Research News

Modest Evidence for Benefit in Studies of Cannabis in MS

While several dozen studies have been conducted into cannabis-based treatments for symptoms of multiple sclerosis (MS), a new systematic review deems most to be of fair to poor quality. Reviewers found modest evidence of benefit and plenty of room for more research.

"Cannabis-based medicine may be useful for refractory MS symptoms, especially spasticity and pain, and side effects are usually well tolerated," study lead author Natasha Breward, a graduate student at the College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, said in an interview. Breward spoke prior to the presentation of the study findings at the 2019 meeting of the Consortium of Multiple Sclerosis Centers.

For the review, Breward and colleagues focused on 60 studies—26 randomized controlled trials and 34 trials with other designs. Forty of the studies used nabiximols, an oromucosal spray that is derived from the cannabis sativa plant and approved for use in multiple countries but not yet in the US.

According to Breward, some of the other treatments included dried cannabis that is smoked or eaten and cannabidiol that's typically delivered with tetrahydrocannabinol (THC) either oromucosally or as an oral capsule.

MS symptoms treated in the studies included spasticity (n = 29), pain (n = 8), and cognition (n = 6). The researchers considered 22 studies to be poor quality, 14 to be fair quality, and 24 to be good/excellent quality.

The researchers found that the cannabis-based medicine "significantly reduced spasticity and pain in several individual good-quality studies," Breward said. The drugs seem to work by inhibiting neurotransmitter release via cannabinoids. "However, the variability in study quality—and in the products and regimens studied—make it hard to draw any conclusions about specific products and doses that may have the most potential benefit," she added.

"Further research should focus on the use of different products and formulations of cannabis-based medicine such as cannabis oil and cannabidiol-prominent products, as no studies have focused on this area," she said. "Research should also look at the potential of cannabis-based medicine for the treatment of disease progression, as cannabinoids are anti-inflammatory and immunomodulatory. Finally, more research regarding the potentially synergistic effects of cannabis-based medicine administered with current MS medications would also be useful."

Randy Dotinga, MDedge.com/neurology

Brain Volumes After TBI Correlate With Clinical Features

Brain volumes of specific regions of interest can be used to classify traumatic brain injury subjects that fall into predetermined symptom categories, according to a study presented at the annual meeting of the American Academy of Neurology.

Traumatic brain injury (TBI) damages brain tissue and causes subsequent volume loss, which may result in clinical symptoms. It is a prevalent worldwide health problem caused by a mechanical insult to the head, resulting in transient or permanent alteration to brain tissue and/or function. Standard neuroimaging with computed cranial tomography (CT) and structural magnetic resonance imaging (MRI) is often unrevealing during the evaluation of patients with TBI, particularly those classified as mild TBI.

In this study, James Rock, MD, of Penn Presbyterian Medical Center and the University of Pennsylvania, and colleagues sought to examine the value of quantitative analysis of regional brain volumes in the evaluation of TBI. The investigators reviewed the medical records and MRI imaging from 44 patients with TBI evaluated at a Level I trauma center. They also read clinical notes to assess reported symptoms and physical findings.

Regional volumes from TBI subjects were derived using the software package Freesurfer image analysis suite (surfer.nmr.mgh.harvard.edu), which utilizes a T1-weighted structural scan to calculate volumetric information. A machine learning algorithm, random forests, was employed across volume measurements from 25 regions of interest to determine the most important regions for classifying subjects based on clinical outcome and symptomology.

Basal ganglia volume showed the highest variable importance with regards to classifying subjects who exhibited symptoms of cognitive dysfunction in quantitative analysis. Left lateral ventricle volume was important in classifying

subjects with motor and vestibular alterations. Left choroid plexus volume was the most important region for classifying subjects with sensation and somatic dysfunction.

In an abstract, the researchers noted that their study is ongoing. "It will be extended to a larger cohort to determine whether volume changes in specific [regions of interest] can act as useful clinical biomarkers for chronic symptoms," they said.

Dr. Diaz-Arrastia received personal compensation from Neural Analytics, Inc; BrainBox Solutions, Inc; and Bioscience Pharma Partners. Dr. Diaz-Arrastia holds stock and/or stock options in Neural Analytics, Inc and has received research support from BrainBox Solutions. The other authors reported no other disclosures.

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What Other Drugs Do Patients Take When They Start MS Therapy?

Concomitant medication use is common when patients with multiple sclerosis (MS) start disease-modifying drugs (DMDs), according to research presented at the 2019 meeting of the Consortium of Multiple Sclerosis Centers. The likelihood of particular comorbidities and concomitant medications varies by age and sex, researchers reported.

"This may have implications for MS treatment," said study author Jacqueline Nicholas, MD, MPH, of Ohio Multiple Sclerosis Center in Columbus and colleagues. "A better understanding of the effects of comorbidities and concomitant medications on the effectiveness and safety of DMDs is needed to support clinical decision making."

Researchers have examined comorbidities in patients with MS, but concomitant medication use among patients starting DMDs is poorly understood, the authors said.

To study this question, Dr. Nicholas and colleagues analyzed retrospective administrative claims data from IQVIA Real-World Data Adjudicated Claims–US database from Jan. 1, 2010, to June 30, 2017. Their analysis included patients with ≥ 2 MS diagnosis claims and at least 1 DMD claim between Jan. 1, 2011, and June 30, 2015. Eligible patients were aged 18 to 63 years and had continuous eligibility with commercial insurance 1 year before and 2 years after DMD initiation. In addition, patients had no evidence of DMD use during the 1-year baseline period.

The investigators used International Classification of Diseases, 9th and 10th revisions, Clinical Modification codes and claims to evaluate patients' comorbidities and concomitant medications during the study period.

The researchers identified 8,251 eligible patients. Patients had a mean age of 43.2 years, and 75.5% were female. Average baseline Charlson Comorbidity Index was 0.41. In the 2 years after DMD initiation, common comorbid diagnoses were hyperlipidemia (30.0%), hypertension (28.2%), gastrointestinal disorders (26.2%), depression (25.5%), and anxiety (20.1%).

Common concomitant medications included antibiotics (70.6%); analgesics (57.0%); corticosteroids (52.0%); antidepressants (47.7%); anticonvulsants (46.7%); anxiolytics, sedatives, or hypnotics (43.2%); spasticity medications (36.2%); and muscle relaxants (35.4%).

Most comorbidities and many medications, including bladder and antifatigue medications, were more common among patients aged ≥ 55 years. Hyperlipidemia, hypertension, and diabetes mellitus were more likely in males than in females. Females were more likely to have gastrointestinal disease, depression, thyroid disease, anxiety, lung disease, and arthritis. In addition, females were more likely than males to use many of the concomitant medications.

Dr. Nicholas disclosed grant support from EMD Serono. A coauthor is an employee of Health Services Consulting Corporation and received funding from EMD Serono to conduct the study. Other coauthors are employees of EMD Serono.

Jake Remaly, MDedge.com/neurology

Depression, Fatigue, Pain, and Anxiety Are Common in the Year After MS Diagnosis

In the 12 months after diagnosis, pain, fatigue, depression, and anxiety are common among patients with multiple sclerosis (MS), researchers reported at the 2019 meeting of the Consortium of Multiple Sclerosis Centers. In a novel study, about half of patients with MS reported clinically significant symptoms of depression or pain, and about 60% reported fatigue during that time.

Pain, fatigue, depression, and anxiety are common in MS, but their prevalence in the first year after diagnosis is not well understood. To examine the rates of these conditions and how often they co-occur during that period, Anna L. Kratz, PhD, associate professor of physical medicine and rehabilitation at the University of Michigan in Ann Arbor, and her research colleagues had 231 adults with MS complete validated surveys at 1, 2, 3, 6, 9, and 12 months after diagnosis to assess symptoms of these conditions.

Overall, 47.2% of patients reported clinically significant levels of depression, 38.5% reported clinically significant levels of anxiety, 50.4% reported clinically significant pain, and 62.2% reported clinically significant fatigue at any point during the year after diagnosis. "Of those who did not have clinically significant symptoms at time of diagnosis, 21.3% went on to develop clinically significant depression, 17.0% anxiety, 30.9% pain, and 34.1% fatigue," the authors reported.

About 23% of patients did not have clinically significant symptoms for any condition, while 20% had clinically significant symptoms for 1 condition, 21% for 2, 19% for 3, and 17% for all 4. Depression and fatigue had the highest rate of comorbidity, whereas pain and anxiety had the lowest rate of comorbidity.

"Important clinical symptoms associated with MS are present at high levels in the first year post diagnosis," Dr. Kratz and colleagues concluded. "While the rates and severity are marginally lower than have been identified in studies of individuals farther into the MS disease course, this study is a reminder that early MS intervention should incorporate interventions for these symptoms that are known to have strong associations with quality of life."

The researchers had no disclosures.

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Experts Propose New Definition and Recommendations for Alzheimer-like Disorder

An international group of experts has proposed a new name, staging criteria, and recommendations for a recently recognized brain disorder that mimics Alzheimer disease and is marked by a proteinopathy caused by malformed transactive response DNA-binding protein of 43 kDa (TDP-43).

The term *limbic-predominant age-related TDP-43 encephalopathy* (LATE) was coined in an effort to raise awareness and kick-start research into this "pathway to dementia," the experts wrote in a report appearing in *Brain*. "As there is currently no universally agreed-upon terminology or staging system for common age-related TDP-43 proteinopathy, this condition is understudied and not well recognized, even among investigators in the field of dementia research," wrote the authors of the report, led by Peter T. Nelson, MD, PhD, of the University of Kentucky, Lexington.

LATE neuropathologic changes, associated with a progressive amnesia syndrome that mimics Alzheimer, are seen in > 20% of individuals aged > 80 years, according to large, community-based autopsy series. It coexists with Alzheimer disease in many patients, lowering the threshold for developing dementia, authors said.

The term LATE is designed to encompass several other terms related to TDP-43 pathology, including hippocampal sclerosis and cerebral age-related TDP-43 with sclerosis, Dr. Nelson and colleagues noted.

The TDP-43 protein is encoded by the TARDBP gene and provides several functions related to the regulation of gene expression, the authors wrote.

Misfolded TDP-43 was known to play a causative role in amyotrophic lateral sclerosis and frontotemporal lobar degeneration, the authors noted, and then was also identified in the brains of older individuals with hippocampal sclerosis or Alzheimer disease neuropathologic changes.

The authors proposed a 3-stage classification system for LATE neuropathologic change based on TDP-43 immunohistochemistry performed during routine autopsy evaluation of the amygdala, hippocampus, and middle frontal gyrus. The amygdala is an area affected early in the course of the disease (Stage 1), whereas involvement of the hippocampus represents a more intermediate stage (Stage 2), and the middle frontal gyrus is more affected in advanced stages of the disease (Stage 3), according to the schema.

Five genes have been identified with risk alleles for LATE neuropathologic changes, authors said. Of note, several groups have found that the apolipoprotein E ∑ 4 allele, known to be a risk factor for Alzheimer disease neuropathologic changes and Lewy body disease, is also linked to increased risk of TDP-43 proteinopathy.

There are no established biomarkers specific to TDP-43 proteinopathy yet, which hampers development of clinical trials designed to test interventions to treat or prevent LATE, Dr. Nelson and colleagues said in their report. LATE also could obscure the effects of potentially disease-modifying agents being tested in Alzheimer disease clinical trials, which can complicate the interpretation of study results, they added.

"Until there are biomarkers for LATE, clinical trials should be powered to account for TDP-43 proteinopathy," they wrote. Dr. Nelson and coauthors reported no author disclosures.

Source: Nelson PT, Dickson DW, Trojanowski JQ, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. *Brain*. 2019;142(6):1503-1527.

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