Suicidality and Cannabidiol: Opportunities and Challenges

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Abstract: Cannabidiol (CBD) is gaining considerable attention in the research community with promising results in a variety of neuropsychiatric conditions. In particular, there are replicated findings for the therapeutic effects of CBD on psychotic and anxiety symptoms as well as substance use disorders, all of which are highly prevalent in patients who present with suicidality. Meanwhile, there has been a lack of suicide research on cannabidiol. This perspective provides an overview of the available evidence, potential reasons behind the halt in suicide research on cannabidiol, and recommendations for future investigations.

Keywords: Cannabidiol, cannabis, marijuana, suicide, adverse events, psychopharmacology.

1. INTRODUCTION
Cannabidiol (CBD), the second most widely studied compound from the cannabis plant after tetrahydrocannabinol (THC), is gaining considerable popularity in the research community. Currently, a simple PubMed search for the term cannabidiol yields more than 3000 citations, with almost 1/3 of them published between 2019-2020.

2. THE EVOLVING HYPE AND HOPE
The FDA recently approved Epidiolex, a CBD medication, for Dravet and Lennox-Gastaut epilepsy syndromes. Beyond epilepsy, CBD is an active line of research with promising results in a variety of psychiatric and neurological conditions [1], including but not limited to schizophrenia [2, 3], anxiety disorders [4], mood disorders [5-7], chronic pain [8], and different substance use disorders [9, 10]. Other than the peer-reviewed literature that hypothesizes further neuropsychiatric applications of CBD, such as in patients with Borderline Personality Disorder [11], a search in clinical trial registries as well as pre-print databases reveals that potential therapeutic effects of CBD are being considered in an even broader range of neuropsychiatric conditions. This extensive hype and hope in the literature is an expected phenomenon with the appearance of a novel therapeutic compound and shall not bring us to the conclusion that CBD is a panacea for all. Meanwhile, there are some replicated findings from previous CBD research that provide us with strong implications for unique areas of investigation.

3. SUICIDALITY AS A TARGET FOR CBD
At the clinical level, suicidality, which encompasses suicidal thoughts, ideation, plans, attempts, and completed suicide, is considerably associated with affective disorders, chronic pain, anxiety, psychosis, substance use disorders, and sleep problems [12]. In particular, extreme anxiety and hyperarousal are among the prominent features of the Suicide Crisis Syndrome, a condition highly predictive of short-term suicidal behavior [13]. Therapeutic effects of CBD are especially replicated in multiple studies on anxiety, psychosis, and substance use disorders [1], and somnolence/sedation are commonly reported as adverse effects of CBD [14]. On the other hand, there is strong evidence of increased suicidal ideation and attempt in the chronic or early-age start of cannabis use [15]. Furthermore, suicidal ideation is a common feature of synthetic cannabinoid-induced psychosis [16]. Several studies have shown that CBD antagonizes the effects of THC, the major psychogenic and arousing compound in the cannabis plant, by reducing intense anxiety and psychosis-like symptoms [17]. CBD has also been recently used to effectively treat cannabis use disorder [9].

At the biological level, endocannabinoid and glutamate/glutamine systems as well as hypothalamic-pituitary-adrenal axis play an important role in suicidality [18-20]. In particular, increased CB1 receptor signaling is reported in suicide cases compared with controls [19]. Also, previous studies consistently demonstrated that in suicidal ideation and behavior, glutamate/glutamine levels are increased in the anterior cingulate cortex (ACC) [21-23]. The ACC is a key brain region involved in cognitive and emotional processes relevant to depression and suicidality [21]. Furthermore, higher cortisol levels in patients with recent suicide attempts and greater cortisol response in patients with suicidal ideation have been reported [18], and CB1 receptors appear
to play an important role in the regulation of the hypothalamo-pituitary-adrenal axis [24]. Beyond the proven effects of CBD on endocannabinoid receptors, such as well-documented CB1 antagonism, it appears that CBD modulates glutamate/glutamine and GABA systems in different brain regions [1, 25]. CBD decreases ACC activity when facing a fearful situation, and it appears that the cognitive and affective impacts of CBD are at least in part mediated by ACC [25, 26]. CBD also inhibits the hypothalamo-pituitary-adrenal axis [1] and decreases salivary cortisol levels [10]. Overall, our knowledge of the exact neural mechanism underlying CBD effects is still very limited. Current evidence and potential mechanisms of action are discussed elsewhere [1, 25].

4. SUICIDALITY AS A PRESUMED ADVERSE EFFECT OF CBD

Despite the available evidence discussed above, we could not find even a single published or ongoing study concerning the impact of CBD on patients with active suicidal ideation or at high risk of suicide. One potential explanation for the negligence towards the therapeutic potential of CBD in suicide research comes from FDA warnings published alongside the Epidiolex manual regarding precautions for suicidality as a presumed adverse effect. Based on our comprehensive search and the details published by FDA, it appears that this warning roots in that suicidality is a known adverse effect associated with other anti-epileptic drugs in general. Meanwhile, biological mechanisms of action of anti-epileptics are widely different, and in the case of CBD, there is not a single study that has reported increased suicidality in any clinical population [14]. Unfortunately, the number of studies on CBD that measured suicidality as an adverse event are very limited, and they have rarely reported the exact number of suicidality adverse events, but have mainly mentioned no difference in suicidality between the treatment arms [27, 28].

5. WHAT IS NEXT?

There are practical steps which need to be taken next. First, a comprehensive assessment of suicidality in the ongoing clinical trials of CBD and clear reporting of the results, especially in populations at higher risk of suicide, should further inform the researchers about the potential impact of CBD on suicidality. The second step would be a thorough assessment of suicidality with a quantitative measure in patients presenting with acute cannabis toxicity. Determining the THC/CBD ratio in hair and urine samples for respective long-term and short-term cannabis use, and correlation analysis with the severity of suicidality should help in clarifying any potential role of CBD in decreasing the risk of suicide. As a third step, CBD could be investigated as an adjunctive therapy to standard of care in two distinct inpatient populations: 1) patients with concurrent substance/cannabis induced psychosis and suicidal ideation and 2) patients experiencing Suicide Crisis Syndrome. Finally, the ongoing neurobiology research on CBD should further elucidate the mechanisms of action of CBD, as well as its true adverse effects and potential therapeutic applications.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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