Response to Stuyt and Hilderbrand re: “Cannabidiol in the Treatment of Post-Traumatic Stress Disorder: A Case Series”

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Dear Editor:

WE THANK Drs. Stuyt and Hildebrand for their comments. I do agree that current cannabidiol (CBD) use has far exceeded our science. This is the very reason that we conducted and published our research. This research was conducted in our spare time in busy clinical practice without funding or compensation of any kind. Thus, we had real limits as to what we could accomplish. We do appreciate the pyramid of evidence-based medicine. At the bottom are expert opinions. The next level is single case reports and case series. We understand that this is lower in quality than observational studies with controls. We apologize that we did not have the capacity for a control group, but this is the nature of a case series.

Our reading of the existing data differs from your interpretation. We see human trials with extinction fear learning data as providing better guidance than behavioral trials on this topic with mice. Das et al.¹ found that 32 mg of CBD (roughly the same dose range that we employed) enhanced consolidation of extinction learning in humans as compared with controls. The basic science also suggests that CBD would be a relevant option: cannabinoid type 1 (CB1) receptors are found on both peripheral and central neurons, particularly in the central regions known to play important roles in anxiety and aversive learning, such as the hippocampus, amygdala, and the cerebral cortex. Many human neuroimaging studies in humans find target alterations by CBD in brain locations relevant to anxiety and trauma patterns.

Recent expert reviews on the topic of CBD and post-traumatic stress disorder (PTSD) find solid promise in the preclinical data.^{2,3} From Orsolini, “Preclinical research has shown promising findings for CBD as an enhancer of fear extinction and therapeutic consolidation of emotional mem-

ories.” From Bitencourt, “Indeed, as observed in rodents, recent studies have confirmed the ability of CBD to alter important aspects of aversive memories in humans and promote significant improvements in the symptomatology of PTSD.” A recent review of human data finds the same result: “We found that cannabinoids may decrease PTSD symptomatology, in particular sleep disturbances and nightmares.”⁴ All are in agreement that more data are needed and in particular more controlled human studies.

Although their letter claims that “we see significant weaknesses they did not acknowledge,” many of the examples of limitations are already described under the *Limitations* section of our article or are otherwise inaccurate. For example:

- (1) “Other weaknesses include the use of two different CBD products and self-dosing by the patients with widely varying regimes, making it impossible for the reader to know what a recommended product/dose regime might be.” Our article: “A precise dosing system for CBD was not established, and regimens varied between patients. Patients also received liquid or oral capsular CBD without a definitive guideline, and typical doses between the two routes of administration differed widely.”
- (2) “There was no documented testing of the THC content in the products and no urine drug screens to identify how many were also exposed to THC (from the product or use of other cannabis products).” Our article addressed incidental exposure to THC. “Although the product was derived from agricultural hemp, it may still contain trace amounts of delta-9-tetrahydrocannabinol.” Also, “The process of extracting CBD oil yields not only a product containing

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almost entirely CBD but also other cannabinoids in trace amounts, and it is not completely free of delta-9-THC.” Patients were also asked about concurrent cannabis use and this was documented in the article. We think drug testing people in addition would have been unnecessary and not in keeping with our usual clinical practice.

- (3) “The return rate of the patients was quite small, with only 4 out of 11 completing the full course of treatment. If this was such a helpful treatment, one would expect patients to continue in treatment.” This statement is misleading as there was no established course of treatment in this retrospective chart review. We set our cutoff time period for analysis to be at 8 weeks, because the percentage of patients with consistent follow-up dropped <50% after this time. The remaining sample size at this point was 11/21, and not 4/11. The 4/11 that the authors cite refers to patients who had continuing follow-up at monthly appointments for 36 weeks.

The claim that the letter sets out to refute is also not the claim that is put forth by our article. We do not state that “... CBD is a safe and effective treatment for PTSD.” This statement is misleading and does not recognize the true intent and scope of our article. We appreciate the feedback and hope we clarified the scope and intent of our article.

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