DEPARTMENT OF HEALTH

Traumatic Brain Injury

ISSUE BRIEF ON TRAUMATIC BRAIN INJURY

Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, clinicaltrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

Traumatic brain injury (TBI), as defined by The Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychology Health, is "an alteration in brain function, or other evidence of brain pathology, caused by external force" (Menon et al., 2010).

TBI can be focal (affecting region of impact) or diffuse (affecting areas remote from region of impact), with injury resulting in primary and secondary effects. Primary injury refers to direct tissue damage that is inflicted on the brain from the initial mechanical impact. In contrast, secondary injury refers to a cascade of effects that occur in the injured brain over a variable, undefined amount of time.

Diagnosis

TBI diagnosis typically occurs through a combination of physical assessments and structural imaging for brain abnormalities. TBIs can be classified as closed (non-penetrating) or penetrating.

The most commonly used physical assessment of TBI is the Glasgow Coma Scale (Teasdale & Jennet, 1974) which is a classification system to indicate severity of TBI based on three components: eye opening, motor response, and verbal response. A summed score is generated from these components ranging from 3-15 (<3 indicates vegetative state on down to brain death), with the following ranges respectively indicating level of severity: Mild = 13-15, Moderate 9-12, and Severe 3-8.

Neuroimaging techniques can be used to assess structural damage, with computerized tomography (CT) being the most popular first option. A commonly used CT classification of TBI is the Marshall classification system (Marshall et al., 1992) with the following classifications:

- Diffuse Injury I (no visible pathology): no visible intracranial pathology.
- Diffuse Injury II: midline shift of 0 to 5 mm; basal cisterns remain visible; no high or mixed density lesions >25 cm^3.
- Diffuse Injury III (swelling): midline shift of 0 to 5 mm; basal cisterns compressed or completely effaced; no high or mixed density lesions > 25 cm^3.
- Diffuse Injury IV (shift): midline shift > 5 mm; no high or mixed density lesions > 25 cm^3
- Evacuated Mass Lesion V: any lesions evacuated surgically.
- Non-evacuated Mass Lesion VI: high or mixed density lesions > 25 cm^3; not surgically evacuated.

Prevalence

A recent estimate has indicated that approximately 2.8 million emergency department (ED) visits, hospitalizations, and deaths that occur in the US lead to a TBI diagnosis (Taylor et al. 2017). According to the Centers for Disease Control and Prevention, the number of emergency department (ED) visits in the US due to TBI went up between 2001 and 2010 (700 per 100,000 in 2010; CDC, 2016). TBI-related hospitalizations in the US have remained relatively the same during the same time period (just under 100 per 100,000), while TBI-related deaths have decreased over time (17 per 100,000 in 2010; CDC, 2016; Taylor et al., 2017). TBI is more common in males (Taylor et al., 2017; Maas et al., 2008). One US estimate put the annual cost burden of TBI at $60 billion (Thurman, 2001).

Global rates of TBI have been increasing, particularly as developing countries are adopting greater motor vehicle use (Redelmeier et al., 2003). In developed countries where the aging population is growing, the incidence of TBI due to falls has been increasing while TBI attributed to motor vehicle accidents has decreased (Maas et al., 2008; Taylor et al., 2017). The decrease in motor vehicle-related TBI in the US has been attributed to greater public health awareness and safety initiatives.

Current Therapies

Current therapies for TBI depend on TBI severity and symptoms presented by the patient. Mild TBIs may not require any particular treatments apart from over-the-counter medications, with regular consultation with a healthcare practitioner to monitor patient's status for any worsening of symptoms (Mayo Clinic). For penetrating TBIs, surgery is common to remove hematomas (clotted blood), repair fractures in the skull, stop bleeding in the brain, or as a means of relieving intracranial pressure (decompressive craniectomy). Pharmacotherapies are chosen based on patient symptoms and may include any of the following: diuretics (to relieve swelling and intracranial pressure), antiseizure medications (for seizure control post-TBI), antidepressants and/or antianxiety medications (for controlling emotional lability), anticoagulants (for reducing blood clotting), muscle relaxants (to reduce muscle spasms), and stimulants (to increase attention or alertness; Mayo Clinic; National Institutes of Health).

There has been particular interest within the scientific community to explore existing and new pharmacotherapies for neuroprotection in TBI. This is most likely spurred by the current state of evidence showing a lack of any particular agent for improving neurological outcome in TBI patients. McConeghy et al. (2012) recently summarized the state of clinical research for neuroprotective agents, and these are discussed directly below.

Calcium-channel blockers (to prevent neuronal excitotoxity and cell death) have generally been shown to be ineffective in TBI. Furthermore, these agents have other systemic effects that hinder TBI recovery (e.g., systemic blood pressure effects).

Corticosteroids (to prevent swelling) have shown some efficacy. However, high doses of corticosteroids make this treatment option undesirable, and some data suggests increased mortality rates in moderate to severe TBI patients on these agents compared to placebo.

Cyclosporin A (to offset calcium dysregulation) has shown some potential on improving neurological outcomes, but further investigation is necessary. Some phase II trials have indicated that cyclosporin A is relatively safe with some indication of better outcomes on the Glasgow Outcome Score-Extended (GOSE; Wilson et al., 1998) compared to placebo.

Deltibant (a bradykinin antagonist) did not show statistically improved outcomes compared to placebo, although there may be some indication that it may decrease intracranial pressure (ICP) >15 mm Hg for a longer period of time compared to placebo.

A few different agents have been investigated for their potential to attenuate excitotoxicity and excessive glutamatergic activity that is typically found in TBI. Dexanabinol, which will be discussed later in the "Preclinical Studies" and "Clinical Trials" sections of this brief, is a cannabinoid that does not have cannabimimetic effects but rather acts as a non-competitive NMDA-receptor antagonist. Dexanabinol showed some initial promise in the preclinical phase (animal models of TBI), but equal success was not evident when investigated in humans. Magnesium sulphate (to attenuate calcium influx at NMDA receptors) did not show any improved outcomes over placebo and was associated with a possible increase in mortality rates. Lastly, selfotel (a competitive NMDA antagonist) was determined to not show any favorable outcomes.

Progesterone has shown some initial promise in improving neurological outcomes and mortality rates; however, a more recent clinical trial has contradicted this finding in severe TBI patients (Skolnick et al., 2014).

Statins, which are commonly used to improve cardiovascular outcomes, have also been investigated for any role in improving TBI outcomes, and one statin (rosuvastatin) has shown, in an under-powered study, some possibility for improving memory function.

Other agents reviewed by McConeghy et al. were pegorgotein, tirilizad, and zinc supplementation – all of which did not show any particular promise in clinical trials for improving neurological outcomes over placebo or comparator groups.

Preclinical Studies

Preclinical studies on TBI tend to focus on how to manipulate the endocannabinoid system (eCB) to improve TBI outcomes. Endocannabinoids are compounds that are naturally occurring within the brain (endogenous) that influence cannabinoid receptor function and other physiological processes that subsequently affect brain functioning. This section will briefly discuss a paper summarizing preclinical work on the potential restorative role of the eCB system in TBI or related pathologies (Schurman et al. 2017). This will be followed by research on a particular cannabinoid that showed some early promise at the preclinical level (Shohami et al., 1997). This particular cannabinoid is discussed here because it is the only one found in the literature where 1) both preclinical and clinical data exists, and 2) it was not treated as a pre-treatment (prior to injury) or investigated retrospectively.

Schurman LD, Lichtman AH. Endocannabinoids: a promising impact for traumatic brain injury. *Frontiers in Pharmacology*. 2017; 8:69. doi: 10.3389/fphar.2017.00069.

This is a review paper that came out recently to summarize preclinical literature on the role of the endocannabinoid (eCB) system in TBI. The eCB system appears to be involved in several physiological processes that are implicated in repair. In particular, this review focuses on two of the most well-studied eCBs, anandamide and 2-Arachidonoylglycerol (2-AG), along with the pathways that modulate their biosynthesis and degradation.

Endocannabinoid levels have been shown to increase as a function of neuronal damage which suggests that eCB system activation may be involved in compensatory self-neuroprotection efforts. For example, slowing down the breakdown of anandamide and 2-AG in the brain (which then gives these eCBs a longer period of time to act on receptor targets) can slow down cell death. Increasing anandamide levels (by inhibiting fatty acid amide hydrolase (FAAH) activity, which breaks down anandamide) as well as 2-AG levels (by inhibiting monoacylglycerol lipase (MAGL) activity, which breaks down 2-AG) has been shown in rat models to reduce neuronal cell death. Excessive glutamate release, which is a pathology of TBI, has also been shown in preclinical research to be attenuated by increasing 2-AG levels (via inhibition of MAGL activity).

Inhibiting the enzymes FAAH and MAGL may also play a role in neuroinflammation. For example, anandamide and 2-AG share a commmon metabolite called arachidonic acid (AA). AA has been shown to be involved in inflammatory responses in the brain. Therefore, by inhibiting FAAH and MAGL (which decreases amount of AA in the brain), inflammatory responses can be attenuated.

The blood brain barrier (BBB) is compromised in some central nervous system insults, with TBI being one of them. Schurman et al. cite independent literature indicating that exogenous delivery of 2-AG or anandamide, or the inhibition of FAAH or MAGL can prevent BBB breakdown in various central nervous system diseases.

Shohami E, Gallily R, Mechoulam R, Bass R, Ben-Hur T. Cytokine production in the brain following closed head injury: dexanabinol (HU-211) is a novel TNF-α inhibitor and an effective neuroprotectant. *Journal of Neuroimmunology*. 1997; 72: 169-177.

Prior research leading up to the study reviewed here had previously shown evidence of dexanabinol's (HU-211; (+)-(3S,4S)-7-hydroxy-Δ^6-tetrahydrocanabinol 1,1-dimethylheptyl) neuroprotective effects. HU-211 is a synthetic cannabinoid that does not bind to brain CB1 receptors and does not produce cannabimimetic effects. Rather, HU-211 acts as a noncompetitive NMDA-receptor antagonist (a glutamatergic receptor) which has previously shown to decrease calcium (Ca^{2+}) neuronal influx in a rat model, thereby attenuating excitotoxic effects that may lead to cell death (brain trauma often causes an influx of Ca^{2+} into neuronal cells, which triggers excessive release of glutamate which damages cells). Other prior research using rat models has also shown that HU-211 attenuates the degradation of the blood brain barrier (BBB) as well as playing a role in decreasing cerebral edema and improving some memory functions.

In this paper, the authors explored the effects of HU-211 on tumor necrosis factor-α (TNF-α) levels. An increase in TNF-α levels in the brain had previously been documented in traumatic brain injury. HU-211 was injected into rats soon after undergoing a closed head injury, and this treatment was compared to control in the inhibition of TNF-α as well as comparing this experimental treatment to other compounds that have previously been shown to inhibit TNF-α.

A closed head injury (CHI) was induced by dropping a calibrated weight onto a defined region of the exposed skull. TNF-α levels were maximally found roughly 4 hours after CHI. For the experimental study, HU-211 was administered intravenously within 5 minutes post-CHI at a dose of 5 mg/kg (controls received a vehicle solution intravenously). TNF-α bioactivity was markedly reduced in the treatment group compared to control. Pentoxifylline (PTX) and tumor necrosis factor binding protein (TBP) administered concomitantly with rh-TNF- α (r-hTNF+TBP) – two other compounds previously shown to decrease TNF-α bioactivity – was confirmed to decrease TNF-α levels compared to control, confirming HU-211's comparative effectiveness in reducing TNF-α post-CHI. Rats were also examined on their recovery of reflexes and motor functions with a neurological severity score (NSS). All three treatments (HU-211, PTX, r-hTNF+TBP) showed changes in NSS at 24 hours post-CHI compared to controls, with HU-211 showing the most change indicating greatest recovery of reflexes and motor functions.

Evaluation of the NSS at other time points post-CHI continued to show that all 3 treatments lead to significant changes on the NSS compared to controls. All 3 treatments also showed significant reduction in cerebral edema at 24 hours post-CHI compared to controls, with HU-211 showing the greatest reduction. Blood brain barrier (BBB) integrity was also highest with HU-211 and TBP compared to control when measured 4 hours post-CHI with Evans blue (dye that allows for measuring BBB integrity). Lastly, there was a reduction in hippocampal cell death (region involved in learning/memory) with HU-211 and TBP administration, with HU-211 showing greatest reduction in hippocampal cell death.

Clinical Trials

Clinical trials investigating the effects of cannabis or cannabinoids on TBI have been restricted to the synthetic cannabinoid dexanabinol (HU-211), which is the compound that showed some promise in the preclinical literature (see "Preclinical Studies" section in this brief). However, the transition from preclinical to clinical study of this particular compound on TBI has not shown the same potential – this clinical literature is summarized below.

Knoller N, Levi L, Shoshan I, Reichenthal E, Razon N, Rappaport ZH, et al. Dexanabinol (HU-211) in the treatment of severe closed head injury: a randomized, placebo-controlled, phase II clinical trial. *Crit Care Med*. 2002; 30(3): 548-54.

This was a prospective, multi-center, randomized, double-blind study investigating the safety of dexanabinol (HU-211; a compound discussed previously in the Preclinical Studies section) compared to placebo on patients 16-65 years old with severe traumatic brain injury. A total of 67 patients participated in the study (drug treatment group: n = 30; placebo: n = 37). Roughly half had a Glasgow coma score (GCS) of 7-8 and a CT classification of 2. Patient mortality and adverse events (AEs) were reviewed after a single 48 mg dose of dexanabinol (or placebo). Those not succumbing to death or serious AEs from this group were then randomized into a higher, 150 mg dose of dexanabinol (or placebo). The following primary outcomes were measured: intracranial pressure (ICP), adverse events, cardiovascular functions including cerebral perfusion pressure (CPP), and clinical laboratory results. While this study was underpowered to detect any statistical differences on neurologic outcomes in patients, the following secondary measures were still included in the study: Galveston orientation and amnesia test (GOAT), Glasgow outcome score (GOS), and disability rating scale.

Results indicated that the mean percentage of time that ICP was <25 mm Hg was significantly lower in the dexanabinol group compared to placebo on the 2nd and 3rd day after injury, indicating that dexanabinol may be better at controlling ICP compared to placebo. In addition, the mean percentage of time that CPP was <50 was 0 on the 2nd and 3rd day after injury in the dexanabinol group compared to placebo; dexanabinol appeared to better manage CPP than placebo. Both groups reported similar number of AEs, and the AEs reported were typical of traumatic brain injury. GOS (a measure of neurologic recovery) showed improvements across patients irrespective of treatment group (meaning dexanabinol wasn't superior to placebo on GOS). The percentage of patients achieving good neurologic recovery

was significantly better at one month post-injury for the dexanabinol group compared to placebo, but this was not maintained in 3- and 6-months post-injury, indicating whatever benefit dexanabinol may afford for good neurologic recovery is lost over time.

While ICP and CPP scores appeared promising in this study, it is important to note that this was a study with a small sample size. Furthermore, due to the small sample size (which underpowers the study), interpretations on efficacy as measured by neurologic recovery are speculative until a larger scale study can support or refute those claims. Maas et al.'s (2006) study, which follows directly below, tried to address this major limitation (small sample size) to better address efficacy of dexanabinol on neurologic outcomes.

Maas AIR, Murray G, Henney H, et al. Efficacy and safety of dexanabinol in severe traumatic brain injury: results of a phase III randomized, placebo-controlled, clinical trial. *Lancet Neurol*. 2006; 5: 38-45.

This was a prospective, multi-center, randomized, double-blind parallel assignment of dexanabinol (HU-211; a compound discussed previously in the Preclinical Studies section) or placebo to adult patients who experienced severe traumatic brain injury. Inclusion criteria included patients who had a traumatic head injury within the last 6 hours and had a Glasgow Coma Motor score between 2-5. Patients were administered either 150 mg of dexanabinol or placebo intravenously within 6 hours of their injury. A total of 861 patients were randomized, with 846 of them reaching the primary outcome measure: 6-month post-injury Glasgow Outcome Scale Extended (GOSE). Secondary measures included: 1) 3-month post injury GOSE, 2) mortality rate at 10 days, 3) mortality rate at 6 months, 4) intracerebral pressure during first 74 hours since trauma, 5) neuroworsening at 10 days, 6) SF-36 quality of life scale at 6 months, and 7) Barthel index at 6 months. Results on the 6-mo GOSE showed no differences between patients treated with dexanabinol or placebo. Analyses on mortality rates, occurrences of neuroworsening, or recovery-related events were also no different between treatment groups. Intracranial pressure and cerebral perfusion pressure were also found to be no different between treatment groups. 32 patients receiving the placebo arm reported treatment-related adverse events, while 25 patients receiving dexanabinol reported treatment-related adverse events.

Ongoing Clinical Trials

As of early September 2018, no ongoing clinical trials examining the efficacy or safety of cannabis or cannabinoids on TBI were found on ClinicalTrials.gov.

Observational Studies

One observational study examining the effects of cannabis or cannabinoids on TBI was identified. As a retrospective study (more susceptible to bias and confounders relative to prospective studies), the conclusions that can be drawn are somewhat limited. The presence of

cannabis use was determined by urine toxicology screening (for presence of THC) in TBI patients, and mortality rate was retrospectively examined.

Nguyen BM, Kim D, Bricker S, Bongard F, Neville A, Putnam B, et al. Effect of marijuana use on outcomes in traumatic brain injury. *Am Surg*. 2014; 80(10): 979-83.

This study reviewed records of trauma patients (16+ years old) and identified those who were admitted to a surgical intensive care unit over a two-year period at a California hospital (January 1, 2010 - December 31, 2012). Of 7,977 trauma patients that were evaluated in this time period, 538 of them had TBI, with 82.9% of these TBI patients (n = 446) having been screened for illicit drug use. Of the 446 drug-screened patients, 82 of them tested positive for THC while the remaining 364 patients were THC-negative. Mortality rates of the THC-positive group were significantly lower than the THC-negative group. A regression analysis found that a THC-positive screen, being 45+ years old, and scoring >4 on the head Abbreviated Injury Score (Head AIS) were each independent predictors of mortality. Apart from the retrospective nature of this study being a limitation, there are limitations surrounding what can be stated regarding patient cannabis use, where THC can be detectable for days to weeks. Therefore, this study is unable to clarify the role of chronic vs. acute cannabis use in the pattern of results. Another limitation is the specific focus on mortality rates as an outcome measure for TBI; inclusion of additional outcome measures for TBI would provide a more comprehensive understanding of the potential role of cannabis on TBI prognosis.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of TBI were found.

The National Academies of Sciences, Engineering and Medicine published a report on the health effects of cannabis and cannabinoids in 2017. This report included a review of evidence on the effects of cannabinoids on TBI or intracranial hemorrhage (the latter not necessarily always associated with TBI and can be a symptom of other disease states). The committee for this report concluded that “there is limited evidence of a statistical association between cannabinoids and better outcomes (i.e., mortality, disability) after traumatic brain injury or intracranial hemorrhage” (see Conclusion 4-15; National Academies of Sciences, Engineering, and Medicine, 2017).

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