

# The Complicated Relationship Between COVID-19 and Cannabis: A Year in Review

With false claims circulating about the effectiveness of cannabis to treat COVID-19 and studies rapidly pouring out of labs and hospitals, it is challenging to make sense of it all. *AJEM* spoke with leading cannabis researchers and physicians to reflect on what we've learned after a year of COVID-19. In short, it's complicated. Medical cannabinoid therapy can both hurt and help patients who are infected with COVID-19, and the effect seems to be highly dependent on the patient's stage of COVID-19 infection.

Some researchers and physicians say they are concerned that cannabis, especially when taken at high doses, might be harmful to those who are infected with the novel coronavirus, particularly anyone at high risk for a severe response to the virus. Patients may be especially vulnerable in the early stages of COVID-19 infection when the immune system must mount a strong response, leading some experts to particularly worry about those with underlying conditions who smoke and vape.

Others point to emerging research showing that cannabinoids may be beneficial in late-stage severe disease during a cytokine storm. They are hopeful that medical cannabis may play a role in reducing the risks of SARS-CoV-2 infection by modulating angiotensin converting enzyme 2 (*ACE2*) expression, which has been shown to control the novel coronavirus' access to a human cell.

The vaccination period is also unclear. Should medical cannabis physicians be advising patients to reduce cannabis consumption during vaccination to ensure the body is able to develop effective antibodies?

"It's a complex situation. We don't have good clinical end point data to say this is not good or this is good," said Barry Mennen, MD, an urgent care and family physician in Maryland who prescribes medical marijuana to patients.

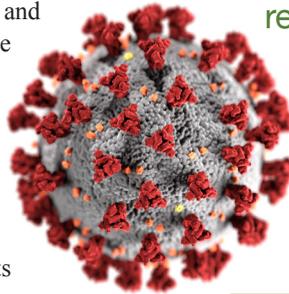
## Medical Cannabis Physicians Advise Caution

Dr. Mennen is asking his patients to reconsider their medical cannabis use during the ongoing crisis, saying there is

Preclinical research on certain cannabinoids appear promising for anti-inflammatory effects, which may impact the hyperinflammation response seen in some patients with more severe disease.

I expect to see a substantial increase in research in this area over the next 12 months.

—DANI GORDON, MD



compelling evidence from other viral infections indicating that medical cannabis could potentially increase the risk for a severe response. He is most concerned about patients who have comorbidities that put them at risk for COVID-19, or those who live or work in situations with a high risk for exposure to the virus.

"What we can say is that it's probably prudent at this point to either reduce or end cannabinoid use while the pandemic is still occurring, especially for patients who are more vulnerable to health issues."

There is insufficient evidence that medical cannabis puts all patients in jeopardy, he said. "All I can say is, the best data we have suggests there could be an extra risk."

With medical cannabis, it is difficult to isolate how each of the various components that go into a single product can influence the immune system.

Medical cannabis that uses a full extract oil or flower product contains hundreds of cannabinoids, along with other bioactive compounds like flavonoids and terpenoids. Together, these may have an immune-modulating effect; however, it is difficult to know precisely how they affect the immune system, particularly in the context of a new and poorly understood virus, said Dani Gordon, MD, a UK-based physician and an expert in cannabis medicine.

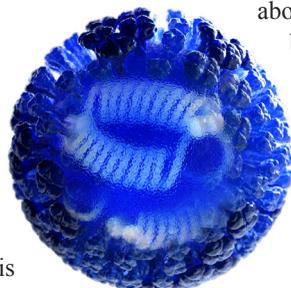
## COVID-19 and Cannabis

continued from page 33

“No large human studies of cannabinoid therapy or medicinal cannabis have shown a specific effect on the COVID-19 virus. Preclinical research on certain cannabinoids appear promising for anti-inflammatory effects, which may impact the hyperinflammation response seen in some patients with more severe disease,” said Dr. Gordon. “I expect to see a substantial increase in research in this area over the next 12 months.”

Dr. Gordon is not advising people to stop their medical cannabis use, especially if they rely on it to successfully control seizures and other serious symptoms. However, she recommends that they use the lowest effective dose, and begin with lower delta-9-tetrahydrocannabinol (THC)/higher cannabidiol (CBD) products. She also recommends they avoid smoking and be closely monitored by their physician if they are in a high-risk group and develop symptoms of COVID-19.

**M**edical cannabinoid therapy can both hurt and help patients who are infected with COVID-19, and the effect seems to be highly dependent on the patient’s stage of COVID-19 infection.



She advises anyone using high-THC cannabis recreationally to stop for now if they are in a high-risk group for COVID or begin to develop symptoms. Her recommendation is based on the public health approach known as the “precautionary principle,” which calls for caution in order to avoid serious harms to human health in conditions of scientific uncertainty.

“If something might be bad or we’re not sure, but it may have a serious consequence or contribute to a serious disease, it’s best to avoid it until we know more,” Dr. Gordon said.

### Cannabinoids and the Immune Response to Infectious Agents

Physicians and scientists who are concerned about medical and recreational cannabis in light of COVID-19 point to a 2017 peer-reviewed paper that examined the immunoregulatory role of cannabinoids during infectious disease. In the report published before the emergence of SARS-CoV-2, the virus that causes COVID-19, Jorge Morales-Montor, PhD, and his colleagues showed that cannabinoid compounds

affect different types of infectious agents in various ways—sometimes allowing their replication or by eliminating them.<sup>1</sup>

But the review raises questions about potential harms of THC in the presence of a number of infectious agents, notably influenza. Specific to influenza, they reported that in in vivo studies of mice, THC administration after an immune challenge with influenza virus A/8 resulted in increased viral loads by higher hemagglutinin 1 expression and diminished CD4+ and CD8+ lymphocyte and macrophage recruitment into the lungs. Other immune parameters affected included cytokine secretion by CD4+ T cells and natural killer (NK) cells, in addition to a lower overall percentage of subpopulations of antigen-presenting cells in the lungs of infected mice.<sup>1</sup>

In an email interview with *AJEM*, Dr. Morales-Montor, who is a researcher in the Department of Immunology at the Institute of Biomedical Research, National Autonomous University of Mexico, said the role of medical cannabis in COVID is controversial. Although the endocannabinoid system (ECS) is involved in important physiologic processes like sleep and immune response, its role in infection has not been well studied.

But the evidence suggests some caution is warranted about cannabinoids in the COVID-19 pandemic because there is a potential for a negative effect on the immune system, he said.

“The use of cannabis, in general, increases susceptibility to infectious diseases, regardless of whether they are caused by bacteria, viruses, parasites, or to a lesser degree, fungi.” And the observed results for influenza, particularly, raise concerns about cannabis and COVID-19, Dr. Morales-Montor said.

“The observed results demonstrate that THC administration diminishes the immune response against the influenza virus. Thus, with COVID-19 being a respiratory infection also, it is very critical to take this information into account before any intervention with cannabinoids is (considered),” he said. Dr. Morales-Montor added that he would recommend “a change in habit” to anyone who currently consumes cannabinoids.

However, studies showing the overall clinical effectiveness of THC as a therapeutic target in the ECS are conflicting for various infections. For instance, studies support the idea that the ECS could be used as an effective therapeutic target in sepsis treatment. Cannabinoid receptor CB<sub>1</sub> is important in the development of an efficient innate immune response, whereas CB<sub>2</sub> prevents additional inflammatory damage during sepsis. In hepatitis C, studies have shown that moderate use of cannabis may help treatment adherence by stabilizing weight loss and nausea; however, long-term daily use has been associated with fibrosis progression.<sup>2,3</sup> Moreover,

**C**annabis has to be taken very carefully because in some cases, it may be beneficial and in others it may be critical.

—JORGE MORALES-MONTOR, PhD

ECS activation by the CB<sub>1</sub> agonist arachidonyl-2'-chloroethylamide promotes HCV replication in hepatocyte cultures. In HIV, in vivo studies found THC increases HIV replication (in addition to the expression of *CCRg* and *CXCR5* chemokine receptors), reduces CD4+ T cells and interferon- $\gamma$  producing cells, and suppresses NK cell activity.<sup>1</sup>

The effects of cannabinoids are also unclear in bacterial infections. In vivo and in vitro studies, as well as clinical case reports, show no consistent relationship and there are no clearly established benefits or harms.

“The use of cannabis is a double-edged sword, depending on the pathology we may be talking about,” Dr. Morales-Montor said. The general idea is that cannabinoids may have an effect on inflammation; however, the overall effect, whether positive or negative, depends on several physiologic factors including the developmental stage, sex, and age of the exposed person, the dose, the time of exposure to the infectious agent, and the presence of other comorbidities.

Speaking generally about cannabis in infection, Dr. Morales-Montor said, “It has to be taken very carefully because in some cases, it may be beneficial and in others it may be critical.”

### Medical Cannabis Patients May Be at Increased Risk

The Centers for Disease Control and Prevention (CDC) warns that people at high risk for a severe illness from COVID-19 include those  $\geq 65$  years of age and individuals of any age who have underlying medical conditions, particularly if not well controlled, including chronic lung disease or moderate-to-severe asthma, serious heart conditions, diabetes, chronic kidney disease undergoing dialysis, and liver disease, as well as those who are immunocompromised and those with severe obesity.<sup>4</sup>

Many individuals who rely on medical cannabis fall into these categories. According to a study published in *JAMA Internal Medicine*, an increasing proportion of older Americans use medical or recreational cannabis, and many have conditions that put them at higher risk for a severe infection with COVID-19.<sup>5</sup> In a secondary analysis of adults

$\geq 65$  years of age in the National Survey of Drug Use and Health (2015–2018), the prevalence of past-year cannabis use among adults in this age group rose from 2.4% to 4.2% ( $P=0.11$ ), a 75% relative increase. In terms of chronic disease, among adults with diabetes, there was a 180% relative increase from 1% in 2015 to 2.8% in 2018.

Aurelius Data, a Montana-based global patient perception data company in plant-based medicine, has been collecting data from medical cannabis users since the COVID outbreak began in the United States in an attempt to better understand the risks to this population, along with any supply and drug interaction issues, said Julie Armstrong, CPhT, and CEO of Aurelius Data. Results from Aurelius Data’s anonymous surveys suggest that many patients who rely on medical cannabis for treatment of various medical conditions during this pandemic are at high risk for infection with COVID-19. Among 450 people who responded to the online survey to date, 18% have one of the high-risk comorbidities identified by the CDC and 76% take medical cannabis daily for treatment.<sup>6</sup>

“It’s frightening because we know if they’re using THC on a daily basis and they have one of these precursor conditions, they could seriously increase their risk,” she said. “We’re not recommending people stop using cannabis as medicine—just significantly reduce the proportion of THC while you have COVID. That’s really the message.”

In spring 2020, Aurelius Data issued a caution statement to the public, warning about potential harmful side effects that can come from consuming cannabis products with THC while infected with COVID-19.

Public health experts also raised an alarm about smoking and vaping cannabis, which were the primary methods of consumption reported by users in the Aurelius survey. Smoking and vaping can damage the lungs, allowing the virus to more easily attach to lung cells and enter the lungs, prompting health warnings from the Massachusetts attorney general<sup>7</sup> and the National Institute on Drug Abuse.<sup>8</sup>

“We are acutely aware that medicinal marijuana patients, in particular, are probably going to be disproportionately affected by illnesses like COVID because upper respiratory acute viruses can be exacerbated by any kind of combustion or smoke inhaled into the lungs,” said Ms. Armstrong.

**W**e’re not recommending people stop using cannabis as medicine—just significantly reduce the proportion of THC while you have COVID.

—JULIE ARMSTRONG, CPhT

## COVID-19 and Cannabis

continued from page 35

We are acutely aware that medicinal marijuana patients, in particular, are probably going to be disproportionately affected by illnesses like COVID because upper respiratory acute viruses can be exacerbated by any kind of combustion or smoke inhaled into the lungs.

—JULIE ARMSTRONG, CPhT



### Cannabis and Cytokine Storms

Emerging research suggests there may be a role for cannabis in assisting the immune response in patients who are at risk for cytokine storms. A number of patients with COVID-19 develop mild or severe cytokine storms, which is a cause of death. According to a study by a group of Chinese immunologists, a proportion of COVID-19 patients transit into a severe stage of illness, manifested as an extra-pulmonary systemic hyperinflammation syndrome.<sup>9</sup> Tests reveal that markers of systematic inflammation appear to be extremely elevated. “Therefore, how to block the cytokine release storm and when to initiate anti-inflammation therapy is critical for reducing the death rate of COVID-19,” they wrote.

A 2015 study of mice suggests that THC, through its anti-inflammatory properties, may suppress Staphylococcal enterotoxin B (SEB)-induced inflammatory lung injury by modulating critical microRNA involved in SEB-induced toxicity and death.<sup>10</sup>

This may suggest a potential benefit for THC, said Bonni Goldstein, MD, Medical Director and owner of Canna-Centers Wellness and Education, in California. “THC modulates the immune system, keeping it from overreacting and causing hyper inflammation,” she wrote in a post on LinkedIn. She called for more research to look at THC in the setting of COVID.

The past year saw a number of new research studies examining the role of medicinal cannabis in the immune response. In an animal model study, researchers from the Medical College of Georgia at Augusta University, led by immunologist Babak Baban, PhD, MPH, MBA, showed that CBD reduces *ACE2* expression and proinflammatory cytokine production in lung inflammation.<sup>11</sup> Findings

revealed that CBD dampened the cytokine storm after the mice were induced with acute respiratory distress syndrome (ARDS)—the leading cause of mortality in respiratory viral infections like COVID-19. The authors note that CBD may act as a protective factor against ARDS and the cytokine storm.

In Canada, Igor Kovalchuk, MD, and Olga Kovalchuk, PhD, at the University of Lethbridge, report that high-CBD *Cannabis Sativa* extracts appear to modulate *ACE2* gene expression and *ACE2* protein levels, and *ACE2* is known to be pivotal gateway for COVID-19 to infect human cells. The researchers, who have developed more than 800 *C. sativa* lines and extracts under a Health Canada research license, screened 30 preselected *C. sativa* extracts, looking for effects on *ACE2* gene expression. Importantly, the tests were done using artificial human 3D models of oral, airway, and intestinal tissues rather than humans, which limits the significance of the findings. In their paper, they identified 13 extracts that modulate *ACE2* gene expression and protein levels, and noted that several extracts also downregulated serine protease TMPRSS2, another critical protein required for SARS-CoV-2 entry into host cells.<sup>12</sup> In a second paper, they demonstrated that other extracts are efficiently downregulating several proinflammatory cytokines involved in COVID-19 disease, potentially preventing the development of cytokine storm.<sup>13</sup>

These studies received funding from 2 companies: Pathway TX Inc., a research company dedicated to developing custom cannabis therapies to treat specific diseases, and Swysh Inc., a cannabinoid oral health product developer. Dr. Igor Kovalchuk is CEO of both.

He said he hopes that an extract of a high-CBD *C. Sativa* line could be used to develop a mouthwash or throat gargle product for clinical and at-home use that would decrease viral entry via the oral mucosa. He said that a study is already underway in partnership with US-based company Good Pharmaceuticals. “Of course, it’s risky now to do a clinical trial because we do not know whether it will be successful or not,” he said.

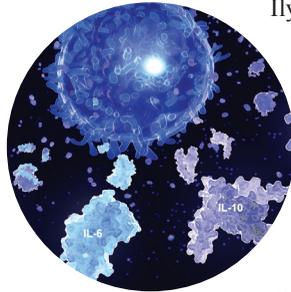
First released as a preprint, the publication received a substantial amount of buzz in the lay press, but also criticism from the scientific community. Matt Elmes, PhD, Director of New Product Development at CannaCraft, wrote a 2890-word commentary on the preprint, detailing his concerns including that the researchers performed the experiments only in artificial cell culture models, did not disclose the statistical models used, selected haphazard experiments to carry out, and omitted key information.<sup>14</sup>

“Sure, it’s feasible that cannabis reduces *ACE2* expression and thereby lowers infectivity of COVID-19, but the data presented here give me very little confidence in that conclusion,” Dr. Elmes concluded.

In a commentary on the overall state of evidence for cannabis in the time of COVID-19, Michelle Sexton, ND, of the Department of Anesthesiology at the University of California, San Diego, said the evidence does not exist to make a case for medical cannabis currently in treatment or prevention of COVID-19.<sup>15</sup> Based on the existing clinical literature, an effective anti-inflammatory dose of CBD is likely to be quite high, and not approximated in most of the hemp-based products currently marketed.

“Reduced innate defense is being considered as a driving feature of COVID-19, and to be clear, no data suggest that THC or CBD is a proven therapeutic intervention for treating COVID-19,” she wrote.

**E**merging research suggests there may be a role for cannabis in assisting the immune response in patients who are at risk for cytokine storms. A number of patients with COVID-19 develop mild or severe cytokine storms, which is a cause of death.



At the University of Miami, researchers conducted a study examining the effects of COVID-19 on cannabis patients.<sup>16</sup> Study results from the anonymous survey of 1202 medical cannabis users reveal that although the majority of participants have at least 1 preexisting chronic health condition, only some switched from smokable to nonsmokable forms of cannabis. The authors note the importance of clinicians discussing cannabis use with patients who have chronic health conditions.

“The global qualifying conditions for medical cannabis, although not uniform, all include individuals with compromised immune systems and other chronic health conditions. Therefore, this is a population that we cannot forget about in our joint effort to flatten the curve,” said lead author Denise C. Vidot, PhD, trained epidemiologist and Assistant Professor at the School of Nursing and Health Studies, University of Miami.

## Countering False Claims

Ms. Armstrong said she is worried about the many false claims made online suggesting that medical cannabis can treat or even prevent COVID. Several cannabis companies have already been called into question for making statements that cannabis can be beneficial. In Arizona, state regulators sent a cease-and-desist order to a marijuana dispensary that ran an ad suggesting a cannabis product could provide immunization against COVID-19.<sup>17</sup>

Ms. Armstrong said bogus claims made about cannabis demonstrate the need for better research into medical cannabis. “It should be something we’re studying on a daily basis,” she said.

## Ongoing Studies

In an ongoing prospective study, researchers led by Ilya Kagan, PhD, RN, and Moshe Yeshurun, MD, at Rabin Medical Center in Israel are examining treatment with 150 mg CBD twice daily for 14 days among patients in a COVID-19 isolation ward. Preliminary results are encouraging and justify future plans for a randomized controlled trial. The study, which is set to recruit 40 patients, aims to examine whether CBD is beneficial for patients with severe ARDS.<sup>18</sup>

Another population that needs further study are long-haulers, or patients with long-term coronavirus symptoms such as chronic fatigue syndrome. “I have received multiple first-hand reports of people in the community self-treating symptoms of long COVID with CBD and cannabis, both inhaled and oral form, with success on subjective well-being including improvements in fatigue and brain fog,” said Dr. Gordon.

## References

1. Hernández-Cervantes R, Méndez-Díaz M, Prospéro-García Ó, Morales-Montor J. Immunoregulatory role of cannabinoids during infectious disease. *Neuroimmunoregulation*. 2017;24(4-5): 183-199.
2. Costiniuk CT, Mills E, Cooper CL. Evaluation of oral cannabinoid-containing medications for the management of interferon and ribavirin-induced anorexia, nausea and weight loss in patients treated for chronic hepatitis C virus. *Can J Gastroenterol*. 2008;22(4):376-380.
3. Hézode C, Roudot-Thoraval F, Nguyen S, et al. Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. *Hepatology*. 2005;42(1):63-71.
4. Centers for Disease Control and Prevention. People who are at higher risk for severe illness. Accessed March 13, 2021. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html>.

continued on page 39

---

## COVID-19 and Cannabis

continued from page 37

5. Han BH, Palamar JJ. Trends in cannabis use among older adults in the United States, 2015-2018 *JAMA Intern Med* 2020; 180(4):609-611.
6. Aurelius Data's anonymous survey. March 15, 2021. <https://covid.aureliusdata.com>
7. Office of Attorney General Maura Healey. Smoking vapist & COVID-19. Accessed March 13, 2021. <https://www.mass.gov/doc/covid-vaping-advisory/download>
8. National Institute on Drug Abuse. COVID-19: potential implications for individuals with substance use disorders. Accessed March 13, 2021. <https://www.drugabuse.gov/about-nida/noras-blog/2020/04/covid-19-potential-implications-individuals-substance-use-disorders>
9. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents*. 2020;55(5):105954.
10. Rao R, Nagarkatti PS, Nagarkatti M.  $\Delta(9)$  tetrahydrocannabinol attenuates staphylococcal enterotoxin B-9nduced inflammatory lung injury and prevents mortality in mice by modulation of miR-17-92 cluster and induction of T-regulatory cells. *Br J Pharmacol*. 2015;172(7):1792-1806.
11. Khodadadi H, Salles EH, Jarrahi A, et al. Cannabidiol modulates cytokine storm in acute respiratory distress syndrome induced by simulated viral infection using synthetic RNA. *Cannabis Cannabinoid Res*. 2020;5(3):197-201.
12. Wang B, Kovalchuck A, Li D, et al. In search of preventive strategies: novel high-CBD Cannabis sativa extracts modulate ACE2 expression in COVID-19 gateway tissues. *Aging* (Albany NY). 2020;12(22):22425-22444.
13. Kovalchuk A, Wang B, Li D, et al. Fighting the storm: could novel anti-TNF $\alpha$  and anti-IL-6 C. sativa cultivars tame cytokine storm in COVID-19? *Aging* (Albany NY). 2021;13(2):1571-1590.
14. Cannabis & COVID-19: breaking news or bogus science? Project CBD. Accessed March 12, 2021. <https://www.projectcbd.org/medicine/cannabis-covid-19-breaking-news-or-bogus-science>
15. Sexton M. Cannabis in the time of coronavirus disease 2019: the yin and yang of the endocannabinoid system in immunocompetence. *J Altern Complement Med*. 2020.;26(6):444-448.
16. Vidot DC, Islam JY, Camacho-Rivera M, et al. The COVID-19 cannabis health study: results from an epidemiologic assessment of adults who use cannabis for medicinal reasons in the United States. *J Addict Dis*. 2021;39(1):26-36.
17. Anglen R. Phoenix marijuana dispensary hawks COVID-19 'immunization stabilizer,' state orders it to stop. Accessed March 12, 2021. <https://www.azcentral.com/story/news/local/arizona-investigations/2020/04/06/phenix-marijuana-dispensary-hawks-covid-19-immunization-stabilizer-mark-bmovich-carsten-loelke/2946325001/>
18. Cannabidiol treatment for severe and critical coronavirus (COVID-19) pulmonary infection. Accessed March 12, 2021. <https://clinicaltrials.gov/ct2/show/NCT04731116>