Research Article

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Marijuana: Proposed Treatment in Trauma Patients

B Phillips*, B Keath, J Wu, M Hartmann,W Weber, J O'Connor, and J A Asensio

Department of Surgery, Creighton University School of Medicine Omaha, Nebraska.

Department of Clinical and Translational Science, Creighton University School of Medicine Omaha, Nebraska.

***Corresponding author**

Bradley J. Phillips, MD, Vice Chair of Surgery – Surgical Research, Associate Professor of Surgery, Department of Surgery, Creighton University School of Medicine, Creighton University Medical Center, 601 North 30th Street, Suite 3701 Omaha, NE 68131-2137, Tel: 402-717-4842; BradleyPhillips@creighton.edu.

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Abstract

Background: *A standardized treatment approach for trauma patients who test positive for marijuana/THC does not currently exist in the literature. Several medications are recommended to treat withdrawal and the cannabinoid hyperemesis syndrome.*

Methods: *A literature search was conducted through Medline and PUBMED following PRISMA guidelines. Key phrases searched for included "marijuana treatment, trauma marijuana patients, and THC interactions with other medications". Article selection was based on relevance, with focus on diagnosis and management of marijuana positive patients. All studies, regardless of publication date, were considered due to the paucity of published literature.*

Results: *Of the 1853 studies identified, 24 were selected to have material relevant and useful to this review. Both retrospective and prospective reports were identified in order toclosely examine the relationship between marijuana use and Injury Severity Scores, hospital length of stay, and related hospital costs.*

Limitations: *Limitations of this article are similar to all PRISMA-guided review articles: the dependence on previously published research and availability of references as outlined in our methodology.*

Conclusion: *Patients experiencing marijuana withdrawal should be evaluated for divalproex to reduce marijuana cravings; nefazodone to decrease anxiety and muscle pain; and lofexidine to improve sleep as well as help address withdrawal related stress. Administration of benzodiazepines can be considered to limit aggression. Lorazepam and haloperidol have been shown to be effective for cannabinoid hyper emesis syndrome. All trauma patients should receive tobacco, alcohol, and drug screening, followed by reflex confirmatory blood testing to increase accuracy. Patients testing positive for marijuana should be individually addressed, since cannabis and cannabinoids have been found to alter anesthetic potency. In addition, all marijuana/THC patients should undergo counseling in an effort to reduce use and prevent further morbidity and use related complications.*

Keywords: Marijuana Treatment, Trauma Patients, Marijuana Withdrawal, Cannabinoid Hyperemesis Syndrome

Introduction

At present, a standardized treatment approach to trauma patients who test positive for marijuana/THCdoes not exist. Marijuana use and subsequent withdrawal is likely to occur in the complex setting of co-morbid substance abuse and psychiatric illness, such as depression [1]. The default withdrawal approach is psychological support, sleep management, and the use of various medications as needed for symptoms [2]. Physicians treating patients who are possibly addicted to other substances should exercise caution when considering administration of some of the medications suggested in this paper.

Long-term marijuana use can cause the cannabinoid hyperemesis syndrome, which is easily misdiagnosed without a drug screen. Hyperemesis without a drug screen should increase the suspicion of underlying marijuana use. False-positive results are possible in long-term users, undermining the acute validity of positive screens in general. However, with the use of confirmatory blood tests this effect can be minimized. Marijuana may also interact with commonly administered inpatient medications as well as the potency of anesthetics, thus impacting the emergency care of trauma patients.

There is debate in the literature regarding patients who test positive for marijuana and their ability to provide informed consent for a procedure [3, 4]. From a review of published reports, marijuana-

intoxicated patients may only be able to provide consent for procedures based on the success rate of the procedure and how likely the patient is to die without treatment. In our center, a mandatory drug screen is implemented in order to establish the validity of informed consent and thus the utilization of emergency-consent measures.

Methods

For this study, relevant medical literature was searched through PubMed, Google Scholar, and Medline following PRISMA guidelines. The search terms included "marijuana treatment," "trauma marijuana patients," "trauma THC patients," "THC interactions with other medications," "marijuana withdrawal," and "cannabinoid hyperemesis syndrome." The PRISMA checklist and algorithm was used to ensure a complete and detailed approach to finding relevant literature. Articles were reviewed for significance by title and abstract, then all sources discussing marijuana positive patients that also contained material on treatment, interactions with other medications, and trauma were comprised. The integrated material totaled 24 articles and case studies.

Results

A total of 1853 studies were identified following the guidelines of the initial search, 59 of these were found to be appropriate after screening the title, abstract, and body of each paper. Twenty-four studies were then found to have material relevant and useful to our study. The literature search yielded the following results for each search term:"marijuana treatment"–541 results, 9 relevant, 4 selected; "trauma marijuana patients"–159 results, 12 relevant, 4 selected; "trauma THC patients"–36 results, 6 relevant, 4 selected; "THC interactions with other medications"–243 results, 16 relevant, 4 selected; "marijuana withdrawal"–786 results, 11 relevant, 5 selected; "cannabinoid hyperemesis syndrome"–88 results, 5 relevant, 3 selected.

The studies identified were a mix of retrospective and prospective reports that identified demographic information and correlation between marijuana use to Injury Severity Scores, hospital length of stay, and related costs of hospital resources

Discussion

Marijuana's Effect on Immunity and Cell Response

Cannabis exposure impairs cell-mediated immunity. Although remaining immune function may be sufficient for the vast majority of young cannabis users, cannabinoids modulate known inflammatory responses [5]. More specifically, exposure to delta-9-tetrahydrocannabinol (THC – the "active" ingredient in marijuana) results in suppression of T-cell proliferation by reduction ofIL-12 and IFN- γ production. Activation of cannabinoid (CB) receptors also inhibits secretion of other pro-inflammatory cytokines from astrocytes and macrophages [6]. Cannabinoid substances also decrease basal and prostanoid-stimulated cyclic AMP accumulation in intact neuroblastoma cellsand may shift immune responses across phenotypes [6,7]. Two early studies suggest that T-lymphocytes might be decreased in number as well as in ability to respond to an immunologic challenge. Further studies have also confirmed an immunosuppressant action of cannabis in animals [5]. However, cannabinoid substances fail to act as stimulatory agonists or competitively antagonize the adenylate cyclase response to prostanoid agonists. Additionally, activation of CB1 receptors in the atria and the vas deferens, two sympathetically innervated peripheral organs, inhibits the release of noradrenaline [7]. Norepinephrine inhibition induces relaxation and apathy in patients. This inhibition of noradrenaline release is delta-9-THC concentration-dependent [8].

Marijuana's Interaction with Anesthetics and Other Medications

There is an important distinction between the effects of cannabinol/cannabinoids and cannabis on anesthetics. Cannabis itself is able to prolong both pentobarbitone and ether anaesthesia.This interaction between cannabis and pentobarbitone-induced anesthesia is independent of any effects that cannabis may have on the endogenous levels of norepinephrine, dopamine, and 5-hydroxytryptamine. It is important to recognize that this increased incapacitation is due to the effect of cannabis, and not another medical cause. In contrast, cannabinol cannot potentiate the effects of pentobarbitone anesthesia. Literature also suggests that cannabinol might reduce the duration of anesthesia, especially in combinations with other cannabinoids. Specifically, pentobarbitone is susceptible to cannabinol interaction [9]. Anesthesia interactions are specifically important for trauma patients, as many patients require intubation. Given that the urinary half-life of marijuana is 0.8-9.8 days, with a mean of 3 days + 2.3, it is important to determine a baseline THC level while monitoring the patient closely when anesthetized [10]. Published literature does not have a standardized adjustment rate for anesthetic based on the level of marijuana in a patient's system. Hence, further research needs to be conducted on how to best sedate marijuana/THC-positive patients.

Marijuana Withdrawal Syndrome

Marijuana withdrawal syndrome is often mild and short lived but nonetheless relevant to treatment [11]. The "marijuana withdrawal syndrome" (MWS) occurs most commonly in chronic, daily users forced to undergo sudden abstinence – for example, in a trauma setting [12]. MWS presents in roughly half of chronic marijuana use patients [13]. Symptoms include restlessness, irritability, various degrees of agitation, insomnia, sleep disturbance, nausea, and muscle cramping [11]. Withdrawal is also associated with increased aggression and a lack of sociability. These symptoms are known to peak on days three to seven of a chronic users' abstinence [14]. "Heavy use" is generally characterized as the use of marijuana 22-30 days in a month, while chronic use can be defined as intermittent but regular use for one year or longer [15].

MWS is gaining recognition as a clinically significant component to marijuana dependence, as the user often finds the best relief to their symptoms is further marijuana use [12]. Identification and the appropriate medical treatment of MWS may assist not only in improving inpatient care, but also in recovery by preventing relapses following discharge.

Treatment of Marijuana Withdrawal Syndrome

Since up to 50% of chronic, heavy users experience MWS, medical treatment should be administered based on the manifestation of symptoms. Roughly half of patients presenting with a marijuana-positive drug screen will experience time-dependent increases in irritability and restlessness that are characteristic of MWS [13]. Withdrawal prevention and treatment along with addressing insomnia and marijuana cravings are most critical for prevention of relapse. Hospitalization during this period allows medical staff an opportunity to break the chemical cycle of addiction.

Benzodiazepines are currently recommended for patients experiencing increased aggression from withdrawal. However, benzodiazepines are addictive and should be administered with caution. In the presence of psychotic symptoms, oral atypical antipsychotics alone, without benzodiazepines, are considered the best treatment option [16]. Divalproex can assist in reducing marijuana cravings while increasing the objective amount of time a patient spends asleep. Interestingly, patients have reported subjective feelings of decreased sleep with more frequent awakenings while on divalproex. Divalproex may also worsen overall mood and hinder performance on a range of cognitive tasks [17]. Compliance in taking this medication has reportedly been poor, suggesting it was not well tolerated or received [12]. Side effects of divalproex include birth defects, suicidal ideation, and damage to the liver and pancreas.

Nefazodone is an antidepressant that restores serotonin and norepinephrine balance. Nefazodone has been shown to significantly decrease anxiety and muscle pain in marijuana patients,although it has not been shown to affect irritability and decreased appetite. High doses of nefazodone are limited by the United States Food and Drug Administration due to hepatotoxicity; thus administration should be reserved for patients with severe anxiety and/or muscle pain not alleviated by other treatment options [12]. Nefazodone should be avoided in patients experiencing concomitant marijuana, alcohol or barbiturate drug withdrawal due to hepatotoxicity risk.

Lofexidine is an alpha-2A-adrenergic receptor agonist. It is generally used as an antihypertensive and to alleviate the physical symptoms of opioid withdrawal. Lofexidine has been demonstrated to improve both subjective and objective measures of a patient's sleep during withdrawal. Patients on lofexidine report greater ease with sleep onset and longer periods of sleep during withdrawal. Improvements in sleep during the withdrawal and abstinence periods are essential to decreasing relapse in marijuana use. Lofexidine is also helpful in decreasing overall marijuana relapse, although it is unclear whether it is superior to divalproex in accomplishing this. However, lofexidine may worsen abstinence related anorexia and weight loss; it also does not alleviate mood symptoms or cravings of marijuana withdrawal. Although Lofexidine decreases blood pressure, clinically significant hypotension was rarely associated with use. It is worth noting that lofexidine substantially increased sedation when combined with a sedative or an anesthetic, although the effect did not appear to be aversive [13].

Lofexidine has also been shown to decrease stress, providing another argument for administration to withdrawal patients. Marijuana withdrawal is similar to opioid withdrawal in relation to noradrenergic hyperactivity activity. As mentioned above, alpha-2A-adrenergic receptor agonists have been used to treat physical symptoms in opioid withdrawal through reduction of norepinephrine release. Decreased norepinephrine release is the presumed mechanism of lofexidine's utility in treatment of both opioid and marijuana withdrawal. A recent study of opioid-dependent patients on naltrexone demonstrated that lofexidine administration reduced stress and substance induced craving. Lofexidine also decreased opioid relapse compared to the placebo and literature also documents association of lofexidine with decreased stress induced drug seeking behavior. Lofexidine may also be capable of decreasing marijuana relapse in trauma patients through a mechanism similar to opioid relapse, by decreasing withdrawal-related noradrenergic hyperactivity [13].

Cannabinoid Hyperemesis Syndrome

Cannabinoid hyperemesis syndrome (CHS) is characterized by cyclic vomiting and compulsive bathing behavior in people who chronically use cannabis on a daily basis. As a potentially misdiagnosed cause of nausea, cyclical vomiting, and abdominal pain, the effects of CHS on an undiagnosed patient can lead to a decreased quality of life and productivity. Misdiagnosis of a CHS patient can also lead to repeated and unnecessary overuse of healthcare resources [18]. Lorazepam has been used to treat patients undergoing chemotherapy and cyclic vomiting syndrome. It acts as an antiemetic, amnestic, and anxiolytic. Lorazepam has also recently been used to treat a small number of patients with CHS, with good results. One specific patient was administered IV lorazepam (1mg) with improvement in symptoms within ten minutes. The patient reported cessation of nausea, abdominal pain, and food aversion. Although lorazepam could help manage the acute hyperemetic phase of CHS to relieve nausea, vomiting, abdominal pain, and food aversion, it should be used with caution due to the susceptibility of CHS patients to substance use and the physical and psychological dependence potential of benzodiazepines [19].

Haloperidol has been promoted in the anesthesia literature to reduce postoperative nausea and vomiting; it has also been proposed to treat CHS. Haloperidol is frequently used in emergency departments to treat psychosis, agitation, and emesis. Haloperidol can also be used to treat CHS-induced epigastric pain, nausea, and vomiting. When haloperidol was given to a CHS patient, symptoms ceased within an hour [20]. However, providers should be aware of the myriad of side effects associated with haloperidol, including dry mouth, headache, and loss of appetite.

Potential Issues with a "Positive Drug Test"

Susceptibility of urine drug screens to changes in urinary output are problematic. The rise and fall of substance levels can be misinterpreted as new substance use, rather than carry-over from previous use [21]. Urine creatinine has been suggested as one way to reduce variability in interpreting drug concentrations due to changes in urine volume. Creatinine clearance ratios can be used to measure the ratio of substance clearance to creatinine. While a drug dose is excreted in rapidly decreasing concentration in the urine over a few days following administration, creatinine is excreted in approximately equal daily quantities. Excretion of the marijuana metabolite11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THCCOOH) reaches a peak in 6 to 28 hours and declines rapidly in the following one to two weeks. However, the concentration of THCCOOH does not continually decrease, in fact, it often follows a "sawtooth" pattern of levels that depend on urine volume. Monitoring creatinine and THCCOOH levels can ascertain the relative quantity of THC present and possibly predict the onset of withdrawal [21]. When the quantity of THCCOOH in the patient's urine is close to zero, it is reasonable to begin monitoring for withdrawal symptoms.

Patients with a positive urine drug screen should undergo reflex blood testing, which are now standard for testing for marijuana use in California and Colorado. The highest mean THC concentration is usually measured one hour after ingestion [22]. Multiple blood draws can establish a timeline of how long the patient will be

intoxicated, and/or when they are likely to experience symptoms of withdrawal. The standard 'legal' cut-off for intoxication is 5 ng THC/ml blood(but this has been decided legally and not necessarily with medical controls [23]. Long-term, heavy marijuana users can produce a false positive test. The main component screened for in marijuana, delta-9-tetrahydrocannabinol (d-9-THC), is rapidly absorbed and stored in fatty tissues [15]. Higher concentrations of marijuana have also been found in the blood of patients who have smoked, rather than ingested the compound [22]. Long-term, heavy users can have considerable THC stores, which can be steadily released into the blood causing a false-positive drug test [15]. Levels of 2 to 22 ng/ml have been measured in heavy users up to 24-hours following last reported marijuana use [15]. Although uncommon, ibuprofen and naproxen have also been known to cause false-positive tests in 0.4% of patients, including occasional or non-users [24].

Marijuana/THC-Positive Patients and Informed Consent

The question of informed consent is particularly relevant in the case of marijuana/THC- positive trauma patients. Heavy marijuana use is associated with residual neuropsychological effects even a day following supervised abstinence from the drug, raising the ethical question of whether or not patients can give informed consent.4 Thus; it is questionable if marijuana positive patients are truly competent to give informed consent before they are completely "sober". According to Drane, marijuana positive intoxicated patients are able to provide informed consent for procedures that are not extensively dangerous and are objectively in the patient's best interest; however there is a paucity of literature to support this conclusion.3 When there is little uncertainty in diagnosis, the available treatment is generally effective, and the patient is likely to die without the treatment, it can be presumed the patient will not actively refuse treatment.3 This is frequently the case in trauma patients. Each marijuana-positive patient should be treated on an individual basis, based on the amount of marijuana in his or her system and level of cognition. A mental status exam should be performed on these patients to better assess their ability to give consent and healthcare providers as well as hospital administrators should address this significant issue from a systems perspective.

Limitations

The amount of published research specifically addressing treatment of patients testing positive for THC in a trauma center is limited. The increase in volume of THC-positive patients in trauma centers provides strong support that further investigation and development of protocols for management of these patients should be investigated and established.

With respect to recommendations made in this review, the side-effects and impact on potential drug-drug interactions should always be taken into consideration when evaluating a patient for withdrawal medications. For example, administration of divalproex should be performed with careful monitoring of toxicity symptoms, as many neurologic findings in marijuana users may be blunted, altered, or difficult to evaluate. Benzodiazepines are an option and should be administered with reservation and caution because of their high addictive potential as a result of hospitalization.

Conclusions

In spite of logistical problems with urine drug screen sensitivity and subsequent differentiation of acute cannabis intoxication, this review of the literature supports the idea that an awareness of marijuana/THC can enhance clinical care and the overall management of patients. Use of current medications can ease withdrawal symptoms when side effects are taken into consideration for each individual patient. Divalproex can reduce marijuana cravings and benzodiazepines reduce aggression. Nefazodone has been shown to decrease anxiety and muscle pain in severe cases where alcohol intoxication is not present. Lofexidine can increase the patient's ability to fall and remain asleep, addressing a primary withdrawal symptom responsible for relapse. Marijuana can also interfere with anesthetics as well as cellular immunity and function. Long-term marijuana use can also cause cannabinoid hyperemesis syndrome, which can be easily misdiagnosed. Lorazepam and haloperidol are both helpful in treating patients with CHS.

Marijuana may or may not be a "gateway drug", but the presence of marijuana/THC in a trauma patient should be screened for, and then treated to optimize overall outcomes. Patients who are positive for marijuana may be able to provide consent, but this issue should be addressed proactively by both healthcare providers and hospital administrators. Overall, further investigation of appropriate medication and integration of management is necessary to ascertain the best overall approach of a trauma patient who tests positive for marijuana/THC.

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