



MPP's model medical marijuana bill allows patients to obtain a medical marijuana card if they have a qualifying medical condition and their licensed health care practitioner believes they are likely to receive therapeutic or palliative benefit from the use of medical marijuana. The qualifying medical conditions listed in the bill are as follows (the state department of health can add others):

1. Cancer, glaucoma, positive status for human immunodeficiency virus, acquired immune deficiency syndrome, hepatitis C, amyotrophic lateral sclerosis, Crohn's disease, ulcerative colitis, Alzheimer's disease, post-traumatic stress disorder, autism with self-injurious or aggressive behavior, or the treatment of these conditions, and
2. A chronic or debilitating disease or medical condition or its treatment that produces one or more of the following: cachexia or wasting syndrome; severe, debilitating pain; severe nausea; seizures; or severe and persistent muscle spasms, including but not limited to those characteristic of multiple sclerosis.

Key medical references addressing marijuana's ability to alleviate these conditions are below, with related symptoms or conditions grouped together.

Nausea, Appetite Loss, Wasting, Cachexia, Cancer, and HIV/AIDS

In its 1999 report "Marijuana and Medicine: Assessing the Science Base," the Institute of Medicine concluded, "Nausea, appetite loss, pain and anxiety are all afflictions of wasting, and all can be mitigated by marijuana." Marijuana and its active components (cannabinoids) can both stimulate appetite and reduce the nausea, vomiting, and weight loss experienced by patients in many circumstances, including the side effects of drug therapies given for cancer, HIV infection, and hepatitis C. Observational studies suggest this may improve treatment adherence among patients experiencing gastrointestinal toxicity from drug therapy.

Cancer References

(1) Vincent Vinciguerra, et al., "Inhalation Marijuana as an Antiemetic for Cancer Chemotherapy," *New York State Journal of Medicine* (October 1988).

In this clinical trial sponsored by the state of New York, "Fifty-six patients who had no improvement with standard antiemetic agents were treated and 78% demonstrated a positive response to marijuana ... inhalation marijuana is an effective therapy for the treatment of nausea and vomiting due to cancer chemotherapy."

(2) Richard Musty and Rita Rossi, "Effects of Smoked Cannabis and Oral Δ9-Tetrahydrocannabinol on Nausea and Emesis After Cancer Chemotherapy: A Review of State Clinical Trials," *Journal of Cannabis Therapeutics* 1, no. 1 (2001): 43-56.

Musty and Rossi reviewed data from a series of state-sponsored clinical trials of marijuana for relief of nausea and vomiting caused by cancer chemotherapy conducted in the 1970s and 1980s, concluding, "Patients who smoked marijuana experienced 70- 100% relief from nausea and vomiting, while those who used the THC capsule experienced 76-88% relief."

(3) Manuel Guzman, "Cannabinoids: Potential Anticancer Agents," *Nature Reviews* 3 (2003): 745-766.

In this review article, Dr. Guzman, a leading cancer researcher, examined the data regarding use of marijuana and cannabinoids in cancer treatment. He concluded that marijuana/cannabinoids can be useful in preventing or treating "chemotherapy-induced nausea and vomiting." He also noted that cannabinoids have potential as antitumor agents: "Regarding effectiveness, cannabinoids exert a notable antitumour activity... Regarding toxicity, cannabinoids not only show a good safety profile but also have palliative effects in patients with cancer, indicating that clinical trials with cannabinoids in cancer therapy are feasible."

(4) K. Nelson, et al., "A Phase II Study of Delta-9-Tetrahydrocannabinol for Appetite Stimulation in Cancer-Associated Anorexia," *Journal of Palliative Care* 10, no. 1 (1994): 14-8.

In this study of patients with anorexia due to advanced cancer, the researchers concluded, "THC is an effective appetite stimulant in patients with advanced cancer. It is well tolerated at low doses."

(5) Marta Duran, et al., "Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting," *Journal of Clinical Pharmacology* 70, no. 4 (2010): 656-63.

The researchers who conducted this double-blind, placebo-controlled clinical trial concluded that compared to the placebo, the whole plant cannabis (marijuana) medicine "added to standard antiemetic therapy was well tolerated and provided better protection against delayed CINV [chemotherapy-induced nausea and vomiting]."

(6) Kramer, Joan L. (2015). "Medical Marijuana for Cancer," *CA: A Cancer Journal for Clinicians*, 65(2): 109-122.

This literature review found significant evidence for marijuana use improving appetite, nausea, and pain. All but one of the studies analyzed noted an improvement in nausea, with smoked marijuana at least as effective as THC or

synthetic cannabinoids. Additionally, the synthetic compound nabilone was found to produce more central nervous system side effects than marijuana or THC. The study also found a large consensus on the ability of marijuana to treat pain. Patients with a higher marijuana tolerance experienced greater pain tolerance with marijuana use. Marijuana was also shown to effectively improve appetite, with one study showing improvements in appetite for those with wasting syndrome.

(7) McAllister, Sean D., Murase Ryuichi, Christian, Rigel T., Lau, Darryl, Zielinski, Anne J., Allison, Juanita, Almanza, Carolina, Pakdel, Arash, Lee, Jasmine, Limbad, Chandani, Liu, Yong, Debs, Robert J., Moore, Dan H. & Desprez, Pierre- Yves. (2011). "Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis," *Breast Cancer Research Treatment Journal* 129: 37-47.

Using human breast cancer cells grown in a culture, researchers observed CBD pathways to the down-regulation of inhibitors related to breast cancer. Using this, the researchers determined CBD acts as an inhibitor for human breast cancer. Similar results were observed when experimenting on immune competent mice, where treatment with CBD reduced both the size and mass of tumors.

(8) National Academies of Sciences, Engineering, and Medicine. 2017. *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*. Washington, DC: The National Academies Press.

In a systematic review of relevant research conducted from 1999 through 2016, the authors of this landmark meta-analysis state, "There is conclusive evidence that oral cannabinoids are effective antiemetics in the treatment of chemotherapy-induced nausea and vomiting."

HIV/AIDS References

(1) Donald Abrams, et al., "Short-Term Effects of Cannabinoids on Patients With HIV-1 Infection: A Randomized, Placebo-Controlled Clinical Trial," *Annals of Internal Medicine* 139, no. 4 (2003): 258-266.

This preliminary, short-term clinical trial, conducted over 21 days using 62 HIV-infected patients, was designed to examine the short-term safety of smoked marijuana and oral THC on HIV-infected patients, including potential interactions with HIV protease inhibitors, viral load, and CD4 and CD8 counts. Secondary endpoints included weight, caloric intake, and appetite. No safety concerns emerged with either treatment, and the authors concluded, "Our short-duration clinical trial suggests acceptable safety in a vulnerable immune-compromised patient population." Both the marijuana and oral THC groups gained significantly more weight than the placebo group.

(2) B.D. de Jong, et al., “Marijuana Use and Its Association With Adherence to Antiretroviral Therapy Among HIV-Infected Persons With Moderate to Severe Nausea,” *Journal of Acquired Immune Deficiency Syndromes* 38, no. 1 (2005): 43- 6.

Use of illicit drugs is typically associated with poor adherence to medication regimens. This observational study sought to determine whether this common assumption applies to HIV/AIDS on antiretroviral therapy (ART). Marijuana-using patients who suffered moderate to severe nausea were far more likely to be adherent to ART than those suffering nausea who did not use marijuana (OR = 3.3). The authors concluded, “These data suggest that medicinal use of marijuana may facilitate, rather than impede, ART adherence for patients with nausea, in contrast of other illicit substances,” particularly in the case of “use of smoked marijuana specifically for amelioration of nausea.”

(3) M. Haney, et al., “Dronabinol and Marijuana in HIV-Positive Marijuana Smokers. Caloric Intake, Mood, and Sleep,” *Journal of Acquired Immune Deficiency Syndromes* 45, no. 5 (2007): 545-54.

In this controlled clinical trial, both marijuana and oral THC (dronabinol) use resulted in increased caloric intake and body weight. Strikingly, a dronabinol dose “eight times current recommendations” was required to approximate the effect of relatively low-potency (3.9% THC) marijuana, and only the marijuana improved ratings of sleep. While both drugs produced some intoxication, researchers reported “little evidence of discomfort and no impairment of cognitive performance.”

(See the section on chronic pain below for studies of marijuana for HIV-associated peripheral neuropathy.)

Hepatitis C References

(1) D.L. Sylvestre, B.J. Clements, and Y. Malibu, “Cannabis Use Improves Retention and Virological Outcomes in Patients Treated For Hepatitis C,” *European Journal of Gastroenterology and Hepatology* 18 (2006): 1057-63.

A prospective observational study was conducted on 71 patients to define the impact of cannabis use during interferon/ribavirin treatment for the hepatitis C virus. Compared to non-users, marijuana users had three times the rate of sustained virological response, apparently due to better treatment adherence. The researchers stated, “[T]he use of cannabis during HCV treatment can improve adherence by increasing the duration of time that patients remain on therapy; this translates to reduced rates of post-treatment virological relapse.”

(2) B. Fischer, et al., “Treatment For Hepatitis C Virus and Cannabis use in Illicit Drug User Patients: Implications and Questions,” *European Journal of Gastroenterology and Hepatology* 18 (2006): 1039-42.

This commentary, published alongside the above study, placed the results in context, explaining how marijuana “may help address key challenges faced by drug users in HCV treatment (e.g. nausea, depression).”

Other References

(1) Richard W. Foltin, Marian W. Fischman, and Maryanne F. Byrne, “Effects of Smoked Marijuana on Food Intake and Body Weight of Humans Living in a Residential Laboratory,” *Appetite* 11 (1988): 1-14.

This study, involving healthy volunteers living in a residential laboratory, documented marijuana’s efficacy as an appetite stimulant. Compared to placebo, relatively weak marijuana cigarettes (2.3% THC) smoked at scheduled intervals resulted in a 40% increase in daily caloric intake.

(2) R. Layeeque, et al., “Prevention of Nausea and Vomiting Following Breast Surgery,” *American Journal of Surgery* 191, no. 6 (2006): 767-72.

This retrospective review found that a prophylactic regimen combining oral THC with rectal prochlorperazine “significantly reduced the number and severity of episodes” of post-operative nausea and vomiting in breast surgical patients.

Severe, Debilitating Pain

On January 12, 2017, after reviewing more than 10,000 scientific abstracts, the National Academies of Sciences, Engineering, and Medicine released a report that found there is substantial or conclusive evidence that cannabis is beneficial in the treatment of chronic pain.

Studies have shown that marijuana is effective in treating pain, including neuropathic pain, which is commonly seen in multiple sclerosis, HIV/AIDS, and other ailments, and notoriously resistant to treatment with conventional pain drugs. Research also suggests that marijuana use may allow reduced opioid doses when given in combination.

References

(1) Wilsey B, Marcotte TD, Deutsch R, Zhao H, Prasad H, Phan A. (2016). “An Exploratory Human Laboratory Experiment Evaluating Vaporized Cannabis in the Treatment of Neuropathic Pain from Spinal Cord Injury and Disease.” *J Pain*. 2016 Jun 7. pii: S1526-5900(16)30072-4. doi: 10.1016/j.jpain.2016.05.010.

“Using 8-hour human laboratory experiments, we evaluated the analgesic efficacy of vaporized cannabis in patients with neuropathic pain related to injury or disease of the spinal cord, most of whom were experiencing pain despite traditional treatment. ... Using an 11-point numerical pain intensity rating scale as the primary outcome, a

mixed effects linear regression model showed a significant analgesic response for vaporized cannabis."

(2) Wilsey, Barth, et al., "Low Dose Vaporized Cannabis Significantly Improves Neuropathic Pain," *The Journal of Pain: Official Journal of the American Pain Society* 14.2 (2013): 136–148.

This double-blind, placebo-controlled study on 30 human subjects found that even low doses of vaporized marijuana were effective at alleviating treatment-resistant neuropathic pain. "Psychoactive effects were minimal and well tolerated, and neuropsychological effects were of limited duration and readily reversible within 1 to 2 hours."

(3) Donald Abrams, et al., "Cannabinoid-opioid interaction in chronic pain," *Clinical Pharmacology & Therapeutics* (2011): 844-851.

This clinical trial involved 21 individuals with severe pain who were taking sustained-release morphine or oxycodone. It found that vaporized marijuana augmented the analgesic effects of opioids. The authors reported that the adding vaporized marijuana "may allow for opioid treatment at lower doses with fewer side effects."

(4) Mark Ware, et al., "Smoked cannabis for chronic neuropathic pain: a randomized controlled trial," *Canadian Medical Association Journal* (2010): 694- 701.

This trial found that "a single inhalation of 25 mg of 9.4% tetrahydrocannabinol herbal cannabis three times daily for five days reduced the intensity of pain, improved sleep and was well tolerated."

(5) Donald Abrams, et al., "Cannabis in Painful HIV-Associated Sensory Neuropathy: A Randomized Placebo-Controlled Trial," *Neurology* 68, no. 7 (2007): 515-21.

This clinical trial involved HIV/AIDS patients suffering from HIV-associated sensory neuropathy, a painful condition estimated to eventually afflict up to one third of HIV- infected persons. There are presently no FDA-approved treatments for this indication. Donald Abrams and his colleagues tested the efficacy of smoked marijuana on both HIV neuropathy and a type of laboratory-induced pain. Smoked marijuana produced an average 34% reduction in pain and was well tolerated.

(6) R.J. Ellis, et al., "Smoked Medicinal Cannabis For Neuropathic Pain in HIV: a Randomized, Crossover Clinical Trial," *Neuropsychopharmacology* 34, no. 3 (2009): 672-80.

This trial focused on patients with HIV-associated neuropathy refractory to at least two previous analgesic classes. Ellis and colleagues reported, "In the present

experiment, cannabis reduced pain intensity and unpleasantness equally. Thus, as with opioids, cannabis does not rely on a relaxing or tranquilizing effect, (e.g. anxiolysis) but rather reduces both the core component of nociception and the emotional aspect of the pain experience to an equal degree. ... In general, side effects and changes in mood were inconsequential.”

(7) B. Wilsey, et al., “A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain,” *Journal of Pain* 9, no. 6 (2008): 506-21.

This study investigated the efficacy of smoked marijuana in patients suffering from neuropathic pain related to a variety of conditions, including multiple sclerosis, spinal cord injury, diabetes, and complex regional pain syndrome. Wilsey and colleagues concluded, “This study adds to a growing body of evidence that cannabis may be effective at ameliorating neuropathic pain, and may be an alternative for patients who do not respond to, or cannot tolerate, other drugs.”

(8) David Baker, et al., “The Therapeutic Potential of Cannabis,” *The Lancet Neurology* 2, no. 5 (2003): 291-8.

This review, written prior to publication of the clinical trials described above, discussed in detail the biochemical basis for marijuana’s analgesic effects. It also discussed the drawbacks of oral dosing (taking a pill with cannabinoids), explaining that “oral administration is probably the least satisfactory route for cannabis owing to sequestration of cannabinoids into fat from which there is slow and variable release into plasma. In addition, significant first-pass metabolism in the liver, which degrades THC, contributes to the variability of circulating concentrations of orally administered cannabinoids, which makes dose titration more difficult and therefore increases the potential for adverse psychoactive effects. Smoking has been the route of choice for many cannabis users because it delivers a more rapid ‘hit’ and allows more accurate dose-titration.”

(9) M.E. Lynch, J. Young, A.J. Clark, “A Case Series of Patients Using Medicinal Marijuana for Management of Chronic Pain Under the Canadian Marijuana Medical Access Regulations,” *Journal of Pain and Symptom Management* 32, no. 5 (2006): 497-501.

This case series is based on 30 patients qualified to use medical marijuana under Canadian regulations, seen at a pain management center in Nova Scotia. All suffered from chronic, severe pain that had not responded to conventional approaches. On an 11-point scale, 93% reported pain relief equal to six or greater, and many reported relief of other symptoms such as spasticity, poor sleep, nausea, and vomiting. 70% reported being “able to decrease use of other medications that had been causing side effects (e.g., NSAIDs, opioids, and antidepressants).”

(10) Johnson, Jeremy R., Burnell-Nugent, Mary, Lossignol, Dominique, Ganae-Motan, Elena Doina, Potts, Richard & Fallon, Marie T. (2010). "Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC extract in Patients with Intractable Cancer-Related Pain," *Journal of Pain and Symptom Management* 39(2): 167-179.

This study compared the efficacy of a THC:CBD extract, a strictly THC extract, and a placebo for pain relief in patients suffering from intractable cancer-related pain. On the numerical rating scale for pain, the THC:CBD extract showed a statistically significant reduction in pain from the placebo, while the THC extract did not. A statistically significant odds ratio of 2:1 was shown between patients using the THC:CBD extract versus placebo for patients who experienced a reduction in pain of greater than 30%.

(11) Webb, Charles W. & Webb, Sandra M. (2014). "Therapeutic Benefits of Cannabis: A Patient Survey," *Hawai'i Journal of Medicine & Public Health* 73(4): 109-111.

Researchers handed out surveys to 100 patients returning for annual medical marijuana recertification in the state of Hawaii. Of the 94% of patients that responded, 97% used medical marijuana for pain relief with an average pain improvement from 7.8 to 2.8 on a ten-point scale. Additionally, 50% of the patients reported relief from anxiety, 45% reported relief from insomnia, and 71% reported no adverse side effects at all. The study concluded that medical cannabis has the potential to treat numerous medical conditions.

Glaucoma

Glaucoma is a leading cause of blindness, damaging the optic nerve, which is responsible for carrying images from the eye to the brain. High pressure within the eye is one of the main risk factors for this optic nerve damage. There currently is no cure for glaucoma. Marijuana helps relieve the pressure within the eye, thus preventing damage.

Although other drugs are considered first-line glaucoma treatments, some patients and physicians have found marijuana useful when conventional drugs fail. One of the three patients who still receive medical marijuana from the federal government – Elvy Musikka – is a glaucoma patient, who also successfully argued in a Florida court case that marijuana was medically necessary to maintaining her vision.

(1) J.E. Joy, S.J. Watson, and J.A. Benson, *Marijuana and Medicine: Assessing the Science Base* (National Academy Press, 1999).

"In a number of studies of healthy adults and glaucoma pressure, IOP (intra-ocular pressure) was reduced by an average of 25% after smoking a marijuana cigarette that contained approximately 2% THC — a reduction as good as that observed with

most other medications available today.”

Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig’s disease, is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord, progressively reducing the ability of the brain to initiate and control muscle movement. Some research has shown that cannabinoids can delay the progression of ALS. Some ALS patients have indicated that medical marijuana has helped alleviate their symptoms, such as pain, appetite loss, depression, and drooling.

References

(1) Gregory T. Carter and Bill S. Rosen, “Marijuana in the Management of Amyotrophic Lateral Sclerosis,” *American Journal of Hospice and Palliative Care* 18, no. 4 (2001): 264-69.

This review article, co-authored by a leading ALS and palliative medicine researcher from the University of Washington, concluded that marijuana may help with many symptoms of ALS, including pain, spasticity, drooling, dysautonomia, and wasting. The authors also discussed how marijuana’s antioxidative and neuroprotective effects may prolong neuronal cell survival, and concluded, “In areas where it is legal to do so, marijuana should be considered in the pharmacological management of ALS.”

(2) E. de Lago, J. Fernández-Ruiz, “Cannabinoids and Neuroprotection in Motor- Related Disorders,” *CNS and Neurological Disorders — Drug Targets* 6, no. 6 (2007): 377-87.

This review explored in detail the mechanisms of cannabinoid neuroprotection related to a variety of disorders, including ALS.

(3) Dagmar Amtmann, et al., “Survey of Cannabis Use in Patients With Amyotrophic Lateral Sclerosis,” *American Journal of Hospice and Palliative Medicine*, March-April 2004.

This anonymous survey of 131 people with ALS found that 10 percent had reported using marijuana in the past year, reporting relief of multiple symptoms. The authors concluded, “...results indicate that cannabis may be moderately effective at reducing symptoms of appetite loss, depression, pain, spasticity, and drooling.”

Crohn’s Disease and Ulcerative Colitis

Crohn’s disease and ulcerative colitis are marked by inflammation of the digestive tract, most commonly the lower part of the small intestine. Both conditions can cause severe abdominal pain, nausea, and weight loss – all symptoms that marijuana

can help mitigate, as noted in other sections of this document. Preclinical research has demonstrated the role of the endocannabinoid system, the body's natural, marijuana-like chemicals, in protecting the GI tract, providing support for anecdotal reports of relief.

References

(1) J.E. Joy, S.J. Watson, and J.A. Benson, *Marijuana and Medicine: Assessing the Science Base* (National Academy Press, 1999).

"For patients ... who suffer simultaneously from severe pain, nausea, and appetite loss, cannabinoid drugs might offer broad-spectrum relief not found in any other single medication."

(2) F. Massa, M. Storr, and B. Lutz, "The Endocannabinoid System in the Physiology and Pathophysiology of the Gastrointestinal Tract," *Journal of Molecular Medicine* 83, no. 12 (2005): 944-54.

This review article noted, "Under pathophysiological conditions induced experimentally in rodents, the endocannabinoid system conveys protection to the GI tract (e.g. from inflammation and abnormally high gastric and enteric secretions). Such protective activities are largely in agreement with anecdotal reports from folk medicine on the use of *Cannabis sativa* extracts by subjects suffering from various GI disorders."

(3) Timna Naftali, et al., "Cannabis induces a clinical response in patients with Crohn's disease: A prospective placebo-controlled study," *Clinical Gastroenterology and Hepatology* (2013).

This placebo-controlled clinical trial found that complete remission was achieved in five out of 11 subjects who were administered cannabis, compared to one of the 10 who received a placebo. "A clinical response was observed in 10 of 11 subjects in the cannabis group and four of 10 in the placebo group. Three patients in the cannabis group were weaned from steroid dependency. Subjects receiving cannabis reported improved appetite and sleep, with no significant side effects." (*technical parentheticals within the quote deleted*)

(4) Adi Lahate, et al., "Impact of Cannabis Treatment on the Quality of Life, Weight, and Clinical Disease Activity in Inflammatory Bowel Disease Patients: A Pilot Prospective Study," *Digestion* (2012).

This study found that inhaled cannabis improves quality of life in patients with Crohn's disease and ulcerative colitis. After three months of treatment, patients had a statistically significant increase in weight and improvement in clinical disease activity index. The data showed "a statistically significant improvement in almost all aspects of patients' daily life." This included "a statistically significant physical pain reduction during treatment, as well as improvement in mental distress ..." In

addition, none of the patients “complained of any side effect that disturbed their working ability. In fact, as was shown in the results, there was a statistically significant improvement in patients' ability to work after treatment.”

(5) Timna Naftali, et al., "Treatment of Crohn's Disease with Cannabis: An Observational Study," *Israel Medical Association Journal* (2011).

This study of 30 patients found that 21 had significant improvement with cannabis treatment. “The mean number of bowel movements decreased from eight to

five a day and the need for other drugs was significantly reduced ... the number of patients requiring steroid treatment was reduced from 26 to 4. Fifteen of the patients had 19 surgeries during an average period of 9 years before cannabis use, but only 2 required surgery during an average period of 3 years of cannabis use.” The authors noted the effects could be due to cannabis' anti-inflammatory properties. In addition, “Cannabinoids influence gastrointestinal motility and, in particular, have an anti-diarrheal effect ...”

Alzheimer's Disease

In preliminary research, THC has been shown to reduce agitation in severely demented Alzheimer's patients. Preclinical research also suggests that marijuana components may help slow the progression of Alzheimer's disease.

References

(1) S. Walther, et al., “Delta-9-Tetrahydrocannabinol for Nighttime Agitation in Severe Dementia,” *Psychopharmacology* (Berl) 185, no. 4 (2006): 524-8.

This open-label pilot study reported, “Compared to baseline, dronabinol led to a reduction in nocturnal motor activity ($P=0.028$). These findings were corroborated by improvements in Neuropsychiatric Inventory total score ($P=0.027$) as well as in subscores for agitation, aberrant motor, and nighttime behaviors ($P<0.05$). No side effects were observed.”

(2) G. Esposito, et al., “The Marijuana Component Cannabidiol Inhibits Beta-Amyloid-Induced Tau Protein Hyperphosphorylation Through Wnt/beta-catenin Pathway Rescue in PC12 Cells,” *Journal of Molecular Medicine* 84, no. 3 (2006): 253-8.

“Here, we report that cannabidiol inhibits hyperphosphorylation of tau protein in Abeta-stimulated PC12 neuronal cells, which is one of the most representative hallmarks in AD. ... These results provide new molecular insight regarding the neuroprotective effect of cannabidiol and suggest its possible role in the pharmacological management of AD, especially in view of its low toxicity in humans.”

(3) A. Shelef, Y. Barak, U. Berger, D. Paleacu, S. Tadger, I. Plopsky, and Y. Baruch, "Safety and efficacy of medical cannabis oil for behavioral and psychological symptom of dementia: An open label, add-on, pilot study," *Journal of Alzheimer's Disease* (2016) 51: 15-19.

This four-week, open-label prospective trial found a significant reduction in the neuropsychiatric inventory score — specifically regarding delusions, agitation/aggression, irritability, apathy, sleep, and caregiver distress — in Alzheimer's disease patients who were administered medical cannabis oil. "CONCLUSION: Adding [medical cannabis oil] to [Alzheimer's disease] patients' pharmacotherapy is safe and a promising treatment option."

Multiple Sclerosis and Muscle Spasms

Clinical trials involving whole plant marijuana and various marijuana extracts have found that patients reported relief of muscle stiffness, pain, and spasticity.

References

(1) Jody Corey-Bloom, et al., "Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial," *Canadian Medical Association Journal* 184, no. 10 (2012): 1143-1150.

This placebo-controlled, crossover trial of 37 participants with multiple sclerosis and spasticity found that smoked cannabis was superior to placebos in reducing pain and spasticity. The authors recommended that, "Future studies should examine whether different doses can result in similar beneficial effects with less cognitive impact." There were no serious adverse events during the trial.

(2) J. Zajicek, et al., "Multiple Sclerosis and Extract of Cannabis: Results of the MUSEC trial," *Journal of Neurology, Neurosurgery & Psychiatry* 83: no 11 (2012): 1125-1132.

This double blind, placebo controlled, phase III clinical trial found that patients found almost twice as much relief from muscle stiffness from oral cannabis extract than from the placebo.

(3) A Novotna, et al., "A randomized, double-blind, placebo-controlled, parallel- group, enriched-design study of nabiximols* (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis," *European Journal of Neurology* 18, no. 9 (2011): 1122-1131.

This phase 3 double-blind, placebo-controlled study on patients whose multiple sclerosis spasticity was not fully alleviated by other therapies found that more than 47% had their spasticity improve by at least 20 during the first four weeks of the trial. This trial involved Sativex, which is a cannabis extract that is approved for multiple sclerosis spasticity in several European countries, New Zealand, and

Canada, but which is not legally available to patients in the United States.

(4) J. Zajicek, et al., “Cannabinoids for Treatment of Spasticity and Other Symptoms Related to Multiple Sclerosis (CAMS Study): Multicentre Randomised Placebo-Controlled Trial,” *The Lancet* 362 (2003): 1517-26.

This trial, using an oral cannabis extract, reported “evidence of a treatment effect on patient-reported spasticity and pain ($p=0.003$), with improvement in spasticity reported in 61% ($n=121$, 95% CI 54.6–68.2), 60% ($n=108$, 52.5– 66.8), and 46% ($n=91$, 39.0–52.9) of participants on cannabis extract, 9-THC, and placebo, respectively.”

(5) D.T. Wade, et al., “Long-Term Use of a Cannabis-Based Medicine in the Treatment of Spasticity and Other Symptoms in Multiple Sclerosis,” *Multiple Sclerosis* 12 (2006): 639-45.

In this long-term follow-up of a clinical trial of a marijuana-based oral spray, patients were followed for as much as 82 weeks. The marijuana spray demonstrated long-term relief of spasticity, pain, and bladder issues related to MS, “without unacceptable adverse effects.”

(6) Collin, C., Davies, P., Mutiboko, I.K. & Ratcliffe, S. (2007) “Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis,” *European Journal of Neurology* 14: 290-296.

This double-blind study compared the effects of a placebo versus a whole plant based treatment containing THC and CBD. Over a six-week period of use, 40% of the subjects treated with cannabis saw a reduction in spasticity of more than 30% and 17.5% saw a reduction greater than 50%. A number of subjects also saw an increase in muscle power in their legs, and 57% of the subjects experienced a global improvement in symptoms. The authors noted surprise at the low dropout rate of subjects for such a high dosage of THC, which the authors attributed to the CBD in the medicine. The authors concluded that cannabis-based medications could be useful in symptomatic relief of spasticity for patients with MS.

(7) Flachenecker, Peter, Henze, Thomas & Zettl, Uwe K. (2014). “Long-Term Effectiveness and Safety of Nabiximols (Tetrahydrocannabinidol/Cannabidiol Oromucosal Spray) in Clinical Practice,” *European Neurology* 72: 95-102.

Multiple sclerosis patients taking nabiximols — a THC/CBD spray — were surveyed over a 12-month period. On a 10-point spasticity scale, a statistically significant average reduction from 6.0 to 4.8 was observed after the first month, with scores remaining constant for the remaining 11 months. Eighty-four percent of the subjects reported no adverse side effects. The authors concluded the data confirmed long-term efficacy of nabiximols for MS patients.

(8) National Academies of Sciences, Engineering, and Medicine. 2017. *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*. Washington, DC: The National Academies Press.

In a systematic review of relevant research conducted from 1999 through 2016, the authors of this landmark meta-analysis state, “There is substantial evidence that oral cannabinoids are an effective treatment for improving patient-reported multiple sclerosis spasticity symptoms.”

Epilepsy and Seizures

Considerable data from animal models as well as some human clinical evidence suggest a role for marijuana in the treatment of seizure disorders such as epilepsy.

References

(1) M. Hausman-Kedem M, et al., “Efficacy of CBD-enriched medical cannabis for treatment of refractory epilepsy in children and adolescents - An observational, longitudinal study.” *Brain and Development*. Apr 16, 2018.

This observational study of 57 epilepsy patients in the Pediatric Neurology Unit at the Tel Aviv Medical Centre, Israel found a substantial reduction in seizure activity following administration of a cannabis extract for at least three months. Fifty-six percent of the patients had at least 50% reductions in seizure frequency. They were administered an extract with a 20:1 ratio of the cannabinoids cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC).

(2) Alsasua del Valle, “Implication of Cannabinoids in Neurological Diseases,” *Cellular and Molecular Neurobiology* 26, no. 4-6 (2006): 579-91.

This wide-ranging review of the neurobiology of marijuana and its constituents in relation to neuroprotection and neurological disease noted, “It has been known for centuries that exogenous cannabinoids have anti-convulsant activity.”

(3) K. Mortati, B. Dworetzky, and O. Devinsky, “Marijuana: an Effective Antiepileptic Treatment in Partial Epilepsy? A Case Report and Review of the Literature,” *Reviews in Neurological Diseases* 4, no. 2 (2007): 103-6.

Mortati and colleagues reported the case of a 45-year-old male with cerebral palsy and epilepsy “who showed marked improvement with the use of marijuana.” The authors reviewed the current literature and concluded, “Although more data are needed, animal studies and clinical experience suggest that marijuana or its active constituents may have a place in the treatment of partial epilepsy.”

(4) D.W. Gross, et al., “Marijuana Use and Epilepsy: Prevalence in Patients of a Tertiary Care Epilepsy Center,” *Neurology* 62, no. 11 (2004): 2095-7.

In this patient survey, of 28 epileptic patients who actively used marijuana, 68% reported that it improved severity of seizures and 54% reported improvement of seizure frequency. None reported that it worsened these symptoms.

5) Tzadok, M., et al. "CBD-enriched medical cannabis for intractable pediatric epilepsy: The current Israeli experience." *Seizure*, 35:41 (2016).

This study involved 74 children and adolescents with intractable epilepsy who had failed to respond to at least seven other medications, and in 66% of cases had not found relief from a ketogenic diet, vagal nerve stimulator implantation, or both. The patients all received an oral formulation of cannabidiol and tetrahydrocannabinol at a 20:1 ratio for at least three months. The average treatment was nine months.

Researchers said the "highly promising" results were, "Most of the children (66/74, 89%) reported reduction in seizure frequency: 13 (18%) reported 75-100% reduction, 25 (34%) reported 50-75% reduction, 9 (12%) reported 25-50% reduction, and 19 (26%) reported <25% reduction. Five (7%) patients reported aggravation of seizures which led to CBD withdrawal. In addition, we observed improvement in behavior and alertness, language, communication, motor skills and sleep."

Post-Traumatic Stress Disorder

Post-traumatic stress disorder involves a person developing characteristic symptoms — such as flashbacks, numbing, and avoidance — after personally experiencing an extremely traumatic stressor. Available treatments are often not effective. Unfortunately, there has been limited research on whole plant marijuana and PTSD, including due to the U.S. federal government refusing to provide marijuana to an FDA-approved and institutional review board-approved study. However, there are clinical trials ongoing in Israel, where an open pilot study found marijuana effective at alleviating symptoms of combat veterans. In addition, other human and animal evidence supports the therapeutic potential of cannabis and cannabinoids in treating PTSD symptoms.

References

(1) Torsten Passie, et al., "Mitigation of post-traumatic stress symptom by Cannabis resin: A review of the clinical and neurobiological evidence," *Drug Testing and Analysis* (2012): 649-659

This is a case report of a 19-year-old patient who had severe PTSD, including panic attacks and self-mutilation. He discovered that his major symptoms were dramatically reduced by smoking cannabis resin. As the abstract explains, "The major part of this review is concerned with the clinical and preclinical neurobiological evidence in order to offer a potential explanation of these effects on symptom reduction in PTSD." It noted, "Evidence is increasingly accumulating that

cannabinoids might play a role in fear extinction and antidepressive effects."

(2) George Fraser, "The Use of a Synthetic Cannabinoid in the Management of Treatment-Resistant Nightmares in Posttraumatic Stress Disorder (PTSD)," *CNS Neuroscience & Therapeutics* 15, no 1. (2009): 84-88.

This study involved administering a nabilone — a prescription drug made of a synthetic cannabinoid (component of marijuana) to patients with treatment-resistant nightmares who had PTSD. They reported, "The majority of patients (72%) receiving nabilone experienced either cessation of nightmares or a significant reduction in nightmare intensity. Subjective improvement in sleep time, the quality of sleep, and the reduction of day-time flashbacks and night sweats were also noted by some patients."

(3) Eti Ganon-Elaza and Irit Akirav, "Cannabinoids Prevent the Development of Behavioral and Endocrine Alterations in a Rat Model of Intense Stress," *Neuropsychopharmacology* (2012): 456-466.

In this study, synthetic marijuana was given to rats after a traumatic event. It was able to block symptoms of PTSD after the rodents were exposed to extreme stress. All of the rats experienced anxiety, but symptoms of PTSD disappeared in the group given marijuana within the two or 24-hour time frame. The findings concluded that, "cannabinoids could serve as a pharmacological treatment of stress- and trauma-related disorder."

(4) George R. Greer M.D., Charles S. Grob M.D. & Adam L. Halberstadt Ph.D. (2014). "PTSD Symptom Reports of Patients Evaluated for the New Mexico Medical Cannabis Program," *Journal of Psychoactive Drugs* 46(1): 73-77.

In 2011, 34% of patients participating in New Mexico's medical cannabis program were diagnosed with PTSD. Authors evaluated patients based on the Clinician-Administered PTSD Score (CAPS). The results showed a statistically significant decline in the CAPS scores for patients using cannabis across all major categories in the CAPS evaluation. Based on these conclusions, the authors showed that cannabis is associated with a reduction in PTSD symptoms for some patients and supported a placebo-controlled study for further research.

(5) Papini, Santiago, Sullivan, Gregory M., Hein, Denise A., Shvil, Erel & Neria, Yuval. (2015). "Toward a translational approach to targeting the endocannabinoid system in posttraumatic stress disorder: A critical review of preclinical research," *Biological Psychology* 104: 8-18.

This study trained mice to develop fear-based responses to certain stimuli and then examined the effects of cannabinoids on the treatment of PTSD developed through previous conditioning. The study confirmed previous research that disruption of CB1 receptors impairs fear extinction (the ability of an organism to stop reacting negatively to stimuli after the negative consequences of that stimuli cease). The

study also found some success in treating rats with CB1 agonists during extinction therapy and found similar results for humans. The study concluded that using CB1 agonists could be used to improve the effectiveness of extinction therapy for those with PTSD or for those at risk for developing PTSD.

(6) Roitman, Pablo, Mechoulam, Raphael, Cooper-Kazas, Rena & Shalev, Arie. (2014). "Preliminary, Open-Label, Pilot Study PTSD," *Clinical Drug Investigation* 34: 587-591.

This study examined the effects of orally ingested THC for 10 subjects with post-traumatic stress disorder. Patients experienced only mild side effects like dry mouth or dizziness in some cases, and none of the side effects were severe enough to cause the patients to drop out of the study. The data showed a statistically significant relationship between using THC to treat PTSD and an improvement in overall severity of sleep quality, nightmare frequency, and PTSD hyperarousal symptoms like feelings of tenseness or being easily startled. The authors recommend further research based on the results of the pilot study.

Autism with Self-Injurious or Aggressive Behavior

Some individuals on the autism spectrum have outbursts that include harm to themselves or others, such as aggression and self-injurious behaviors. Self-injury may include biting, head banging, self-choking, scratching, or hair-pulling. Some parents of children with autism in the United States — including in states where cannabis is not legal — have found that cannabis preparations quell those dangerous behaviors, where other treatments have failed. (See: "VIDEO: Texas parents treat daughter's severe autism with marijuana vapor, results are stunning," *MySA.com*, Feb. 23, 2017.)

While clinical research remains limited so far, and is notoriously difficult to conduct in the United States, studies are underway in Israel. Preliminary results show that patients are reporting less anxiety, fewer outbursts, and more successful communication. (See: Dina Kraft, "Israel's Booming Medical Marijuana Industry Now Offers Hope to Autism Patients," *Haaretz*, September 25, 2017.)

(1) Bar-Lev Schleider, Lihi, et al. (2019). "Real life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy," *Scientific Reports* 9: Article 200.

This study assessed outcomes for 93 autism spectrum disorder (ASD) patients who underwent medical marijuana treatments in Israel from 2015 to 2017. Researchers found that 84% of those assessed experienced moderate to significant improvements in their conditions. The authors conclude, "Cannabis in ASD patients appears to be a well tolerated, safe and effective option to relieve symptoms associated with ASD."

(2) Aran, Adi, et al. (2019). “Brief Report: Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems — A Retrospective Feasibility Study,” *Journal of Autism and Developmental Disorders* 49: 1284-88.

Researchers assessed the efficacy and tolerability of cannabidiol-rich cannabis with 60 children diagnosed with ASD and experiencing severe behavioral problems. After observing behavioral outbreaks improved in 61% of these patients, the study authors recommend further research and clinical trials for ASD children and cannabis.

Vaporization as an Alternative to Smoking

One often-mentioned objection to medical use of marijuana is the respiratory risk associated with smoking. For this reason, the Institute of Medicine urged development of a “nonsmoked, rapid-onset cannabinoid delivery system.” Published research suggests that vaporization — in which marijuana is heated to the point where cannabinoid vapors are released, but not to the point of combustion — represents a viable solution to this problem.

References

(1) A. Hazekamp, et al., “Evaluation of a Vaporizing Device (Volcano) for the Pulmonary Administration of Tetrahydrocannabinol,” *Journal of Pharmaceutical Sciences* 95, no. 6 (2006): 1308-17.

This laboratory test of a commercially available vaporizer known as the Volcano used language striking similar to that of the Institute of Medicine, concluding, “Our results show that with the Volcano a safe and effective cannabinoid delivery system seems to be available to patients.”

(2) D.I. Abrams, et al., “Vaporization as a Smokeless Cannabis Delivery System: A Pilot Study,” *Clinical Pharmacology and Therapeutics* 282, no. 5 (2007): 572-8.

In this clinical trial, again using the Volcano vaporizer, volunteers were randomly assigned to either smoke or vaporize marijuana of three different strengths.

Vaporization was comparable to smoking in terms of THC delivery, but dramatically reduced the amount of carbon monoxide, indicating “little or no exposure to gaseous combustion toxins.” The researchers concluded that vaporization “therefore is expected to be much safer than smoking marijuana cigarettes.”

(3) M. Earleywine and S.S. Barnwell, “Decreased Respiratory Symptoms in Cannabis Users Who Vaporize,” *Harm Reduction Journal* 4, no. 11 (2007).

This internet sample of nearly 7,000 participants compared self-reported

respiratory symptoms among marijuana users whose primary method was smoking with those whose primary method was vaporization, reporting, “use of a vaporizer predicted fewer respiratory symptoms even when age, sex, cigarette smoking, and amount of cannabis used were taken into account.”

(4) Earleywine, Mitch & van Dam, Nicholas T. (2010). “Case studies in cannabis vaporization,” *Addiction Research and Theory*, 18(3): 243-249.

This study found four cannabis smokers reporting negative respiratory symptoms and asked them to begin using a vaporizer. After one month of use, the smokers self-reported dramatic improvements in respiratory symptoms and lung function. The authors concluded that vaporization can improve respiratory-related side effects of cannabis use and recommended further study.