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Cannabis: A potential efficacious intervention for PTSD or simply snake oil?

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The ancient Egyptians used willow bark as a remedy for aches and pains, even though they were unaware that salicylic acid was responsible for its anti-pyrogenic and anti-inflammatory actions.[1] Based on anecdotal reports and social media chatter, cannabis might yet displace salicylic acid as the most prolific cure-all. Like the bark of the willow, the marijuana plant and its derivatives have been used to diminish treatment-resistant epilepsy and to reduce chronic pain,[2] even before it was understood that the active components of the cannabis plant, Δ^9-tetrahydrocannabinol (THC) and canabidiol (CBD), contributed to these outcomes. Cannabis is also touted to be effective in attenuating a wide range of conditions, including asthma, inflammatory bowel disease, glaucoma, multiple sclerosis, menstrual cramps, AIDS, nausea and cancer. Beyond these effects on physical conditions, cannabis has been reported to improve neurocognitive and psychiatric conditions, such as Alzheimer disease, anxiety disorders and bipolar disorder.[2,3]

Progress in understanding the potential positive and negative impact of cannabis within clinical situations has been limited, and only a handful of high-quality clinical trials were reported to have used cannabinoids in the treatment of numerous illnesses.[2] As a result, our understanding of the potential adverse effects of chronic cannabis use remains meager. Nonetheless, there are indications that cannabis promotes cognitive disturbances, impairs neuronal plasticity and organization in the adolescent brain, promotes persistent functional brain changes, promotes abuse liability and, in highly vulnerable individuals, may exacerbate the course of schizophrenia.[4-6] At the same time, it may be essential not to go overboard; caution has been recommended concerning "the real risks" of marijuana, and calls have been made for evidence-based analyses of the links between this agent and the occurrence of mental illnesses.[7]

Increased attention has focused on the potential use of cannabis in the treatment of posttraumatic stress disorder (PTSD). However, as we all know, treatment of PTSD has been a hard nut to crack. Ideally, the neurobiological mechanisms of psychological disorders could be assessed using animal models.[8] Yet, even under the best conditions, this can be difficult to achieve, especially in relation to PTSD. Among other things, paradigms used to model PTSD are frequently the same as those used to model depressive disorders and anxiety (e.g., freezing in response to conditioned fear cues; response to novel stimuli after exposure to uncontrollable footshock; forced swim performance following prolonged restraint).[9,10] To be sure, PTSD shares several endophenotypes with depression and anxiety, making it difficult to distinguish underlying processes within animal models. Furthermore, PTSD develops in only a small portion of individuals who experience extreme stressors, whereas this is rarely considered in most animal models.[10] Several published reviews of the literature have offered varied suggestions that could be instrumental in enhancing the validity of animal models. Ultimately, these models would necessarily require multiple behavioural tests to simulate the presumed symptoms of PTSD in humans, although simulating intrusive thoughts is obviously not possible. As well, it is necessary to consider sex differences, the history of traumatic encounters across the lifespan, analyses of PTSD-related genetic and epigenetic influences (e.g., methylation of *FKBP5* and *NR3C1* genes, which affect glucocorticoid receptors, modulate glucocorticoid sensitivity and are associated with corticotropin releasing hormone receptor 1)[11,12] and possibly even actions related to trauma encountered in earlier generations that might have engendered epigenetic changes.[9,13]

To appreciate the processes that govern the development, maintenance and treatment of PTSD, it would be necessary to consider the actions of stressors on varied neurobiological processes. Ordinarily, acute stressful events influence autonomic nervous system functioning, promote gut microbial changes, stimulate the release of numerous metabolic hormones and several neurotransmitters (e.g., glucocorticoids, monoamine functioning, γ-aminobutyric acid, glutamate), and affect neurotrophin functioning as well as microglia activity and the resultant release of proinflammatory cytokines within the brain.[9,14] With chronic stressor experiences, some of these same neurobiological processes may be

sustained, eventually leading to excessive neuronal activation or taxing of critical resources (allostatic overload), favouring the development of psychological pathologies.[15] The sheer number of stressor-provoked neurobiological changes makes it difficult to identify which of these (or their interactions) contribute to the emergence of PTSD, and indeed, the disorder is likely biochemically heterogeneous.

The brain processes that govern the development and persistence of PTSD have yet to be identified fully, and most of what is known comes from preclinical animal studies (despite the problems inherent with animal models). Sites involved in threat detection, fear learning (or alternatively disturbed fear extinction), contextual processing, emotion regulation and executive function appear salient in this regard. Accordingly, PTSD features in humans were attributed to neuronal dysfunction within the medial prefrontal cortex, anterior cingulate cortex and hippocampus and with diminished connectivity between the ventromedial prefrontal cortex and amygdala.[16] Furthermore, low endocannabinoid (eCB) tone contributes to the amygdala hyperactivation as well as the anxiety and hyperarousal symptoms characteristic of PTSD.[17] The hyperarousal anxiety may, in turn, be fundamental in promoting many of the most debilitating aspects of PTSD, including sleep disturbances, memory and cognitive impairments, altered pain sensitivity, as well as depression, anxiety, emotional numbing and suicidality.[18,19] Hyperarousal anxiety may also serve as a driver for symptoms that comprise re-experiencing, avoidance and emotional numbing.[20] In addition, other features of PTSD, such as dissociation, are more prominent in females than in males.[20] These distinguishing characteristics of PTSD may offer clues as to the most efficacious treatments of the disorder.

Given that eCB processes are affected by stressors and can affect anxiety and fear,[21] it was hypothesized that eCB functioning is tied to the development of PTSD, possibly through a corticotropin-releasing hormone–mediated reduction of anandamide in several brain regions.[17] Paralleling this view, it was maintained that pharmacological manipulations of endogenous cannabinoids could be used in the treatment of PTSD.[22] As in the case of many other purported benefits of cannabis, much of the supportive evidence in humans has come from anecdotal or case reports as well as observational studies that provide little evidence of a causal connection. For instance, individuals presenting with PTSD characteristics frequently use cannabis in an effort to self-medicate, reporting that the drug diminished anxiety and arousal and enhanced sleep.[17]

Importantly, PTSD was associated with increased expression of cannabinoid receptor type 1 (CB1) and reduced peripheral levels of the eCB anandamide[8] as well as a compensatory increase of CB1 availability, which was linked to excessive threat processing and with features of anxious arousal.[23] In essence, a deficiency of eCB signalling reflects a stress endophenotype underlying PTSD,[17] raising the possibility that endocannabinoid manipulations could be potentially useful in a therapeutic capacity.[24]

There have been indications that cannabis or some of its components, primarily THC and CBD, diminish particular symptoms of PTSD. In this regard, in a small study ($n =$ 10), 5 mg of THC twice a day as an add-on treatment enhanced sleep quality and reduced the frequency of nightmares, PTSD hyperarousal (based on the Clinician-Administered PTSD Scale) and global symptom severity.[25] The synthetic analogue of THC, nabilone, similarly enhanced sleep, reduced nightmares and diminished other PTSD symptoms among patients.[26] It seems, however, that the positive effects of THC in relation to PTSD are limited, leaving many features of this condition unaffected.[2] Unfortunately, the available data showing a cannabinoid–PTSD link in human clinical trials have been relatively sparse and yielded mixed results, ranging from ameliorated symptoms to cautions concerning its efficacy.[2,27] Furthermore, because PTSD is so often comorbid with depressive illnesses and anxiety disorders, it is uncertain whether the eCB links reflect a direct causal connection to PTSD or actions related to anxiety or depression.

In addition to potentially reducing PTSD symptoms, cannabis also mitigates the propensity for inflammation[14] and may be useful in psychological conditions that involve elevated inflammatory processes within the brain. This would include a subset of depressed individuals in whom inflammation may be a component of the illness and may contribute to threat processing linked to PTSD in trauma survivors.[9] In fact, anti-inflammatory agents can diminish PTSD features in an animal model, and in humans PTSD was accompanied by elevated circulating proinflammatory cytokines.[28,29] Thus, cannabinoids could potentially act against PTSD by activation of cannabinoid receptor type 2 (CB2) receptors, which promote anti-inflammatory actions involving microglia.[30,9]

Behavioural and neurobiological changes in rodents vary as a function of the nature of the stressor experienced and its chronicity[9,31] and vary with the passage of time, as observed in the development of neuronal sensitization.[32] The evolution of PTSD may likewise involve dynamic processes, including a phase soon after trauma, wherein features of the illness incubate and emerge with time-dependent variations in the sensitization of neuronal functioning.[33] Whether further changes in the processes subserving PTSD develop over the ensuing months is uncertain; nor is it clear whether different treatments at various phases of the illness would be most effective. It has been maintained that treatment with cortisol (or related compounds) or those that affect norepinephrine at specific post-trauma periods may prevent the development of PTSD, possibly by affecting the consolidation or reconsolidation of fear-related memories.[34] The actions of cannabinoids on PTSD symptomatology may likewise come about owing to any number of processes, including disruption of fear memory consolidation, decreasing salience of ordinarily significant stimuli, or facilitating the extinction of fear memories.[35,36] As cannabinoid variations may function as a fundamental component of adaptation to a stressor,[23] such changes may also evolve with time following trauma experiences, as observed in relation to trauma memories.[37] It should also be considered that the cluster of PTSD symptoms as well as the magnitude and type of trauma experienced in humans vary over time

following the trauma and in turn that the efficacy of cannabis-related treatments may also vary.[38]

Much still needs to be assessed concerning the efficacy and safety of cannabis in treating PTSD and other conditions. Among other things, questions remain concerning effective doses for different conditions, how long the drug needs to be taken before positive effects can be expected, potential sex differences in the effectiveness of cannabinoid action, and to what extent adverse outcomes can be expected in some people. Moreover, given the differential effects of THC and CBD in relation to affective behaviours and cognitive functioning,[39] it is necessary to determine the ratio of the different cannabis components (e.g., THC in relation to CBD) that are most effective at promoting therapeutic effects while minimizing adverse effects. It is also possible that cannabis or some of its components might serve as a useful tool in creating openness or a bridge to assist psychotherapy, much as 3,4,-methylenedioxymethamphetamine might have such actions,[40] although perhaps through different mechanisms.[41,42]

Considerable research in animals has pointed to benefits of cannabinoids in the treatment of PTSD. Legal restrictions that existed regarding access and use of cannabis had, unfortunately, limited the evaluation of the medical use of cannabis in humans,[43] including treatment of psychological disorders. The limited research in humans has nevertheless suggested that cannabis can ameliorate particular features of PTSD. However, these studies had a small number of participants, did not distinguish between the conditions that promoted the disorder (e.g., an acute traumatic experience, chronic stressor encounters, multiple trauma experiences), and did not consider the time at which the disorder was treated relative to when the trauma was experienced. In effect, the studies were typically of low quality, and large-scale studies remain to be conducted evaluating the efficacy of cannabis use in the treatment of PTSD. Nonetheless, the preclinical studies, together with the few clinical studies reported, support further detailed investigation into the use of cannabinoids in the treatment of PTSD. As in the case of so many other medical conditions for which new treatments have emerged at a rapid pace, it is important to distinguish between actual remedies versus those that are simply hopes. It is unfortunate that research pertaining to cannabis safety and efficacy for various illnesses has not kept pace with social reforms concerning its use. As indicated in a recent headline,[44] within the United States, "Legal weed is everywhere — unless you're a scientist." The recent legalization of cannabis within Canada may provide the opportunity to conduct the necessary research to determine whether cannabis-based treatments are more than snake oil.

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