Cannabis and Cannabinoid Research
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PERSPECTIVE

Cannabinoids and the Coronavirus

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Introduction

These are uncertain times as we attempt to manage our lives during the Coronavirus Covid-19 pandemic. It is not surprising, as possible treatments for Covid-19 are discussed, that people wonder about a role for cannabinoids, another topic associated with a lack of clarity about their therapeutic efficacy. Patients commonly ask clinicians about the benefits and risks of cannabinoids and now patients have begun to ask about cannabinoids as they relate to Covid-19. This interest creates an opportunity to strengthen the therapeutic alliance between patients and clinicians and to increase the likelihood that patients receive evidence-based treatments that may help them.

State of the Science of Therapeutic Use of Cannabis and Cannabidiol

Two cannabinoids related to delta-9-tetrahydrocannabinol (THC), dronabinol and nabilone, were approved by the U.S. Food and Drug Administration (FDA) for chemotherapy-induced nausea and vomiting in 1985, with dronabinol gaining a second indication for appetite stimulation in wasting conditions, such as AIDS, in 1992. A third cannabinoid, cannabidiol (CBD), was approved by the FDA in 2018 for the treatment of two forms of pediatric epilepsy, Dravet syndrome and Lennox–Gastaut syndrome. Beyond the four indications for which cannabinoids are FDA approved, the best evidence appears to be for chronic pain (including neuropathic pain) and muscle spasticity resulting from multiple sclerosis. These conditions have multiple positive randomized controlled trials (RCTs) and multiple systematic reviews supporting their use.

The National Academies of Science, Engineering, and Medicine Committee on the Health Effects of Marijuana concluded that there is "conclusive or substantial evidence" that cannabis is effective for the treatment of chronic pain in adults based upon their assessment that the literature on chronic pain has supportive findings from good-quality studies with no credible opposing findings.[1] A meta-analysis of 28 studies determined that there was "moderate-quality evidence" supporting the use of cannabinoids in the treatment for chronic pain.[2] Other reviews describe the evidence for cannabinoids in chronic pain as weaker.[3,4] For example, a 2017 meta-analysis of 27 studies examining the effectiveness of cannabis as pharmacotherapy for chronic pain found weak evidence that cannabis alleviates neuropathic pain, and no evidence suggesting that cannabis was useful in treating other types of pain.[3]

The quality and the quantity of the evidence for cannabinoids for chronic pain are lacking. The quality of the evidence supporting the use of cannabinoids for pain is suboptimal, with small sample sizes, heterogeneity in outcome measures, and short study durations as some of the weaknesses of the studies evaluated as part of the aforementioned meta-analyses. Systematic reviews of largely the same studies may yield different conclusions depending on the inclusion or exclusion of small studies, which may overestimate effect, or pharmaceutical studies, which tend to be positive. States and companies continue to profit from the sale of cannabis, yet few fund the cannabis studies that are needed. As a result, the question of cannabinoid efficacy for pain remains confusing.

There is evidence to support the use of cannabis and cannabinoids to treat spasticity resulting from multiple sclerosis. A recent meta-analysis evaluating 17 RCTs of cannabis and cannabinoids included >3000 patients with aggregate data showing modest, but statistically significant, positive effects on spasticity as well as pain and bladder dysfunction in this population.[5] Similarly, the American Academy of Neurology published guidelines that specified nabiximols, a medication available in Europe and Canada that features THC and CBD

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in an ~1:1 ratio, as having the highest level of empirical evidence supporting its use as pharmacotherapy for spasticity and pain associated with multiple sclerosis.[6]

Cannabinoids and Viral Illnesses

Limited evidence demonstrates a possible role for cannabinoids as therapeutics in viral illnesses. Despite coronaviruses representing a large family of viruses, there have not been any investigations of cannabinoids' effects upon this family. It is not clear whether the anti-inflammatory activity of THC and CBD, thought to be an attribute when considering their therapeutic potential for many diseases, would be an advantage or a disadvantage when considering cannabinoids as treatment for viruses. THC or CBD may be beneficial in viral infections where the host inflammatory response is pathogenic.[7] This occurs in Covid-19: the coronavirus SARS-CoV-2, for unclear reasons, triggers a cytokine storm—the production of excessive levels of cytokines—resulting in hyperinflammation. Cannabinoids could possibly be a part of a treatment regimen, with nonsteroidal anti-inflammatory drugs (NSAIDs) and other medications that target immune pathways, that could downregulate the cytokine storm.[8] Anti-inflammatory activity may not be an advantage when combating viruses because it may mitigate host immune responses to acute viral infections, leading to disease progression and possibly death.[9,10]

Studies of the effects of compounds that contain both THC and CBD on viruses are limited. There are no studies that directly assess the efficacy of cannabis upon viral illnesses. Nabiximols improved motor activity as measured by presence of central nervous system infiltrates, microglial activity, and axonal damage, while restoring myelin morphology in a viral model of multiple sclerosis.[11] In an observational study of people living with HIV, cannabis exposure was linked to lower odds of neurocognitive impairment (OR 0.53, 95% CI 0.33–0.85).[12]

CBD has several characteristics that make it an appealing agent to explore for antiviral activity. As opposed to THC, CBD is nonintoxicating with no abuse potential. Other plant-derived compounds with a variety of chemical structures have shown antiviral activity.[13] In addition, CBD can induce apoptosis in mammalian cells, thought to be an essential component of host responses to viral infections.[14,15]

Three preclinical studies have examined a possible role for CBD as an antiviral agent. One study demonstrated a direct antiviral effect against hepatitis C virus (HCV) but not hepatitis B virus in cell lines cultured to produce these viruses.[16] CBD concentration-dependently inhibited HCV replication by up to 86.4% ($EC_{50} = 3.2\ \mu M$), which is comparable with interferon alpha at 10 IU/mL. Another investigation showed an indirect viral action of CBD against Kaposi's sarcoma-associated herpesvirus (KSHV) in a model of KSHV-infected human dermal microvascular endothelial cells (HMVECs).[17] CBD up to 10 μM did not affect the ability of KSHV to infect HMVECs after 48 h of pretreatment, but it reduced KSHV-infected cells proliferation ($IC_{50} = 2\ \mu M$) and enhanced apoptosis ($EC_{50} = 1\ \mu M$). CBD treatment also prevented the transformation of normal cells into KSHV-associated cancers. A final study illustrated that CBD mitigated effects of neuroinflammation induced by Theiler's murine encephalomyelitis virus (TMEV).[18] CBD treatment (5 mg/kg) reduced leukocyte infiltration and microglia activation in the brain of TMEV-infected mice, improving motor symptomatology and neuroinflammation in the chronic phase of the infection.

Coronavirus May Create a Clinical Opportunity

These studies suggest that CBD is a reasonable candidate to be studied in preclinical coronavirus models. We are very far from the level of evidence required to consider using cannabinoids as pharmacotherapy for viral illnesses, but the perpetual high level of interest in cannabinoids as medicine presents an important opportunity for clinicians. In these uncertain times, patients' questions about how cannabis or CBD may help them—if responded to sensibly and empathically—may increase the likelihood that patients will receive evidence-based treatment that they might otherwise not receive. Thus, clinicians should be curious about our patients' experiences with cannabinoids and the at least perceived benefits resulting from their use or their hopes about how cannabinoids may help a medical condition they are trying to manage. Being able to converse with patients openly on these issues and having a benefit-to-risk discussion with them will increase the chances that they receive evidence-based treatment, which may or may not include the use of cannabinoids.

Attached to this opportunity is the responsibility to educate our patients in a clear evidence-based manner about both the future of cannabinoids and the limitations of our current knowledge. The Internet is a leading source of health-related information[19] and many are tempted to exaggerate the current state of

cannabinoid science or misrepresent it entirely. We must do our best to help our patients feel comfortable asking questions about complex topics that affect their health to counterbalance the supply of misinformation available at the click of a computer key.

The importance of the clinician's role is highlighted in these anxiety-provoking times of uncertainty. It is our duty to our patients to remain as calm as possible and to remain focused on delivering evidence-based clinical care. Patients rely on their clinicians to know the evidence on acute issues such as Covid-19 as well as controversial topics such as cannabinoids. If we can combine sensibility, empathy, and an evidence-based approach in the face of the coronavirus pandemic, we can have a significant impact on many patients' lives.

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Abbreviations Used

CBD = cannabidiol
FDA = Food and Drug Administration
HCV = hepatitis C virus
HMVECs = human dermal microvascular endothelial cells
KSHV = Kaposi's sarcoma-associated herpesvirus
RCT = randomized controlled trial
THC = delta-9-tetrahydrocannabinol
TMEV = Theiler's murine encephalomyelitis virus