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Medical Cannabis Reduced Agitation in Acquired Brain Injury: A Case Study

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Introduction

Neuropsychiatric comorbidities are considered to be among the most disabling sequelae following acquired brain injury, including traumatic brain injury (TBI) and stroke, with long-term prevalence reaching 54% (1;2). Chronic neuropsychiatric symptomatology from acquired brain injuries is associated with poor outcomes in vocational activities, interpersonal relationships, independent living, increased patient/family distress, and increased health care utilization (3;4). The literature on the treatment of neuropsychiatric conditions in general with medical cannabis (MC) is still in its infancy, with mixed results regarding its efficacy (5;6). However, given MC's psychopharmacological properties and its increased availability, this potential therapeutic agent for acquired brain injury deserves further investigation.

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The main exogenous cannabinoids in MC are Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD), which can act on several molecular targets throughout the body and collectively mediate potential therapeutic effects (6). THC binds to cannabinoid receptors in brain regions, such as the hippocampus, striatum, and cingulate, which are important for cognitive and emotional functioning (7). The potential therapeutic mechanism of action for THC includes partial agonization of the CB1 receptor, resulting in cannabis's antinociceptive, antiemetic, anxiogenic and cognitive blunting effects (6;8). In contrast, CBD acts on a variety of receptors, including 5-HT1a, GPR55, and TRPV1 receptors which mediate the anxiolytic, sedative, antipsychotic and anticonvulsant effects (6;8). CBD may mitigate some of the effects of THC, such as cognitive impairment and induction of psychotic symptoms (6). Although many of these therapeutic effects are desirable to treat neuropsychiatric symptoms following acquired brain injury, other effects can be potentially deleterious. These effects include physical symptoms (e.g., dizziness, vomiting), respiratory issues associated with smoked cannabis, product-use associated lung injury/death associated with vaping, potential worsening of psychiatric symptoms (5;9;10), and problematic use leading to dependence (11). Perhaps the most worrisome potential side-effect of MC following acquired injury is cognitive dysfunction, including deficits in verbal learning/memory, psychomotor speed, attention, and inhibition, all of which have been previously reported in the recreational cannabis (RC) literature (6;7;12).

Studies on the treatment of acquired brain injury with MC are limited. Preclinical trials and observational studies in humans suggest that cannabinoids may be therapeutic for primary and secondary neurobiological mechanisms associated with acquired brain injury (13;14). However, there has been only one Phase III randomized controlled trial exploring the neuroprotective properties of cannabis in which patients with severe traumatic brain injury (TBI) were administered a single intravenous 150mg dose of dexamabinol versus placebo (15). These results were negative. Studies exploring the potential therapeutic effects for neuropsychiatric symptoms associated with acquired brain injury have been restricted to a survey of RC use (16) and an abstract reporting a retrospective chart review of MC use (17). In both studies, patients with acquired brain injury reported improvement in mood, anxiety, headache, sleep, and quality of life as a result of using either RC or MC.

Given that a non-trivial number of patients with acquired brain injuries are using cannabis products in an attempt to self-medicate, it is important to better understand the potential benefits and risks. Here we present a case of a patient with acquired brain injury who used MC to treat neuropsychiatric symptoms, demonstrating its potential use in this population.

Case Report

Mr. X is a 38-year-old Hispanic male who was seen in an outpatient psychiatry clinic for treatment of anxiety three years after he sustained two acquired brain injuries. Mr. X sustained a mild traumatic brain injury with a loss of consciousness of approximately one minute as a result of being struck by a backhoe at his place of employment. There was no posttraumatic or retrograde amnesia, disorientation, or post-concussive symptoms observed following the injury. Two weeks later, he sustained a right middle cerebral artery stroke with endocarditis being the presumed etiology (see Figure 1). When he presented to the clinic, he

met criteria for posttraumatic stress disorder (PTSD) and major depressive disorder. He exhibited disinhibition with physical agitation, including head-banging and hitting himself. Symptoms of anxiety were presumed to be multifactorial in etiology, with contributions from premorbid psychiatric conditions, organic brain damage, as well as an adjustment reaction to new neurological symptoms and disability. He had also been previously diagnosed with post-stroke spasticity, central pain syndrome, and major neurocognitive disorder. Performance was impaired on a cognitive screening measure at his initial visit (Montreal Cognitive Assessment: 20/30). Mr. X had a history of stimulant, alcohol, and opioid use disorders before the stroke. At the time of treatment, he was consuming one to two alcoholic beverages on weekends and smoked half of a pack of cigarettes per day. He was also prescribed oxycodone 15mg extended-release daily with additional prescription of oxycodone 5mg as needed.

Mr. X was given self-report measures to track functioning over time, including the PTSD Checklist - Civilian Version (PCL-C) (18) and the Patient Health Questionnaire (PHQ-9) (19), which is a measure of depressive symptoms. He also completed the Agitated Behavior Scale (ABS) (20) to monitor agitation during recovery from acquired brain injury as well as the Neurobehavioral Symptom Inventory (NSI) (21). The latter assesses acquired brain injury-related symptoms, including physical symptoms such as dizziness and headaches, cognitive symptoms, such as forgetfulness and poor concentration, and psychiatric symptoms, such as depression and anxiety. At the initial visit, his scores were elevated for all scales, indicating clinically significant symptoms (see Figure 1).

Several treatment trials were initiated to help mitigate symptoms, including an antidepressant (venlafaxine extended-release, patient dose 150 mg BID; maximum 225 mg/day), anticonvulsant (gabapentin, patient dose 600mg BID; maximum 1800mg/day), benzodiazepine (alprazolam, patient dose 0.5mg QD; maximum 10mg), a cognitive enhancer (memantine patient dose 5mg BID; maximum 20mg/day), and a neuroleptic (aripiprazole, patient dose 10 mg QD; maximum 30mg day). These trials were either ineffective or resulted in increased agitation, which made Mr. X and his wife reluctant to try additional traditional medications. Alprazolam, aripiprazole, and memantine were therefore discontinued. Mirtazapine (patient dose 30mg QD; maximum 45 mg/per day), a tetracyclic antidepressant, was effective for improving sleep initiation/maintenance and reduction of PTSD symptoms. However, disinhibition, anxiety, depressed mood, flashbacks, nightmares, and irritability persisted. At his three-month visit, Mr. X and his wife reported that he was using inhaled, RC to reduce his symptoms and inquired about MC. The patient's provider (D.Q.) observed less agitation and no negative effects on motor or mental status that could be detected on clinical exam and agreed to provide medical certification. Mr. X qualified for the state MC program with his diagnosis of PTSD, as TBI nor stroke are currently considered a primary certifying condition in New Mexico. The label on Mr. X's MC indicated that the strain was *Purple Kush, Indica Dominant*, 2 grams with THC content 16.87% and CBD content 0.08%. He used MC up to five times per day as needed and adjusted the amount he used depending on his level of anxiety. One year following initiation of MC, Mr. X continued to report decreased depression, agitation, aggression and anxiety, increased social interactions and with no adverse side-effects. Reliable change indices for PCL-C, NSI, and PHQ-9 (Figure 1) indicated that the decrease in scores represented

clinically meaningful changes (22;23). Because of the improvement in symptoms, additional pharmacological treatment trials were not initiated. At his one-year follow-up visit, Mr. X had discontinued his use of opiates and was on Suboxone therapy, which he has maintained since that time.

Discussion

MC has the potential to become a more commonly prescribed or self-medicated treatment for acquired brain injury. The improvement of symptoms for this medically and psychiatrically complex patient suggests that MC can potentially be effective for neuropsychiatric symptoms in acquired brain injury when other psychotropic treatments have failed.

Regarding the potential therapeutic mechanisms of action for this case, CB1 receptors are distributed in the basal ganglia, cerebellum, hippocampus, and association cortices, spinal cord, and peripheral nerves. CB2 receptors are distributed on cells in the immune system and modulate pain and inflammation. When activated, the receptors directly inhibit the release of acetylcholine, dopamine, and glutamate and indirectly affect γ -aminobutyric acid, N-methyl-D-aspartate, opioid, and serotonin receptors (8). The beneficial effects on neuropsychiatric functioning that were observed were possibly due to variable effects on presynaptic inhibition of neurotransmitter release, especially glutamate. It is also not clear what contribution is due to the minor presence of cannabidiol, which indirectly modulates CB activity. PTSD and agitation-related symptoms may have been mitigated because of the high density of CB1 receptors in the amygdala-hippocampal-cortico-striatal circuits. These brain regions contribute to anxiety, fear-related behavior, hyper-responsiveness to emotional stimuli, and retrieval of fear-based memories (5). Administration of cannabinoids has been associated with reduced activation in this network in response to negative content, including attenuating amygdala response to threatening stimuli and reduction of threat responding in healthy volunteers (5).

The patient in our case did not report any adverse side-effects from MC. However, in addition to exploring the potential benefits of MC, there is also a need to learn about adverse effects, particularly for individuals with compromised brain reserve and cognitive functioning due to acquired brain injury. Past research on RC may or may not generalize to MC use for several reasons. For example, MC users are more likely to use cannabis almost daily, be in poorer medical health, and are less likely to meet criteria for a substance use disorder relative to RC users (24). Moreover, two small pilot studies of individuals using MC for a variety of conditions (e.g. chronic pain, depression, sleep disturbance, and anxiety) demonstrated opposite effects of what is typically observed in RC studies. Specifically, MC users showed improvement in executive functioning and activation in the anterior cingulate and frontal cortices relative to baseline (25;26), opposite to the typical declines in cognitive functioning shown in the RC use literature. It is possible that improvement in clinical symptoms, such as psychiatric symptoms or sleep quality, may be associated with improved cognitive and brain functioning in MC users. It is also possible that there are more favorable ratios of THC to CBD in MC compared with RC (6;25). Alternatively, due to the uncontrolled nature of these studies, it is not clear if these results may be due to practice

effects. Collectively, these findings highlight the importance for empirical research in this area.

Another important consideration is the patient's prior substance use disorder history. RC use often precedes MC use (27), which was true of the patient in this case report. This could be related to patient beliefs, including that cannabis is safer or more natural than traditional medications (27). Additionally, Mr. X stopped taking oxycodone during treatment and started Suboxone therapy. While it would be premature to conclude that his successful discontinuation of oxycodone was a result of MC use, some preliminary studies have shown that MC may improve outcomes for those in substance use treatment (28). It may also reduce opioid withdrawal symptoms (27) and ultimately play a role in harm reduction (28). However, given potential cognitive effects and general safety concerns about MC use, more research is needed before recommending MC in substance use treatment and providers should continue to caution against recreational or self-medicated use.

There are considerable challenges in the clinical care of patients using MC products. Cannabis is currently listed as a Schedule I controlled substance at the federal level in the United States. Substances in this category are considered to have no acceptable medical use and a high potential for abuse (25). Unlike traditional pharmacological interventions, MC is not carefully controlled, with a lack of regulation, quality assurance, and failure to meet basic label accuracy standards for pharmaceuticals (29;30), with the potential for mislabeling of product information (e.g., THC to CBC ratios). Studies have shown over- and underreporting of cannabinoids on product labels, with inaccuracies ranging from 45 –87% of the products tested (29;30). Some states require laboratory confirmation of cannabinoid content (31). However, there is a lack of industry-standard regarding laboratory testing, with one study showing inter-lab differences in cannabinoid content reporting (32). Thus, MC users may not know the true composition of the products they are using. There are also no standards regarding the amount or frequency patients should use per day. Patients may have difficulty accurately reporting on the quantity of MC that they use even when using standard methods, such as the Time Line Follow Back procedure, that are used in research settings to quantify substance use (33). There are many methods of use (e.g., inhalation, ingestion, topical) all of which may have their own specific beneficial and adverse effects. Finally, some MC products, such as hemp-derived products do not require healthcare provider certification or may not be classified as MC by users (25).

There are several alternative explanations for Mr. X's symptom improvement. He was using mirtazapine and venlafaxine at the time he started taking MC, which may have contributed to improvement in symptoms. Moreover, before using MC, some medications were not titrated to their maximum possible dosage, which may have contributed to the lack of therapeutic effects. He discontinued oxycodone, which may have improved psychiatric status. It is also possible that the patient experienced natural recovery of psychiatric symptoms over time post-stroke. We cannot rule out placebo effects or the patient's misattribution of improvement to MC rather than other factors. Finally, formal neuropsychological testing was not conducted pre- and post-MC use to quantify cognitive changes. However, this patient used RC prior to MC, so it would be difficult to know the true cognitive effects of MC. This issue raises the question if cognitive testing should be

recommended before initiation of MC treatment to track potential effects over time. These limitations highlight the complexities of working with patients using MC. Most patients with acquired brain injury will likely have multiple medical and psychiatric comorbidities, all of which can potentially impact the relationship between the effects of MC and acquired brain injury.

In summary, despite the promising results for our case, empirical studies have lagged behind public policy, particularly for MC use in acquired brain injury. Studies have demonstrated that patients with TBI use cannabis to improve mood/anxiety (16;17). However, neither acquired brain injury nor anxiety/depression is listed as qualifying conditions in state MC programs in New Mexico. More importantly, there are no randomized control trials or even cross-sectional studies to examine MC potential use for neuropsychiatric symptoms in acquired brain injury. Future studies must be conducted to better meet the needs of survivors of acquired brain injury and to help inform provider and patient decisions in using MC to treat symptoms.

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Figure 1:

a) FLAIR MRI sequence depicting the acquired brain injury b) Mr. X's symptoms over the course of treatment c) NSI Subscale scores over the course of treatment.

Abbreviations: PCL-C = PTSD Checklist – Civilian Version; NSI = Neurobehavioral Symptom Inventory; PHQ-9 = Patient Health Questionnaire; ABS = Agitated Behavior Scale. Reliable change scores are available for the PCL-C (7-point change indicates reliable change) (22), NSI (8-point change indicates reliable change) (22), PHQ-9 (5-point change indicates reliable change) (23).