonstrated, that ajulemic acid, a major metabolite of THC with CB1 agonist activity, was effective in reducing pain without causing cannabinoid-like CNS side effects, the first evidence for the separability of the psychotropic and analgesic effects of a THC analog in humans (Karst et al., 2003)" [8].

Moreover, it should be noted that several other therapeutic targets for AJA have been suggested, namely, cancer, cystitis, inflammation, multiple sclerosis and disorders of lipid metabolism that have been described in a recent review on AJA by one of the authors of the Vann et al. paper [11]. It is very likely that the therapeutic indices for each of these targets may be different

from that reported by Vann et al. in their models. Thus, caution is advised in generalizing the drug discrimination vs. analgesia data to other therapeutic targets.

In conclusion, while this comprehensive study by Vann et al. will certainly add fuel to the debate, it should not be taken as the final word. Only further studies in humans at therapeutic doses will provide some answers.

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