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Alzheimer's Disease

Alzheimer's disease (AD) is a neurological disorder of unknown origin that is characterized by a progressive loss of both memory and learned behavior. Patients with Alzheimer's are also likely to experience depression, agitation, and appetite loss, among other symptoms. As many as 5.8 million Americans are estimated to be afflicted with the disease. No approved treatments or medications are available to modulate the progression of AD, and few pharmaceuticals effectively treat symptoms of the disease.

Several preclinical studies indicate that cannabinoids and the endocannbinoid system are promising targets for future AD therapies.

Writing in the *Journal of Neuroscience*, investigators at Madrid's Complutense University and the Cajal Institute in Spain reported that intracerebroventricular administration of the synthetic cannabinoid WIN 55,212-2 prevented cognitive impairment and decreased neurotoxicity in rats injected with amyloid-beta peptide (a protein believed to induce Alzheimer's). Additional synthetic cannabinoids were also found to reduce the inflammation associated with Alzheimer's disease in human brain tissue in culture. "Our results indicate that … cannabinoids succeed in preventing the neurodegenerative process occurring in the disease," investigators concluded.[1] Follow-up studies by investigators have demonstrated that the administration of the plant cannabinoid cannabidiol also mitigated memory loss in a mouse model of the disease.[2]

Investigators at The Scripps Research Institute in California reported that THC administration inhibits the enzyme responsible for the aggregation of amyloid plaque — the primary marker for Alzheimer's disease — in a manner "considerably superior" to that of approved AD drugs such as donepezil and tacrine. "Our results provide a mechanism whereby the THC molecule can directly impact Alzheimer's disease pathology," researchers concluded. "THC and its analogues may provide an improved therapeutic [option] for Alzheimer's disease [by]… simultaneously treating both the symptoms and the progression of [the] disease."[3] Investigators at the Salk Institute in 2016 reported similar findings in a series of exploratory studies.[4]

The administration of both THC and synthetic cannabinoid agonists have been shown to influence memory loss in animal models. For example, investigators at Ohio State University's Department of Psychology and Neuroscience reported that older rats administered daily doses of WIN 55,212-2 for a period of three weeks performed significantly better than non-treated controls on a water-maze memory test. Writing in the journal *Neuroscience* in 2005, they reported that rats treated with the compound experienced a 50 percent improvement in memory and a 40-50 percent reduction in inflammation compared to controls.[5] Israeli researchers reported in 2017 that THC administration can reverse age-related memory impairment in rats, and may offer a potential treatment option in patients with dementia and other neurodegenerative illnesses.[6]

Previous preclinical studies have demonstrated that cannabinoids can prevent neuronal cell death.[7] Some experts believe that these neuroprotective properties could play a role in moderating AD.[8] Writing in the *British Journal of Pharmacology* in 2009, investigators at Ireland's Trinity College Institute of Neuroscience concluded, "[C]annabinoids offer a multi-faceted approach for the treatment of Alzheimer's disease by providing neuroprotection and reducing neuroinflammation, whilst simultaneously supporting the brain's intrinsic repair mechanisms by augmenting neurotrophin expression and enhancing

neurogenesis. … Manipulation of the cannabinoid pathway offers a pharmacological approach for the treatment of AD that may be more efficacious than current treatment regimens."[9]

More recently, a 2020 review of the available preclinical literature concluded that cannabinoids possess the ability to mitigate both the neuroinflammation and oxidative stress associated with the onset of AD. Authors concluded: "Targeting the endocannabinoid system can be a promising strategy to develop an effective therapy for the management of AD. Furthermore, cannabinoids may demonstrate a safe and reliable low-cost therapy, with limited side effects. Future research is needed to investigate the use of cannabinoids for the treatment of AD in a clinical trial setting."[10]

Although there are no available human trials assessing the effectiveness of either cannabis or cannabinoids in mitigating the advancement of Alzheimer's disease, a limited number of clinical trials and case studies exist evaluating the impact of both plant and synthetic cannabinoids on certain AD symptoms, such as agitation and anxiety.

For instance, investigators at Berlin's Charite Universitatsmedizin Department of Psychiatry and Psychotherapy reported that daily administration of 2.5 mg of synthetic THC over a two-week period reduced nocturnal motor activity and agitation in AD patients in an open-label pilot study.[11]

Results from a separate study demonstrated that oral administration of up to 10 mg of synthetic THC reduced agitation and stimulated weight gain in late-stage Alzheimer's patients,[12] – a finding that was consistent with previous studies.[13]

In 2016, Israeli researchers assessed the safety and efficacy of THC-infused oil in Alzheimer's patients in a four-week trial. Participants experienced decreased incidences of delusions, agitation, irritability, and apathy following treatment. Their quality of sleep also improved. "Adding medical cannabis oil to AD patients' pharmacotherapy is safe and a promising treatment option," investigators concluded.[14] A 2018 placebo-controlled trial similarly reported that AD-related agitation was reduced significantly in patients taking nabilone.[15]

Most recently, a series of case reports published in the journal *Neurodegenerative Disease Management* documented the use of cannabis products in elderly patients with dementia. Authors reported that a 69-year-old patient showed improved mood and reduced impulsivity following the twice daily use of cannabis. In addition, a 63-year-old patient exhibited reduced irritability and anxiety after initiating the use of CBD three times a day. That subject was able to discontinue the use of alprazolam. The subject also reported improved sleep following the use of THC at night. Finally, a 65-year-old subject exhibited reduced anxiety and better chronic pain management following the use of cannabis. They concluded, "In the absence of clear evidence-based treatments for these symptoms, use of CBD may be useful in improving symptoms among these patients."[16]

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