

Letter to the Editor

Letter: Preclinical assessment of abuse liability of ajulemic acid

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The primary underlying issue that Dr. Burstein raises in his comment [4] on the Vann et al. manuscript [7] is one of predictive validity; i.e., the extent to which preclinical findings can be used to predict clinical efficacy and/or side effects of a novel drug in humans. This issue has bedeviled preclinical research since initiation of the use of results from this type of research in the process of drug development. Yet, the usefulness of such research is widely acknowledged, to the point that presentation of promising preclinical results (as well as toxicity assessment) are required in order to proceed to clinical trials in the U.S. Indeed, development and promotion of ajulemic acid (AJA) has relied upon such results. In the case of drugs (such as AJA) that are similar to known substances of abuse (e.g., in structure, binding affinities or other biochemical or behavioral properties), prediction of psychotropic effects is of particular importance and preclinical evaluation of abuse liability is often performed before these novel drugs are widely marketed.

Four major procedures are most commonly used in preclinical evaluation of abuse liability: pharmacological equivalence, drug discrimination, self-administration, and physical dependence assessment [1]. The tetrad tests are representative of pharmacological equivalence testing. Cannabinoids produce characteristic effects in these tests and a new psychoactive cannabinoid also would be expected to do so. Our research [7] has demonstrated that AJA produces effects similar to those of Δ^9 -tetrahydrocannabinol (Δ^9 -THC) in the tetrad tests, a finding that has been verified by the results of some, but not all, empirical research that has investigated this issue [see 9 for review]. However, as acknowledged in Vann et al. [7] and validated empirically in previous research [11], the tetrad tests are not entirely selective for cannabinoids. Hence, this model cannot be used as a sole predictor for cannabinoid psychoactivity. In contrast, Δ^9 -THC discrimination is the most pharmacologically selective procedure available to predict marijuana-like subjective effects of novel drugs [see 2 for review]. Its pharmacological selectivity has been empirically demonstrated in rats [3], nonhuman primates [12], and in humans [8].

Whereas plant-derived and synthetic cannabinoids that bind to CB1 receptors and/or produce marijuana-like intoxication in humans readily and dose-dependently substitute for Δ^9 -THC in this procedure, drugs from a wide variety of other pharmacological classes do not [10]. Further, potency of cannabinoids to substitute for Δ^9 -THC is highly correlated with their potency for marijuana-like subjective effects in humans [2]. Based upon the Δ^9 -THC discrimination results reported in Vann et al. [7], AJA would be predicted to have Δ^9 -THC-like subjective effects in humans, at least at some doses. Whether these effects would be present at therapeutic doses is the crucial issue.

AJA shows promise for a number of therapeutic indications [9], with potentially varying effective dose ranges. Since the only potential therapeutic indication of AJA empirically evaluated in the Vann et al. [7] study was inflammatory pain (as assessed by complete Freund's adjuvant-induced mechanical hyperalgesia model), results can only be applied to assessment of the therapeutic index for this indication. Any implication that the results would apply to therapeutic effects that occurred at lower dose ranges was not intentional and, as noted in Dr. Burstein's comments, "...caution is advised in generalizing the drug discrimination vs. analgesia data to other therapeutic targets" [4]. However, it is also noted that, to date, pain is the only therapeutic indication for which empirical data on the clinical effectiveness of AJA have been published.

Herein lies a problem: published data from clinical trials of AJA as an analgesic are promising, but not conclusive, concerning its therapeutic index. It may be true that neither healthy volunteers nor pain patients in the clinical trials reported any marijuana-like subjective or cognitive effects at the doses tested (up to 10 mg/day and 80 mg/day in healthy volunteers and pain patients, respectively) [5, 6]; however, the extent to which therapeutically effective analgesic doses were tested in these trials is unclear (see 9 for further discussion). Statistically significant analgesic effects were produced by AJA for only one of the two daily assessments, with a nonsignificant trend evident for the other time point. In addition, the magnitude of the analgesic

effect was similar to the magnitude of changes in analgesia that were observed between patients receiving different sequences of presentation of drug and vehicle in this cross-over design [see Table 1 and Figure 2 in reference 5]. For example, mean baseline pain score on a visual analog scale (week 1, a.m.) for the AJA-placebo group was 45.3. This score was a measure of pain before any drug was administered. AJA produced a 28.84% reduction (a score difference of 13.06). The mean baseline pain score (week 1, a.m.) for the placebo-AJA group was 65.63. The difference between the two baseline scores is 20.33 (which exceeds the actual score difference produced by AJA in the group that received the AJA-placebo sequence). Based upon these findings, it is likely that doses higher than 80 mg/day would be required for adequate pain control in most patients. Since the psychoactivity of higher doses was not assessed in this clinical study, it is currently impossible to determine the therapeutic index for the analgesic effects of AJA in humans. In the absence of such clinical data, I would argue that empirically validated preclinical evaluation procedures represent the best alternative for prediction of the extent to which AJA is likely to have psychotropic cannabinoid effects in humans. Hence, based upon the results of our study [7], I would predict that marijuana-like intoxication would accompany clinical analgesic efficacy for AJA. Dr. Burstein noted in his concluding comment that “[o]nly further studies in humans at therapeutic doses will provide some answers” [4]. I would add that such studies may provide answers not only concerning the therapeutic index of AJA, but also for the broader scientific question of whether or not the psychoactive and therapeutic effects of cannabinoids are separable. I would also add a caveat: while preclinical results from drug discrimination studies may predict psychotropic effects in healthy volunteers (and hence, overall abuse liability), it is unclear the extent to which these findings may apply to pain patients. As can be confirmed by anyone suffering from chronic pain, pain itself can have psychological consequences. These pain-induced changes in subjective well-being may, in turn, alter the subjective effects of drugs such as AJA. This area is in need of additional research.

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