Spinal Cord Series and Cases (2018)4:68
https://doi.org/10.1038/s41394-018-0097-0

PERSPECTIVE

Cannabis conundrum

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Received: 16 May 2018 / Accepted: 16 May 2018

Abstract

As there is a high prevalence of cannabis use in the population of people with spinal cord injury (SCI), it is important for clinicians to understand the positive and negative consequences of cannabis use in order to have educated and constructive discussions with their patients. The recent National Academies of Sciences, Engineering, and Medicine (NASEM) report provided an excellent summary of current cannabis research and touted clinical efficacy for cannabis for neuropathic pain and spasticity, two common secondary conditions after SCI. However, it is important to consider the limitations of the studies examined and the shortcomings of the meta-analysis methodology. We will discuss the fallacies in evidence supporting cannabis use by identifying limitations of current cannabis research that lead to limited generalizeability of the results, including short duration of the studies, small sample sizes, lack of statistical significance, inability to conduct blinded trials, non-standardization of delivery systems and lack of defined dosing, and small clinical benefits. The number of negative side effects associated with cannabis use, including risk of injury, overdose injuries, impairment of cognition, and increased risk of depression and suicide, are a strong argument for more rigorous studies of the efficacy of cannabis, especially in an already vulnerable population.

Introduction

It is imperative for clinicians to understand the positive and negative ramifications of cannabinoid use in persons with spinal cord injury (SCI), as cannabinoid usage has a high prevalence in this population. A recent study revealed that 48% of 116 persons with SCI reported use after their injury [1]. The two conditions that the National Academies of Sciences, Engineering, and Medicine (NASEM) report touted clinical efficacy for cannabinoids were neuropathic pain and spasticity, two commonly seen secondary conditions after SCI [2]. We take exception to the evidence used in the report (and other meta-analyses) to make such recommendations. We will discuss the fallacies in evidence using current available literature. The authors will elucidate problems that were not addressed in the recommendations. These include a wide range of delivery systems, the variability of tetrahydrocannabinol (THC) percentage by delivery method, the rather small change in pain and spasticity scores in studies that have a longer duration of usage, the difficulty with placebo-controlled design with cannabinoids, the relatively high number needed to treat when compared to conventional therapy, and not least the harmful side effects of cannabinoids.

Limitations to studies

The NASEM report provided an excellent summary of marijuana research; however, it is important to consider the shortcomings of the studies examined and the shortcomings of meta-analysis in general [2]. The principle meta-analysis utilized for most recommendations for pain was produced by Whiting et al. [3]. Many of the studies included for pain were short in duration, some as short as 6 h. Short duration studies that found significance in pain relief on the global assessment scale or modified Likert scale did not ask about the short-term psychoactive effects which can be confused with pain control. Most studies of greater than 9 weeks did not reach statistical significance over placebo control for pain relief. In meta-analyses, the delivery systems of cannabinoids were not standardized and included many varying formulations, such as smoked and vaporized cannabis, oromucosal spray, ajuvenic acid capsules, and oral THC. All studies utilized placebo control except one that compared efficacy to amitriptyline. In one analysis, 67% of

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Published online: 07 August 2018

patients could tell whether they were in treatment or placebo group, unmasking the study causing an inherent bias. Of the 79 studies that were evaluated, only 4 were found to have a low risk of bias [3].

Additionally, defined dosing was often absent in these studies and no information regarding dosing to avoid impairment was addressed. This gap in information leaves the practitioner with no guidance regarding starting dose, frequency, titration, and max dosing. An added concern is the ease of accessibility of marijuana. Patients are able to use as much marijuana as they want as often as they desire. The result is an absence of any physician oversight of treatment. We would not consider this acceptable with any therapeutic medication.

We also need to consider that only small clinical benefit was shown in the studies evaluating pain and spasticity. For example, in assessing treatment of spasticity, only subjective improvement was found to be statistically significant and only by a small margin (improved by −0.76 on a numerical rating scale). When looking at number needed to treat for clinical significance, the number was less than "standard of care" therapies and barely significant when compared to placebo (no head to head studies available). Objective results using the Ashworth spasticity scale were not shown to be statistically significant [3].

These studies clearly do not meet the standards we would expect from any FDA-approved pharmaceutical.

It is important to note that marijuana is a highly heterogenetic compound. The potency of marijuana can vary greatly depending on growing conditions, part of the plant used, the preparation for administration, storage, and cultivation techniques [4, 5]. There is also a tremendous amount of complexity in plant composition. According to the popular consumer website Leafly.com, there are nearly 2500 different marijuana plant strains available to consumers [6]. There is also an extensive assortment of accessible marijuana preparations ranging from inhaled, topicals, transdermal, edibles, suppositories, and vaginal products. These many varieties result in variations in onset, intensity, and duration of both therapeutic and adverse effects [7]. With very little data representative of the products that are commercially available and the lack of standardization and reproducibility of these preparations, it is impossible to generalize study outcomes to the products available to marijuana users.

Negative effects of marijuana use

The NASEM report outlines the negative effects of marijuana use stating that there is substantial evidence that marijuana is associated with increased vehicle crashes, and lower birthweights in children born to marijuana users [2]. The neuropsychological effects of cannabinoids that have been reported in literature include schizophrenia or other psychoses. Moderate evidence is also present for increased risk of overdose injuries, impairment in cognition, increased risk of depression and suicide, and social anxiety disorder [2, 8]. The adolescent cannabinoid user seems to have an increased vulnerability to these effects with greater negative impacts on the working memory, object recognition, and impulsivity. These psychological effects and neuropsychological decline continue through midlife even after use is stopped [9–14]. In Colorado, hospital visits after marijuana exposure use have significantly increased since legalization of recreational marijuana [15]. This increase includes a rise in pediatric ingestions, acute intoxications, hyperemesis, and withdrawal [16].

While cannabinoids are often promoted as having a lower lifetime risk of addiction than nicotine, opioids, or cocaine [9], it is important to note that cannabis use disorder rates increase to 25–50% among those who smoke marijuana daily [17, 18].

It is important to remember that most of the cannabis studies cited by Whiting et al. [3] were performed over a period that was less the 6 weeks, which does not allow for proper evaluation of many adverse events. Some negative events that could not be identified because of study duration are cancer, cyclical vomiting syndrome, psychosis, and addiction use disorder. The risk of serious adverse events and number needed to harm cannot be accurately understood from the current studies and meta-analyses.

While we debate the use of marijuana for medical purposes, it is essential that we acknowledge the prevalence of recreational use. The primary use of marijuana in the United States remains recreational (89.5% of adult cannabis users) while only 10.5% report use solely for medicinal purposes, and 36.1% report mixed medical/recreational use [19]. Recreational use resulting in impairment is likely to be associated with greater cognitive and motor function impairment resulting in greater negative consequences [13].

Conclusions

While we agree that discussions regarding marijuana use should be part of patient care, at this point in time relevant outcome data that clearly show clinical significance over usual pharmaceutical cares or placebo are scarce and all but absent in the SCI population. Significant health risks are associated with marijuana use include: potentiation in younger patients, interaction with prescription medications, and exacerbation of comorbid conditions. For the aforementioned reasons, until clinical trials can help further elucidate the efficacy and risk benefit ratio of cannabinoid based products, we must strongly and resoundingly demand improved clinical evidence.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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