

Cannabis Epistemology and the Case-Series Design: An Invited Commentary on a Case Series and a Dismissive Response

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Editor's Note: The publication of “Cannabidiol in the Treatment of PTSD: A Case Series” by Elms et al. in the April 2019 JACM proved to be one of the most downloaded of JACM articles in the last two years. Elizabeth Stuyt, MD, issues a strong challenge to the paper, in which well-known integrative psychiatrist Scott Shannon, MD, was a co-author with Lucas Elms, BS. The rejoinder made clear that there remained a chasm between Stuyt and Shannon regarding the value in publishing a case series with its caveated positive conclusions. To sort through the perspectives, I turned to University of British Columbia cannabinoid research specialist Zach Walsh, PhD, inviting him to review the original paper and the two responses to potentially provide some guidance to the work. Walsh threads a path between the two other authors. We hope that at this early stage of the collective excitement about the potential value in cannabinoids for PTSD, with still little quality evidence, you will find this exchange illuminating. —*John Weeks, Editor-in-Chief* (johnweeks-integrator.com)

THE CASE SERIES describing the use of cannabidiol (CBD) for the treatment of post-traumatic stress disorder (PTSD)¹ provoked a strong critical response.² By invitation from JACM, the authors of the original study rebutted the letter. This back and forth presents an illuminating example of the kind of controversies that characterize the interpretation of cannabis research. Such controversies are not purely academic; dramatic increases in the visibility and availability of cannabinoid medicines coupled with the limitations of treatment options for PTSD and related disorders have resulted in high patient demand for guidance on the best use of cannabinoids for mental health. Clinicians who are confronted with this practical reality are called upon to make complex decisions regarding what is worthy of consideration and dissemination.

The Stuyt and Hildebrand critique decries the case series as emblematic of a putative “craze” surrounding CBD. The word “craze” seems an unfortunate descriptor for the health seeking behavior of individuals with a refractory disorder, and thus a polarizing gambit. A less dismissive attitude will likely be required to further our understanding of why the use of CBD and other cannabis-based medicines has proliferated among PTSD sufferers. Nonetheless, based on the state of the evidence, it is true that we cannot yet rule out that the purported benefits of cannabinoids for PTSD as reported by Elms et al. and others³ are spurious or reflect placebo effects. However, a satisfying explanation for this

phenomenon must not only report null findings but also begin to provide some signal as to why CBD has elicited greater enthusiasm than less expensive and more readily accessible inert products. To be satisfying, such an explanation must also address why these placebo effects appear to be selective for specific conditions such as PTSD.

There is no doubt that appetite for information on cannabinoid medicines has outpaced the evidence base. Unsurprisingly, the article, critique, and rebuttal find common ground in calling for further research. We can all surely endorse this anodyne call but should also recognize the challenges associated with conducting the randomized controlled trials that Elms et al. acknowledge are needed to provide the most rigorous tests of the effectiveness of CBD for PTSD. Not least among these are long-standing barriers to accessing cannabis products for research purposes, and recruiting participants for a placebo-controlled trial of a substance that is widely available outside of the medical system. Such trials will also require funding from reluctant governmental bodies or private entities skeptical of a natural product with an obscure path to commercialization as a pharmaceutical.

Moreover, rigorous efforts to estimate the effectiveness of cannabinoid therapies in key fields have not produced definitive results. For example, recent systematic reviews in the area of pain come to surprisingly divergent conclusions^{4–7} and similar diversity of informed opinion is evident

in mental health.⁸ These differences are attributable in part to discrepancies in the parameters of the literature reviewed. This tendency to differentially emphasize distinct subsets of research is also reflected in the present dialogue, with Stuyt and Hildebrand highlighting a single animal study as evidence of harms⁹ and the Elms et al. response emphasizing literature evincing a positive signal.^{10–12} What both of these admittedly incomplete literature reviews reveal is that the most rigorous research designs have not yet been implemented, and that conclusive results may not arrive as soon as we might hope.

In the absence of strong evidence and faced with the widespread uptake of CBD, clinicians are left in a quandary as to how to best support patients. In this context, providing a measured summary of what is known and unknown regarding the risks and benefits of cannabinoid therapies does not seem to be at odds with best practices. For clinicians interested in following this course, the Elms et al. case series does not—as Stuyt and Hildebrand vigorously assert—provide “no evidence.” Rather, it provides low-quality evidence, and the authors essentially admit as much in their lengthy examination of study limitations.

Admitted limitations notwithstanding, the inclusion of a retrospective chart review of matched non-CBD individuals—as recommended by Stuyt and Hildebrand—should have been feasible and would have increased the contribution of the study. Indeed, were the literature on PTSD and CBD more developed, this case series would not merit much attention. In the meantime, Elms et al. are to be commended for their minor contribution to addressing the challenge of understanding how to use these ancient yet still-mysterious medicines. Likewise readers might be grateful for Stuyt and Hildebrand’s reminder to balance clinician and patient demands with scientific rigor.

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