Take 3 – Practical Practice Pointers© May 27, 2019 Edition

CBD Oil Reprise, Cannabis Dependence, Publication Bias

From a Colleague's Question and the VA General Assembly

1) Use of Cannabidiol (CBD) Oil and THC-A Oil

Question:
I am having many patients asking about CBD oil and I really do not know much about it. Will this make a patient's urine drug screen turn positive for marijuana?

Answer:
CBD oil has shown promise for the treatment of seizure disorders, and early studies show promise from animal research and small, short-term human studies for the treatment of anxiety, addiction, and inflammation, but clinical trials are lacking, and because it is not regulated by the FDA, standardization of "dose" is lacking. Neither CBD oil nor THC-A oil provide the psychoactive experience of THC.

In 2018, the Virginia General Assembly passed, and the Governor signed HB 1251/SB 726 pertaining to the certification for use and dispensing of cannabidiol (CBD) oil or tetrahydrocannabinolic acid, (THC-A) oil. The bill provides that any licensed MD or DO may issue a written certification for the use of CBD oil and THC–A oil for the treatment or to alleviate the symptoms of any diagnosed condition or disease determined by the practitioner to benefit from such use. Under the previous law, this was limited to a neurologist or someone who specialized in the treatment of epilepsy and only for the treatment or to alleviate the symptoms of intractable epilepsy. The written certification is to be on a form provided by the Office of the Executive Secretary of the Supreme Court developed in consultation with the Board of Medicine. **A practitioner who issues a written certification to a patient pursuant to this section must register with the Board.** The Board will, in consultation with the Board of Medicine, set a limit on the number of patients to whom a practitioner may issue a written certification.

The bill also increases the supply of CBD oil or THC-A oil a pharmaceutical processor may dispense from a 30-day supply to a 90-day supply. It also reduces the minimum amount of cannabidiol or tetrahydrocannabinol acid per milliliter for a dilution of the Cannabis plant to fall under the definition of CBD oil or THC-A oil. It is specified that nothing in the bill shall preclude the Board of Medicine from sanctioning a practitioner for failing to properly evaluate or treat a patient's medical condition or otherwise violating the applicable standard of care for evaluating or treating medical conditions.

The bill also reiterated that it is unlawful for any person knowingly or intentionally to possess marijuana unless the substance was obtained directly from, or pursuant to, a valid prescription or order of a practitioner while acting in the course of his professional practice, or except as otherwise authorized by the Drug Control Act (§ 54.1-3400 et seq.). Any person who violates this section is guilty of a misdemeanor and shall be confined in jail not more than 30 days and fined not more than $500, either or both; any person, upon a second or subsequent conviction of a violation of this section, is guilty of a Class 1 misdemeanor.

A patient who has been issued a written certification must also register with the Board or, if such patient is a minor or an incapacitated adult, a patient's parent or legal

guardian must register and register the patient with the Board. A pharmaceutical processor may dispense or deliver cannabidiol oil or THC-A oil only in person to (i) a patient who is a Virginia resident, has been issued a valid written certification, and is registered with the Board or (ii) if such patient is a minor or an incapacitated adult as defined in § 18.2-369, such patient's parent or legal guardian who is a Virginia resident and is registered with the Board pursuant to § 54.1-3408.3. Prior to dispensing, the pharmaceutical processor must verify that the practitioner issuing the written certification, the patient, and, if such patient is a minor or an incapacitated adult, the patient's parent or legal guardian are registered with the Board.

In terms of the impact of these oils on a urine drug screen, I reached out to Kenneth M. Algino, MD, who is System Medical Director, Quest Diagnostics, Roanoke and Chief, Department of Pathology, Carilion Roanoke Memorial Hospital and to Leland McClure III, MSci, PhD, who is Director and Medical Science Liaison for Medical Affairs for Quest Diagnostics and Fellow, American Board of Forensic Toxicology.

They indicated it is first important to define a marijuana metabolite "positive drug test" as THC metabolite (carboxy-THC) at levels equal to or greater than the definitive test cutoff. Definitive testing is testing that is performed using the mass spectrometry (MS) or gas chromatography (GC) method as either a confirmation of presumptive results or as a standalone quantitative assay. Analysis using only presumptive methods (immunoassay, POC devices) is ***not*** enough to determine a true positive result. Whether any substance exceeds test threshold depends upon many factors including dose, hydration station and drug clearance.

Regarding patient use of CBD or hemp oils, the dose of the CBD oil and what material was utilized for manufacturing the CBD product are factors that can impact marijuana metabolite drug test outcomes. While use of CBD/hemp oils usually will not produce a positive marijuana metabolite drug test result, it has been demonstrated that high doses of hemp oil can produce positive results. This would be subsequently shown to be false via gas chromatography or mass spectroscopy (GC/MS) confirmatory testing.

My Comment:
The more research I did on this, the more complex the answer seemed to get. This is yet another area where "the press" has greatly outpaced "the evidence." While I certainly sympathize with patients who are searching for relief from some challenging health issues (often desperately so), we owe it to them (and to our own professional integrity) to proceed with caution and maintain a healthy skepticism for these products, particularly those like CBD oil for which the testimonials are dramatic and extensive. The bottom line for me includes the following:

- Except under defined circumstances, the use of CBD/THC-A oil is still illegal in VA.
- The formulations approved for use in Virginia should not produce a positive urine drug screen at the recommend doses, and GC/MS confirmatory testing should be negative (unless higher doses are being used, which is legal).
- **Most primary care clinicians should avoid certifying the use of these substances** unless they have developed this as an area of expertise and thoroughly understand the intricacies of the law. In VA, this includes registering with the Board of Medicine. In our own department, we are **STRONGLY recommending against this** at the present time.
- Given present VA law, I would not be comfortable prescribing opioids for patients who are certified to take these oil formulations at this time.

References:
Code of VA: Certification for use of cannabidiol oil or THC-A oil for treatment. Link
VA General Assembly effective 3/9/18. Link

From the Literature/Cochrane Database

2) Pharmacotherapies for Cannabis Dependence

Cannabis use is prevalent and widespread, and with the expanding legalization of it in the US, is becoming even more so. The prevalence of past year use in US adults is estimated at 14%, with past month use of 10%. It is also estimated that almost 5% have been dependent on marijuana, as defined by DSM-5, at some time in their lives.

Marijuana produces dependence less readily than most other illicit drugs. Some 9% of those who try marijuana develop dependence compared to 15% who try cocaine and 24% of those who try heroin. However, because so many people use marijuana, cannabis dependence is more than twice as prevalent as dependence on any other illicit psychoactive substance. Dependence may be associated with cognitive impairment, poor school/work performance, and psychiatric comorbidity such as mood disorders and psychosis. Cannabis withdrawal is manifested by multiple signs and symptoms occurring within 1 week after abrupt reduction or cessation of heavy and prolonged use, including irritability, anger, anxiety, depression, and disturbed sleep

There are currently no pharmacotherapies approved for treatment of cannabis use disorders. The Cochrane Library recently updated a review of the pharmacotherapy for cannabis dependence, updating a 2014 review.

There were 21 RCTs involving 1755 participants. All studies involved comparison of active medication and placebo. Abstinence at end of treatment was no more likely with 9-tetrahydrocannabinol (THC) preparations than with placebo. For selective serotonin reuptake inhibitor (SSRI) antidepressants, mixed action antidepressants, anticonvulsants and mood stabilizers, buspirone and N-acetylcysteine, there was no difference in the likelihood of abstinence at end of treatment compared to placebo. There was qualitative evidence of reduced intensity of withdrawal symptoms with THC preparations compared to placebo. Available evidence on gabapentin, oxytocin and atomoxetine was insufficient for estimates of effectiveness.

The authors concluded that for most treatments, there is incomplete or poor-quality evidence, but that the available evidence indicated that there is no medication that has shown consistent value in the treatment of cannabis dependence. Given the limited evidence of efficacy, THC preparations should be considered still experimental.

There are no clinical trials comparing the medication to psychosocial interventions for the treatment of cannabis dependence, but clinical trials show evidence of efficacy for psychosocial interventions. First-line treatment recommendations include cognitive-behavioral therapy (CBT) or motivational enhancement therapy (MET).

My Comment:
The data are humbling. With increasing legalization/access to marijuana, this problem is likely to get worse. Finding creative ways to increase access to CBT or MET seems to be present best answer to addressing dependence issues.

Reference:
Nielsen S, Gowing L, Sabioni P, et al. Pharmacotherapies for cannabis dependence. Cochrane Database Syst Rev. 2019 Jan 28. Link

Brief Review From the Literature

3) Publication "Spin" is Quite Prevalent Despite Peer Review

Clinical researchers are obligated to present results objectively and accurately to ensure readers are not misled. In studies in which primary end points are not statistically significant, placing a spin, defined as the manipulation of language to potentially mislead readers from the likely truth of the results, can distract the reader and lead to misinterpretation and misapplication of the findings. This study looked at the results of cardiovascular randomized clinical trials to determine if statistically nonsignificant primary outcomes were reported accurately and objectively?

The team defined three spin strategies:

- Pivoting to statistically significant secondary results, such as within-group comparison, secondary outcomes, and subgroup or per protocol analyses.
- Interpreting statistically nonsignificant results of the primary outcomes as showing treatment equivalence or ruling out an adverse event.
- Emphasizing the beneficial effect of the treatment with or without acknowledging the statistically nonsignificant primary outcome.

This systematic review included 93 reports of randomized clinical trials from 6 high-impact journals. Positive spin of statistically nonsignificant primary outcomes was found in 57% of abstracts and 67% of main text of the published articles.

The authors concluded that despite peer review, manipulation of language in the cardiovascular literature is common and may have implications for scientific integrity, patient care, peer review, and medical progress. There was no association between spin and conflict-of-interest disclosures from the first or last author. Further, industry-funded research had a lower proportion of spin than nonprofit-funded research.

My Comment:
Sigh .... Another example as to why "healthy skepticism" and keen "critical thinking" skills are essential to practice medicine responsibly and well. The other type of "spin" not addressed in the article is that of press releases, often from the organization of which the authors are affiliated. Many of these are quite over top, and often in my view border on irresponsible sensationalism. I'm a big fan of "keeping hope alive," but it should be done responsibly.

Reference:
Khan M, et al. Level and Prevalence of Spin in Published Cardiovascular Randomized Clinical Trial Reports With Statistically Nonsignificant Primary Outcomes: A Systematic Review. JAMA Netw Open. May 3, 2019;2(5):e192622. Link

Feel free to forward Take 3 to your colleagues. Glad to add them to the distribution list.

Mark

Carilion Clinic Department of Family and Community Medicine