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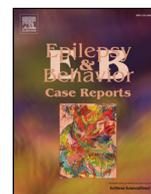
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Case Report

Are there mortality risks for patients with epilepsy who use cannabis treatments as monotherapy? ☆☆☆

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ABSTRACT

Mortality associated with cannabis used for treatment of epilepsy is not well documented. We discuss two fatalities in the setting of epilepsy and self-determined therapy with cannabis (SDTC). One patient had probable sudden unexpected death in epilepsy, the second death was due to seizure-associated drowning. Both directed SDTC over conventional anti-seizure medications. Where recreational cannabis is legal, decisions to use cannabis are often self-directed and independent of physician advice of cannabis risks, in part because physicians may not be aware of the risk of SDTC. Further study of morbidity and mortality of SDTC in patients with epilepsy is needed. © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

In Washington State, marijuana legalization occurred for medicinal purposes in 1996 and for recreational use in 2012 [1]. Cannabis based therapies have been suggested for a broad range of problems including anxiety, insomnia, chronic pain, depression and epilepsy [2]. Publication of prospective trials supporting adjunctive effective use of cannabidiol oil (CBD) for the reduction of convulsive seizures in patients with Dravet (DS) and Lennox–Gastaut syndromes (LGS) occurred in 2017 [3,4]. In our Epilepsy clinic, patient inquiries regarding efficacy of cannabis have increased since 2012 and even more since the landmark trials and further with the USA Food and Drug Administration's rescheduling of CBD in 2018. Specifically, many patients are prepared to discuss cannabis use in the epilepsy clinic and are well versed through reviews available from various online and anecdotal resources, but with limited understanding of available peer-reviewed literature, including side effects demonstrated in the 2017 LGS and DS trials or from studies of artisanal cannabis use in epilepsy [1,3,4].

Extensive patient investigation of information pertaining to cannabis use could be viewed as a version of *self-determined theory* (SDT), an approach that helps build the foundation for an effective provider-patient dyad, particularly if a provider supports the patient's therapy choice [5]. One example of SDT might be a patient's decision to pursue

a vegetarian diet in the setting of elevated blood fats. An example of an autonomous support model of SDT would be a provider who endorses a patient therapy choice from among provider-suggested conventional treatments such as anti-seizure medication that the patient reviewed – on their own – prior to clinic visit, perhaps on Epilepsy Foundation websites. Their choice is supported and refined with provider input based on literature review, standards of care, urgency of treatment, benefit vs. cost discussions and other patient-specific clinical data. That supportive patient-physician dyad can lead to motivation for continued well-being and therapy adherence. SDT works when the relative *benevolence* of the treatment is known by both parties. Concerned *patients and providers* are not well prepared to discuss the risk of self-determined therapy with cannabis (SDTC). Among our patients, SDTC are perceived as having minimal morbidity. Perhaps the most common misperception of SDTC is that because products are *natural*, therefore they are safe. We have yet to hear patient concerns of mortality risk. Perhaps just as importantly, the literature *does not reflect* caregiver concerns of SDTC mortality risks, this may be in part because artisanal cannabis therapies may be vaped, smoked, applied as creams or tinctures, ingested as oils, drops or tablets, and combined with varied CBD to tetrahydrocannabinol ratios. It is hard to keep track of the what, how, where and when of SDTC, let alone risks of them [1].

2. Case reports

With institutional approval, we used medical records to report two deaths of patients whose reliance on SDTC for seizure prevention may not have been benevolent. We classify their deaths based on Nashef

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Table 1
Case report details and circumstances of death including SUDEP classification per Nashef 2012 criteria [5].

Age of onset, age of death	Epilepsy diagnosis, etiology, MRI and EEG results	Seizure types	Medications trialed	Circumstances of death, SUDEP classification
13, 24	Generalized onset; presumptive genetic etiology (brother and father with similar seizure histories). MRI normal. EEG: 3 Hz spike and wave	Generalized onset, tonic clonic	Intermittent zonisamide and levetiracetam use. Cannabis including vaped, smoked, and tincture forms, with tincture use at time of death was 2:1 CBD:THC	In setting of 80 hour work week and over a year seizure free, left epilepsy clinic, went to vehicle, did not start it and was found deceased in car. Compliance on medications was varied with known tendency to dose traditional anti-seizure medications prior to clinic visits but otherwise skip dosing. No post mortem blood work on medication levels. Gene test results appear in the appendix data with – among others – heterozygous changes in CACNA1B, CACNA1H, CACNA2D2. SUDEP classification: probable SUDEP (post mortem data unavailable)
22, 27	Focal onset. History of viral encephalitis, MRI with right pituitary prolactinoma. Prior EEG: right temporal sharp waves.	Focal to bilateral generalized tonic-clonic seizures	Historically used zonisamide, oxcarbazepine, levetiracetam, though discontinued prior to final presentation. Was using CBD tablets dosed at 35 mg nightly.	Found unresponsive and cyanotic in the shower, face and airway submerged under water, her hands were clutching hair, suggesting seizure may have occurred while washing hair. Pulseless in field, resuscitated. Urine toxin positive for cannabis. Progressed to fixed, dilated pupils and criteria consistent with brain death, support withdrawn at 48 h post arrival. Patient lowered conventional anti-seizure medications on her own and preferred CBD therapies. SUDEP classification: <i>not</i> SUDEP given drowning.

SUDEP criteria [6]. Cases appear on Table 1 for ease of review. In brief patient one had generalized epilepsy and had moved away from zonisamide therapies to SDTC. Shortly after completing a clinic visit, he returned to his vehicle, never started it, and was found deceased in the vehicle with no suspicious circumstances evident. Post mortem data of gene test (epiSEEK® triome, Courtagen, 2016) results for is available (Appendix A). Patient two also relied on SDTC and had self-weaned from conventional therapies for treatment of focal epilepsy. She likely seized while showering, obstructed the drain, and had irreversible injuries from drowning despite resuscitation. Both patients were in their twenties.

3. Discussion

Sudden unexpected death in epilepsy (SUDEP) risks are highest with poor control of generalized tonic-clonic seizures [7]. In this cases we did not calculate risk given we do not know the denominator of patients using primarily SDTC to treat their epilepsy. Substance abuse and SUDEP risk upon literature searches combining SUDEP and search terms of *cannabis* or *marijuana* show few results. Legalization of cannabis has shifted public opinion and diminished risk perceptions [8]. We think SDTC may potentially jeopardize epilepsy control, particularly when cannabis is substituted for conventional anti-seizure medications or when the pharmacology of varied forms of artisanal cannabis remains undetermined. In these two reported cases, reliance on SDTC may have worsened outcomes leading to one probable SUDEP and one drowning associated death. Marijuana use has known risks of dependency and withdrawal, while long-term use is associated with declines in memory and higher rates of mood-disorders [8]. Cannabidiol oil may be useful in treating convulsive events in LGS and DS, however, we speculate that confidence in SDTC therapies may be risky and should be tempered by neurology provider guidance, particularly with new data and studies relating SDTC therapies to morbidities and/or sudden mortality in patients with epilepsy [2,3,7].

4. Conclusion

Two cases of sudden death are reported in patients whose self-determined seizure management primarily relied on artisanal cannabis

therapies. Risks of morbidity, mortality and SUDEP in SDTC users need to be further studied. Providers should be aware of the absence of morbidity and mortality data for SDTC in patients with epilepsy may only be due to a failure of reporting.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ebcr.2018.11.007>.

Conflict of interest

Kyla Wright, Devon Kollmyer, Dr Michael Doherty and Nicole Fortier, ARNP have no relevant disclosures.

Ethical statement

Informed consent was not obtained for case write-ups, the patients were deceased. The cases were reviewed by our institutional review board and cleared for research. Our work has been carried out in accordance with The Code of Ethics of the World Medical Association.

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