Medical Marijuana and Parkinson’s Disease

Given limited treatments available, investigating potential benefits of cannabinoids can offer cautious optimism over controversy.

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Although new therapeutics are often the topic of debate and controversy amongst medical professionals, the fervor of debate regarding use of medical marijuana is more so. That is likely the result of society’s familiarity with marijuana, which may be quite familiar to some patients.

Making therapeutic medicines out of plants was the birth of pharmacology and has been done for millennia, yet harnessing what is truly therapeutic, removing what is not while keeping the compound effective is the very essence of the controversy. We are in the moment of finding out if this can be done for marijuana as it segues into the medical realm.

A recent increase in medical marijuana distribution centers across the US has reignited the conversation in the media and politics. Parkinson’s disease (PD) is one of the qualifying conditions for medical marijuana eligibility in many states. However, clinical studies investigating the effectiveness of marijuana for the treatment of motor and nonmotor symptoms in patients with PD are sparse and primarily observational. As such, results are inconclusive and frustrating for both patient and provider.

Clinical Studies

Many studies examining the efficacy of marijuana in PD are limited to questionnaires and observation in patients actively consuming marijuana either prescribed or recreational marijuana. In studies published to date, patients who had at least 3 months of treatment with marijuana used self-report to quantify any changes in their motor and nonmotor symptoms. A majority of patients treated with marijuana reported improvement in overall symptoms, specifically reduction of tremor, muscle stiffness, and pain, and improvement of depressed mood. Worsening of attention, memory, and urination were also reported, and a large percentage of patients reported having at least one adverse event including confusion, anxiety, hallucinations, amnesia, psychosis, a psychotropic event, cough, dizziness, unsteadiness, and breathlessness.

Additional studies listed in the Table have similar outcomes including improvement in tremor, rigidity and bra-

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>STUDY DESIGN</th>
<th>RESULTS</th>
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<tbody>
<tr>
<td>Balash 2017</td>
<td>Observation/questionnaire</td>
<td>82% reported improvement in overall symptoms</td>
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<td></td>
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<td>73% reduced tremor</td>
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<td></td>
<td></td>
<td>72% reduced muscle stiffness</td>
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<td></td>
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<td>81% reduced pain</td>
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<td></td>
<td>77% elevated mood</td>
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<td>60% reported at least 1 adverse event</td>
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<tr>
<td>Lotan 2014</td>
<td>Observation/UPDRS and pain self-reports</td>
<td>Clinical improvement in tremor, rigidity, bradykinesia, and reduced pain</td>
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<tr>
<td>Kindred 2017</td>
<td>Questionnaire</td>
<td>Elevated mood</td>
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<tr>
<td>Shohet 2017</td>
<td>Quantitative pain scales</td>
<td>Reduced pain, reduced tremor</td>
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Abbreviation: UPDRS, Unified Parkinson’s disease rating scale.

PD is a qualifying condition for the use of medical marijuana in CT, FL, GA, IL, MA, NH, NM, OH, PA, VT, and WV.
dykesia, reduced pain, and elevated mood. Interestingly, 1 study found a reduction in pain following treatment delivery via smoking marijuana versus ingesting it as a vapor.

The symptoms that improved in these studies are notable because when they are difficult to control with conventional treatment, we have few options left. Hard to control tremor, for example, may be treatable only with surgery, which is not an option for every patient. Hard to control pain is not unique to patients with PD; however, using stronger pain medications may not be possible due to cognitive and digestive side effects of these medications. Depression is profoundly common and affects disease progression and quality of life in ways that are difficult to overstate. Effective treatment for these nonmotor symptoms currently is suboptimal.

**Molecular Mechanisms**

The impact marijuana has on motor and nonmotor symptoms of PD may be modulated by the dopaminergic, adrenergic, serotonergic, and neuroprotective properties of cannabinoids. Tetrahydrocannabinol or THC and cannabidiol are the two major components of marijuana and are ligands for cannabinoid receptors found in the brain. THC is the primary psychoactive compound that causes the euphoric “high” feeling associated with marijuana consumption.

**Cannabinoid Receptors**

There are 2 known cannabinoid receptors, CB1 and CB2, that have been cloned and well-studied. CB1 is one of the most abundant G-protein–coupled receptors in the central nervous system found in high concentrations on noradrenergic neurons in the basal ganglia, specifically the caudate putamen, substantia nigra, globus pallidus, hippocampus, and molecular layer of the cerebellum. This specific localization of CB1 may explain the impact of marijuana on cognitive and motor activity. CB1 receptors are found in peripheral immunocompetent cells and lymphoid organs and at smaller concentrations in the CNS. CB2 receptors have been found to modulate microglia activation and may play a role in neuroinflammation/neuroprotection.

**Motor Symptoms**

Loss of dopaminergic neurons in the substantia nigra is a hallmark of PD and causes motor symptoms of PD, including resting tremor, bradykinesia, rigidity, and postural instability. Loss of upstream noradrenergic neurons (norepinephrine-containing cells) that innervate dopaminergic neurons causes parkinsonian-like effects in animal models. Effects of medical marijuana on tremor and motor symptoms is likely through effects on dopaminergic and noradrenergic transmission at some level. Although dopaminergic neurons have no cannabinoid receptors, molecular studies suggest modulation of dopaminergic neurons occurs in response to cannabinoids.

In the basal ganglia, excitatory and inhibitory neurotransmission is mediated by corticostriatal projections to the thalamus via the direct and indirect striatofugal pathways. CB1 receptors are found throughout this pathway, and stimulation of this pathway affects dopaminergic transmission in the dorsal striatum. Animal studies suggest the reverse is true in that denervation of dopaminergic neurons effects endocannabinoid transmission, leading to faulty striatal plasticity. Therefore, in the case of PD, in which there is impaired striatal plasticity, reciprocal interactions between cannabinoid and dopaminergic systems may respond to marijuana exposure in the same way that dopaminergic neurons respond to levodopa.

**Nonmotor Symptoms**

Pain is a well-known nonmotor symptom in PD and may be peripheral (musculoskeletal pain) and/or central (nerve pain). The transient receptor potential (TRP) channel family is known to have a role in inflammatory and thermal pain processing, and TRPV1 channels are expressed in the striatum, globus pallidus, and substantia nigra. Endogenous cannabinoids activate TRPV1. Specifically, in the substantia nigra, TRPV1 activation increases the frequency of excitatory postsynaptic currents of dopaminergic neurons. Cross-talk between TRPV1 receptors and dopaminergic neurons was seen in an animal study that showed TRPV1 agonists protect striatal dopaminergic neurons from oxidative stress. A second preclinical study suggests that activation of TRPV1 on astrocytes contributes to an endogenous neuroprotective machinery that may be a therapeutic avenue in PD.

Neuroinflammation and oxidative stress, which cause neuronal cell death, occur in many neurological conditions such as depression, dementia, and headache. These conditions share symptom profiles with the nonmotor symptoms of PD, namely depressed mood, agitation, pain, and cognitive disturbances. Microglia are the immune cells of the brain and are known to be activated by oxidative stress and oxidative damage. Microglia cells have both damaging (M1) and protective (M2) phases of activation, and studies have found that CB2 can modulate this activity. As the microglia activation cycle is likely perturbed in PD, there may be potential for marijuana to reduce oxidative stress and ameliorate the nonmotor symptoms of PD.

**Conclusions**

While these studies and possible molecular mechanisms are promising, a major limitation is the lack of a placebo control. Most studies are observational and rely heavily on self-reported measures of improvement. Route of ingestion also causes an interesting problem. Traditionally, recreational marijuana is smoked, which causes significant variability in

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dosage. Regulations for medical use vary by state, and some states restrict specific forms of ingestion. Since a few studies have reported that smoked marijuana is more effective on pain and tremor compared to vaporized ingestion, this poses a large hurdle for clinicians and researchers.

Although the existing evidence presented here is not directly useful in the clinic today, it does show that there is rationale to consider the use of medical marijuana in PD from a mechanistic point of view. When patients come in to clinic asking, “Would marijuana be helpful for me?” awareness of the molecular mechanisms of marijuana metabolites in the brain can help the clinician to give a well-considered answer. Keeping the perspective that PD is a neurodegenerative condition with limited treatments available, investigating a new one that has potential broad-spectrum applications offers cautious optimism over controversy.


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