Evidence for the use of "medical marijuana" in psychiatric and neurologic disorders

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Abstract

Introduction: Cannabis is listed as a Schedule I substance under the Controlled Substances Act of 1970, meaning the US federal government defines it as an illegal drug that has high potential for abuse and no established medical use; however, half of the states in the nation have enacted "medical marijuana" (MM) laws. Clinicians must be aware of the evidence for and against the use of MM in their patients who may consider using this substance.

Methods: A PubMed database search was performed using the text string: "Cannabis"[Mesh] OR "Marijuana Abuse"[Mesh] OR "Medical Marijuana"[Mesh] OR "Marijuana Smoking"[Mesh] OR "cannabi*" OR "tetrahydrocannabinol." The search was further limited to randomized clinical trial publications in English on human subjects to identify articles regarding the therapeutic use of phytocannabinoids for psychiatric and neurologic disorders. Commercially available products (ie, dronabinol, nabilone, nabiximols) and synthetic cannabinoids were excluded from the review.

Results: Publications were identified that included patients with dementia, multiple sclerosis, Parkinson disease, Huntington disease, schizophrenia, social anxiety disorder, depression, tobacco use disorder, and neuropathic pain.

Discussion: There is great variety concerning which medical conditions are approved for treatment with MM for either palliative or therapeutic benefit, depending on the state law. It is important to keep an evidence-based approach in mind, even with substances considered to be illegal under US federal law. Clinicians must weigh risks and benefits of the use of MM in their patients and should ensure that patients have tried other treatment modalities with higher levels of evidence for use when available and appropriate.

Keywords: medical marijuana, marijuana, phytocannabinoids, cannabinoids, delta-9-tetrahydrocannabinol, tetrahydrocannabinol, THC, cannabidiol, CBD, therapeutic uses of illicit substances

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Introduction

Although medical marijuana (MM) laws[1] have been enacted in half of the United States, marijuana is still classified as a Schedule I substance under the Controlled Substances Act of 1970. Schedule I substances are considered to have a high potential for abuse and no established medical use. Clinicians must be aware of the evidence for and against the use of MM in their patients who ask for authorization to use this substance. When reviewing evidence it is important to take into account what formulation was studied because outcomes have varied considerably based on this factor alone. Some studied forms of MM included oral cannabis extract (OCE), which is typically a pill or capsule made by extracting phytocannabinoids (eg, Δ-9-tetrahydrocannabinol [Δ-9-THC] and cannabidiol [CBD]) from whole-plant cannabis, vaporized or smoked cannabis (cannabinoids are expressed in terms of % concentration), synthetic THC (ie, dronabinol), and other commercially available products

(eg, nabiximols, which is a sublingual form of OCE containing THC and CBD). It is important to mention that some states only allow for certain formulations of MM to be dispensed (eg, New York state only allows for OCE and oil for vaporization, whereas other state laws allow for the purchase of whole-plant cannabis).[2] Notably, onset of action varies substantially depending on route of administration and dosage form; intravenous administration and inhalation have the fastest onset of action and greatest bioavailability, oral administration is subject to first-pass metabolism and reduced bioavailability, and oromucosal routes reduce first-pass metabolism, which increases bioavailability.[3]

Methods

A PubMed database search was performed using the text string: "Cannabis"[Mesh] OR "Marijuana Abuse"[Mesh] OR "Medical Marijuana"[Mesh] OR "Marijuana Smoking"[Mesh] OR "cannabi*" OR "tetrahydrocannabinol." The search was further limited to randomized clinical trial publications in English on human subjects to identify articles regarding the therapeutic use of phytocannabinoids for psychiatric and neurologic disorders. Commercially available products and synthetic cannabinoids were excluded from the review because they are reviewed elsewhere and are unique, patented formulations only available in specific dosage forms.[4] The initial search returned 1507 publications (titles/abstracts of which were reviewed by the author), of which 23 were identified for inclusion based on the criteria outlined above. If a disease state had only one negative published trial, it was included in the Table but excluded from the results.

Results

Multiple Sclerosis

Multiple sclerosis (MS) is the only disease state discussed herein for which there is an approved, commercially available product (Sativex® [nabiximols]), which is marketed in 15 countries outside of the United States—studies using this formulation were not included in this review; however, many noncommercial formulations have been evaluated. Small, double-blind, placebo-controlled trials suggested benefit for spasticity based on subjective ratings, which allowed for more rigorous work.[5-8]

The Cannabinoids in MS (CAMS) study (n = 630), the first large trial of MM for MS, was a multicenter, randomized, 15-week, double-blind, placebo-controlled trial comparing OCE to dronabinol and placebo.[9] The primary outcome of the study was change in spasticity as rated by the Ashworth Scale score; notably, this scale is no longer recommended for spasticity assessment.[9] Results showed that the difference in mean reduction of the Ashworth Scale was not significant for either active treatment versus placebo. Various secondary outcomes were assessed (Table). The only outcome that reached statistical significance was patient-reported measures of spasticity, pain, sleep, and spasms. The authors point out that some patients and doctors became unmasked in the active treatment groups, but the assessors did not. This study suggested that some patient-reported benefits may be seen after 15 weeks of therapy, keeping in mind that these were subjective data being reported by potentially unmasked patients.

A randomized, double-blind, placebo-controlled, crossover study was conducted in 57 patients at a rehabilitation center in Switzerland.[10] The study compared OCE to placebo, which were dosed up to 12 capsules per day, divided to 3 times per day. Similar to the CAMS study, the primary outcome was the total Ashworth Scale score. There were numerous secondary outcomes. Results showed that there was no statistically significant difference in primary or secondary outcome measures for the intention-to-treat analysis set. For the 37 patients who completed the study per protocol (ie, 90% adherence), improvements in spasm frequency ($P = .013$) and in mobility ($P = .01$) were seen after excluding 1 patient who fell in the placebo phase of the study.

A 12-month follow-up to the CAMS study was also completed.[11] Ashworth Scale score reductions from baseline to end point were 1.82 (95% confidence interval [CI], 0.53 to 3.12) for dronabinol, 0.10 (95% CI, −0.99 to 1.19) for OCE, and −0.23 (95% CI, −1.41 to 0.94) for placebo; $P = .04$. Although statistical significance was realized only for the dronabinol group, the clinical significance of this finding remains unclear. There were no significant findings regarding any secondary outcome. Objective benefits were only observed for the dronabinol group, but the study suggested that patient-reported benefits of OCE may be maintained for up to 1 year.

All patients who were recruited for the original CAMS study were assessed for urge incontinence episodes.[12] The primary outcome was a reduction in urge incontinence episodes based on a 3-day urinary diary. Oral cannabis extract reduced urge incontinence episodes by 25% ($P = .005$) and dronabinol by 19% ($P = .039$) relative to placebo. Although there was a lack of improvement in bladder function in the main CAMS study, this publication suggested that cannabinoids may have a clinical effect on lower urinary tract symptoms.

The MS and Extract of Cannabis trial (n = 279) was a multicenter, randomized, 12-week, double-blind, placebo-controlled study comparing OCE to placebo.[13] The study was a follow-up to the CAMS study, and the primary

outcome was an 11-point category rating scale to measure perceived change in muscle stiffness from baseline to end point, where 0 = very much better, 5 = no difference, and 10 = very much worse. A clinically relevant response to the medication, or "relief of muscle stiffness," was defined as a category rating scale score of 0 to 3. Multiple secondary outcomes were assessed (Table). Results showed that 29.4% of patients on OCE achieved "relief of muscle stiffness" versus 15.7% of patients on placebo (OR, 2.26; 95% CI, 1.24 to 4.13; $P = .004$).

Parkinson Disease

The first randomized, double-blind, placebo-controlled trial of OCE in Parkinson disease (PD) was a 10-week crossover study of 18 patients with levodopa-induced dyskinesia.[14] Primary outcome was the Unified Parkinson's Disease Rating Score (UPDRS) questions 32 to 34 (pertaining to dyskinesias) score sum change from baseline to end point. There was no significant difference between active medication and placebo on the primary or secondary outcomes. Notably, 71% of patients correctly identified treatment.

Another randomized, double-blind, placebo-controlled trial of OCE in PD was a 6-week study of 21 patients that compared CBD 75 mg and CBD 300 mg to placebo.[15] Outcome measures in this study were the UPDRS, the Parkinson Disease Questionnaire-39 (PDQ-39—a validated self-rated scale that provides a detailed look at clinically significant outcomes like mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and physical discomfort), and the Udvalg for Kliniske Undersøgelser side effect rating scale. There were no differences on the UPDRS or the Udvalg for Kliniske Undersøgelser side effect rating scale between the active treatment groups and placebo. Significance was realized on the PDQ-39 total score, which saw a significantly greater change on CBD 300 mg versus placebo ($P = .05$).

Social Anxiety Disorder

A preliminary double-blind, placebo-controlled crossover study comparing a single dose of CBD (400 mg) to placebo was conducted in 10 treatment-naive men with generalized social anxiety disorder who were ages 20 to 33 years and without comorbid psychiatric disorders.[16] The single-photon emission computed tomography (SPECT) imaging procedure was used as the anxiety-provoking stimulus. Participants rated their anxiety using the Visual Analogue Mood Scale (VAMS). The VAMS in this study consisted of 16 items, grouped into 4 factors (ie, anxiety, mental sedation, physical sedation, and "other feelings/attitudes") and was measured at −30 minutes (predrug), 0 minutes (dosing time and prestress), 60 minutes (venous

cannula insertion), 75 minutes (pre-SPECT), and 140 minutes (poststress). Results showed that CBD significantly reduced VAMS scores versus placebo on the anxiety factor at times 60, 75, and 140 minutes ($P < .001$). Measures of physical sedation, mental sedation, and "other feelings/attitudes" in patients on CBD were not significantly different from those on placebo; this speaks to the lack of appreciable side effects of CBD in this patient population. In addition, this study showed that CBD had a significant effect on increased brain activity in the right posterior cingulate cortex (measured by Tc-ECD SPECT imaging; $P < .001$), which is thought to be involved in the processing of emotional information.

Another study[17] investigating the use of CBD was conducted in treatment-naive patients with social anxiety disorder (n = 24). The patients were randomized to receive either CBD 600 mg (n = 12) or placebo (n = 12) prior to a Simulated Public Speaking Test (SPST). The SPST, an experimental model for anxiety induction, is thought to have predictive validity in social anxiety disorder because fear of public speaking is a hallmark feature of the illness. The two groups received active treatment or placebo 1.5 hours before the SPST began; measurements on the VAMS and Negative Self-Statements during Public Speaking scale (SSPS-N) were taken over the course of the SPST in all 3 groups. The VAMS was employed to measure anxiety, sedation (ie, mental sedation), cognitive impairment (ie, physical sedation), and discomfort (ie, "other feelings/attitudes"). The CBD group had significantly lower scores than the placebo group during the speech (S) phase on the VAMS anxiety ($P = .012$), cognitive impairment ($P = .009$), and discomfort ($P = .029$) factors. The VAMS sedation factor score was significantly lower on CBD versus placebo at the anticipatory (A) phase ($P = .016$). Regarding the SSPS-N, comparisons showed significant differences between CBD and placebo at the A phase ($P = .043$) and during the S phase ($P = .001$). Some have suggested that CBD's anxiolytic action may be mediated by the 5-HT$_{1A}$ receptors, because it was shown to displace the agonist [3H]8-OHDPAT from cloned human receptors in a concentration-dependent manner; CBD also acts at an agonist at 5-HT$_{1A}$ in signal transduction studies.[18]

Schizophrenia

The first study[19] of using THC in patients with schizophrenia was a 3-day, randomized, double-blind, placebo-controlled study of intravenous THC (doses 2.5 and 5 mg) versus placebo. Patients were stable and were currently taking antipsychotic medication. Results showed that THC significantly increased learning and recall deficits, positive and negative symptoms, general psychopathology, perceptual alterations, akathisia, rigidity, dyskinesia, deficits in vigilance, and plasma prolactin and cortisol levels. The

TABLE: Randomized trials of medical marijuana in psychiatric and neurologic disorders

Study or Condition/Source, y	No. of Participants	Cannabinoid Formulation/Dose	Outcomes	Results/Conclusion
CAMS Study/ Zajicek et al,[9] 2003	630	OCE (Δ9-THC 2.5 mg/ CBD 1.25 mg per capsule) versus dronabinol (synthetic Δ9-THC 2.5 mg per capsule) versus placebo	Primary: Change in spasticity measured by the Ashworth Scale	For both active medication groups, significant improvements were only seen in the subjective "category" rating scales of spasticity, pain, sleep, and spasms. This study suggested that some patient-reported benefits may be seen after 15 weeks of therapy.
		(Weight-based dosing; maximum of Δ9-THC 25 mg/d divided B.I.D.)	Secondary: Kurtzke EDSS, Rivermead Mobility Index, timed 10-m walk, United Kingdom Neurological Disability Score, BI, General Health Questionnaire, 9 "category" rating scales, and questions about overall effect of the medication	
MS/Vaney et al,[11] 2004	57 (Crossover)	OCE (Δ9-THC 2.5 mg/ CBD 0.9 mg per capsule) versus placebo	Primary: Change in total Ashworth Scale score	No difference in any primary or secondary outcome in the intention-to-treat population. Improvements in spasm frequency and mobility were seen in the active medication group after excluding a patient who fell in the placebo phase.
		(Weight-based dosing; maximum of Δ9-THC 30 mg/d divided T.I.D.)	Secondary: Numerous	
CAMS Study, 12-month follow-up/Zajicek,[12] 2005	630	Continuation of CAMS Study; see above	Primary: Change in spasticity measured by the Ashworth Scale	Primary outcome significant for the dronabinol group only. As in the original CAMS Study, ratings of spasticity, pain, sleep, and spasms improved on both active treatments versus placebo. This study suggested that some patient-reported benefits may be maintained for up to 1 year of therapy.
CAMS LUTS Study/Freeman et al,[13] 2006	630	Continuation of CAMS Study; see above	Primary: Reduction in UIEs based on a 3-day urinary diary from baseline to week 13	OCE reduced UIEs by 25% (P = .005) and dronabinol reduced UIEs by 19% (P = 0.039) relative to placebo. This study suggested that cannabinoids may have a clinical effect on LUTS.
The MS and Extract of Cannabis Trial/ Zajicek et al,[10] 2012	279	OCE (Δ9-THC 2.5 mg/ CBD [range, 0.8-1.8 mg] per capsule) versus placebo	Primary: 11-point CRS of improvement in spasticity where 0 = very much better, 5 = no change, and 10 = very much worse; clinically relevant "relief of muscle stiffness" = 0-3	29.4% of patients in the OCE group achieved "relief of muscle stiffness" versus 15.7% in the placebo group. Patients in the OCE group also saw improved muscle spasms and sleep disturbances, absolute measurements of body pain and muscle stiffness, MSSS-88 measures of muscle stiffness, spasms, and effect of spasticity on body movement, and MSWS-12 total score.
		(Weight-based dosing; maximum of Δ9-THC 25 mg/d divided B.I.D.)	Secondary: 11-point CRS of body pain, muscle spasms, sleep disturbance; absolute measures of spasticity, body pain, muscle spasms, sleep disturbance; MSSS-88; MS Impact Scale-29; MSWS-12, and the EDSS	

Study or Condition/Source, y	No. of Participants	Cannabinoid Formulation/Dose	Outcomes	Results/Conclusion
Parkinson disease/ Carroll et al,[14] 2004	18 (Crossover)	OCE (Δ9-THC 2.5 mg/ CBD 1.25 mg per capsule) versus placebo (Weight-based dosing of 0.25 mg/kg Δ9-THC)	Primary: UPDRS questions 32-34 score sum change from baseline to end point	Placebo performed better than OCE as measured by UPDRS questions 32-34 (P = .09, not significant).
Parkinson disease/ Chagas et al,[15] 2014	21	CBD 75 mg and CBD 300 mg versus placebo	Primary: UPDRS, PDQ-39, Udvalg for Kliniske Undersøgelser side effect rating scale	CBD 300 mg significantly improved PDQ-39 total score versus placebo (P = .05). Additionally, improvements were also seen on 2 subscales of the PDQ-39 (ADL and stigma), both P < .05. No differences were realized for any other outcome measure.
Social anxiety disorder/Crippa et al,[16] 2011	10	CBD 400 mg versus placebo	Subjective ratings of anxiety and side effects by VAMS consisting of 16 items, grouped into 4 factors (ie, anxiety, mental sedation, physical sedation, and "other feelings/attitudes") (Head-imaging procedure was the anxiety-provoking stimulus)	CBD significantly reduced VAMS scores versus placebo on the anxiety factor at various times throughout the anxiety-provoking stimulus without demonstrating appreciable side effects.
Social anxiety disorder/ Bergamaschi et al,[17] 2011	24	CBD 600 mg versus placebo	VAMS anxiety, sedation, cognitive impairment, and discomfort; SSPS-N; BSS. (SPST was the anxiety-provoking stimulus)	The CBD group had significantly lower scores during the speech phase of the SPST on VAMS anxiety, cognitive impairment, and discomfort. Significant differences were also realized on the SSPS-N in favor of the CBD group during the anticipation and speech phases of the SPST. No differences were realized on the BSS.
Schizophrenia/ D'Souza et al,[19] 2005	13	THC 2.5 mg and 5 mg intravenously versus placebo	Hopkins Verbal Learning Test, distractibility and vigilance, verbal fluency, PANSS, feeling states, extrapyramidal symptoms, and effects on prolactin and cortisol	THC significantly worsened symptoms as measured by all end points compared with placebo.
Schizophrenia/ Leweke et al,[20] 2012	42	CBD versus amisulpride (Both titrated to 800 mg/d)	Primary: Brief Psychiatric Rating Scale and PANSS scores	Both treatments reduced symptoms as measured by the PANSS by ~30 points from baseline. Additionally, there was no difference in % responders (ie, ≥20% reduction in PANSS) between either group; P = 1.0. Noninferiority could not be demonstrated.

Study or Condition/Source, y	No. of Participants	Cannabinoid Formulation/Dose	Outcomes	Results/Conclusion
Tobacco use disorder/Morgan et al,[21] 2013	24	CBD 400 µg/inhalation versus placebo	Number of cigarettes smoked, VAS craving measure, Tiffany Craving Questionnaire, and side effects using the Mood Rating Scale	Repeated-measures analysis of variance interaction of time $\times$ treatment was not significant ($P = .054$). However, CBD demonstrated a significant reduction in number of cigarettes smoked versus placebo from baseline to end point.
Neuropathic pain/ Wilsey et al,[22] 2008	38 (Crossover)	Cannabis cigarettes (3.5% and 7% THC) versus placebo (Cumulative dose of 9 "puffs" during 2 hours)	VAS pain intensity (0-100)	Versus placebo, cannabis cigarettes significantly reduced pain on the VAS ($\sim$55/100 to $\sim$30/100, $P = .016$).
Neuropathic pain/ Ware et al,[23] 2010	23 (Crossover)	Cannabis smoked in a pipe (2.5%, 6%, and 9.4% THC) versus placebo (Smoked T.I.D. for 5 days, followed by 9-day washouts)	VAS pain intensity (0-10)	Significant difference between placebo and 9.4% THC (0.7-point reduction on average daily pain, $P < .05$). Those using 9.4% THC cannabis versus placebo also reported improved ability to fall asleep easier ($P = .001$), faster ($P < .001$), and were drowsier ($P = .003$).
Neuropathic pain/ Wilsey et al,[24] 2013	39 (Crossover)	Vaporized cannabis (1.29% and 3.53% THC) versus placebo (Administered during 3 study visits; 8-12 puffs per visit [self-titrated])	NNT for 30% pain reduction on VAS pain intensity	NNT = 3.2 for 1.29% THC versus placebo, NNT = 2.9 for 3.53% THC versus placebo.
Neuropsychiatric symptoms of dementia/van den Elsen et al,[36] 2015	50	THC 1.5 mg PO T.I.D.	Primary: Neuropsychiatric Inventory Secondary: Cohen-Mansfield Agitation Inventory, BI, Quality of Life–Alzheimer Disease Scale	No differences in any primary or secondary outcome, tolerated similar to placebo.
Huntington/ Consroe et al,[37] 1991	18	CBD 10 mg/kg PO daily	Primary: Marsden and Quinn's chorea severity	Not effective for chorea, tolerated similar to placebo.
Depression/Kotin et al,[38] 1973	8	THC 0.3 mg/kg PO B.I.D.	15-point "nurse's rating scale," 15-point "patient's rating scale"	Did not produce significant euphoria or an antidepressant response.
Anorexia/Gross et al,[39] 1983	11	THC (maximum 30 mg/d PO) versus diazepam (maximum 15 mg/d PO)	Hopkins Symptom Checklist-90, Goldberg Anorectic Attitude Questionnaire, Goldberg Situational Discomfort Scale, Psychiatric Rating Scale	Neither safe nor effective in the treatment of anorexia nervosa.

Abbreviations: Δ-9-THC = Δ-9-tetrahydrocannabinol; BI = Barthel Index; B.I.D. = two times a day; BSS = Bodily Symptoms Scale; CAMS = cannabinoids in multiple sclerosis; CBD = cannabidiol; CRS = category rating scale; EDSS = Expanded Disability Status Scale; LUTS = lower urinary tract symptoms; MS = multiple sclerosis; MSSS-88 = MS Spasticity Scale; MSWS-12 = MS Walking Scale; NNT = number needed to treat; OCE = oral cannabis extract; PANSS = Positive and Negative Syndrome Scale; PDQ-39 = Parkinson Disease Questionnaire-39; PO = by mouth; SPST = Simulated Public Speaking Test; SSPS-N = Negative Self-Statements during Public Speaking scale; T.I.D. = three times a day; UIE = urge incontinence episodes; UPDRS = Unified Parkinson's Disease Rating Score; VAMS = Visual Analogue Mood Scale; VAS = Visual Analogue Scale.

authors stated that there were no serious short- or long-term adverse events associated with study participation.

The first and only randomized, double-blind, active-controlled, noninferiority trial of OCE in schizophrenia was conducted in Germany in 42 patients who were randomized to receive either CBD or amisulpride (an atypical antipsychotic, established as effective, and used in many non-US countries) during 4 weeks.[20] Only patients with a Brief Psychiatric Rating Scale (BPRS) score ≥36 and a BPRS THOT (thought disorder subscale; ie, grandiosity, suspiciousness, hallucinatory behavior, unusual thought content) score ≥12 were included. Primary outcomes were changes in the BPRS and Positive and Negative Symptom Scale (PANSS) scores during the 28-day treatment period. Patients were then randomized and started on either 200 mg of amisulpride or CBD, increasing to 800 mg/d in 4 divided doses during the first week of the study. Results showed that patients who were treated with amisulpride or CBD showed significant clinical improvement as shown by PANSS total, positive, negative, and general psychopathology score reductions (both reduced PANSS total by ~30 points by day 28). There was also no difference in the proportion of responders (≥20% reduction in PANSS total score) between treatment groups (CBD, 15 of 20; amisulpride, 14 of 19; $P = 1.0$); however, noninferiority was not demonstrated ($P = .27$). Additionally, CBD was associated with fewer extrapyramidal symptoms ($P = .006$), less weight gain ($P = .010$), and lower prolactin increase ($P < .001$), and was well-tolerated. It is important to point out that the lack of a placebo group in this study was a major limitation.

Tobacco Use Disorder

A randomized, double-blind, placebo-controlled study[21] was conducted in 24 cigarette smokers who were randomized to receive either inhaled CBD (n = 12) or placebo (n = 12) for 1 week to test the hypothesis that CBD can reduce nicotine consumption. Cannabidiol or placebo was delivered via a pressurized metered dose inhaler at a dose of 400 μg per depression. Participants were required to text the number of times they used the inhalers per day, the number of cigarettes smoked, and the amount of craving they were experiencing on the VAS craving measure. Craving was also assessed using the Tiffany Craving Questionnaire, and side effects were assessed using the Mood Rating Scale. Repeated-measures ANOVA interaction of time × treatment was not significant ($P = .054$). Cannabidiol demonstrated a significant reduction in cigarettes smoked ($P = .002$) during 1 week, whereas placebo did not (CBD group ~90 to ~55; placebo group ~80 to ~70 cigarettes [numbers estimated from graph; actual numbers not provided]). No significant differences were realized between groups on the Tiffany Craving Questionnaire or the Mood Rating Scale.

Neuropathic Pain

One of the first high-quality trials that evaluated MM in patients with mixed types of neuropathic pain was a randomized, double-blind, placebo-controlled crossover study that included 38 patients.[22] The study compared cannabis cigarettes (3.5% and 7% THC) versus placebo cigarettes (made from the whole plant with cannabinoids extracted). All 3 groups scored an average of about 55/100 on the VAS pain intensity scale prior to treatment. The procedure consisted of three 6-hour experimental sessions. Each experimental session was spaced out by at least 3 days to allow for the metabolism of residual cannabinoids. Results showed that versus placebo, cannabis cigarettes significantly reduced pain on the VAS (0.0035-point decrease per minute; from ~55 to ~30; $P = .016$); there was a ceiling effect of both the 3.5% and 7% cigarettes over time ($P = .95$). Acute cognitive effects on memory with the high-dose cannabis cigarettes were observed.

Another study[23] investigating the use of smoked cannabis in patients with neuropathic pain was a randomized, double-blind, placebo-controlled crossover study that included 23 adults with chronic neuropathic pain secondary to trauma or surgery. The study compared various strengths of cannabis (0% [placebo], 2.5%, 6.0%, and 9.4% THC) smoked in a pipe 3 times a day for 5 days, separated by a 9-day washout in the treatment of neuropathic pain. Results showed that there was a significant difference between 0% (placebo) and 9.4% THC on the VAS (0.7-point reduction on average daily pain; $P < .05$). Patients also reported improved ability to fall asleep easier ($P = .001$), faster ($P < .001$), and were more drowsy ($P = .003$) in those using 9.4% THC versus 0% (placebo). There were no differences in mood or quality of life between various THC doses and placebo. Most common adverse effects included headache, dry mouth, burning sensation in the areas of the pain, dizziness, numbness, and cough.

Another trial identified was a randomized, double-blind, placebo-controlled, crossover study[24] that included 39 patients with mixed neuropathic pain. The study compared vaporized cannabis at strengths of 0% (placebo), 1.29%, and 3.53% THC during 3 study visits; patients were allowed to self-titrate dose (8-12 puffs per visit). In this study the authors calculated number needed to treat for 30% pain reduction for the various strengths of cannabis. Results showed that the number needed to treat was 3.2 for low-dose (1.29% THC) versus placebo and 2.9 for medium-dose (3.53% THC) versus placebo. Notably, the number needed to treat for 50% pain reduction for first-

line medications ranges from 3.6 (TCAs) to 7.7 (pregabalin).[25]

Discussion

The American Academy of Neurology (AAN) published a systematic review[26] and has issued a position statement[27] regarding the use of MM in selected neurologic disorders. The AAN position statement outlines that the legislation around MM is "not supported by high-level medical research." Additionally, the position statement outlines the fact that long-term safety data are unavailable; however, it also calls for reclassification of marijuana from a Schedule I (C-I) controlled substance so that more rigorous research may be conducted. The American Psychiatric Association has also issued a position statement[28] that does not seem to hold the same tone as the AAN's position statement. The statement outlines that, "There is currently no scientific evidence to support the use of marijuana as an effective treatment for any psychiatric illness" and that "several studies have shown that cannabis use may in fact exacerbate or hasten the onset of psychiatric illnesses." The latter of these two statements refers to systematic reviews and meta-analyses that have outlined the risk of psychosis associated with marijuana use.[29-31]

Other potential risks, according to the Substance Abuse and Mental Health Services Administration Web site,[32] include short-term problems with learning and memory, distorted perception, difficulty thinking and solving problems, and incoordination. Substance Abuse and Mental Health Services Administration reports that marijuana smoking also increases the risk of cancer of the head, neck, lungs, and respiratory tract; other publications neither refute nor support this statement.[33] Other adverse effects caused by marijuana include tachycardia, palpitations, hypertension, acute myocardial infarction, ischemic attack, coughing, wheezing, sputum production, lethargy, sedation, slowed reaction time, psychologic dysfunction, and visual disturbances.[34]

One of the most important points to cover is related to the differing formulations that are collectively called "medical marijuana." A big drawback of grouping all MM products together is that they are all different regarding their makeup in terms of THC and CBD content. Some formulations have varying ratios of THC to CBD, other preparations only contain THC, and still others only contain CBD. This is vital to note because THC and CBD behave differently pharmacologically and therapeutically, one of the major differences being that THC produces euphoria and intoxication, and CBD has been shown to antagonize some of the effects of THC and has anxiolytic and antipsychotic effects.[35] That said, product selection for the patient who uses MM is of paramount importance. This

review focused on randomized, double-blind, controlled trials of phytocannabinoids for the treatment of these disorders. It is important to keep an evidence-based approach in mind, even with substances considered to be illegal under US federal law. Clinicians must weigh the risks and benefits of the use of MM in their patients and should ensure that patients have tried other treatment modalities with higher levels of evidence for use when available and appropriate. In this review, studies were identified that evaluated the use of MM in dementia, MS, PD, anorexia, Huntington disease, schizophrenia, social anxiety disorder, depression, tobacco use disorder, neuropsychiatric symptoms of dementia, and neuropathic pain. The strongest evidence seems to be established for treatment of symptoms of MS and neuropathic pain; however, the International Association for the Study of Pain–Neuropathic Pain Special Interest Group (IASP NuePSIG) guidelines have a weak recommendation against the use of cannabinoids based on negative results of trials reviewed and the potential misuse, abuse, and long-term mental health risks in susceptible individuals.[25] It should be noted that most trials reviewed in the IASP NeuPSIG guidelines compared nabiximols to placebo; this formulation was not included in this review. Promising areas of study that require further research include the use of MM in social anxiety disorder and schizophrenia: an important point being that the active medications in these studies were formulations of pure CBD. Data were fairly limited in Huntington disease, PD, and tobacco use disorder, making drawing definitive conclusions difficult. There is probably not a place in therapy for MM in depression, anorexia, and neuropsychiatric symptoms of dementia.

Conclusion

"Medical marijuana" encompasses everything from whole-plant cannabis to synthetic cannabinoids available for commercial use approved by regulatory agencies. In determining whether MM is of clinical utility to our patients, it is important to keep in mind chemical constituents, dose, delivery, and indication. Selection of the patient appropriate for MM must be carefully considered because clinical guidelines and treatment options with stronger levels of evidence should be exhausted first in most cases. There seems to be strongest evidence for the use of MM in patients with MS and in patients with neuropathic pain; moderate evidence exists to support further research in social anxiety disorder, schizophrenia, PD, and tobacco use disorder; evidence is limited for use in patients with dementia, Huntington disease, depression, and anorexia. Future research for the use of MM in other psychiatric and neurologic diseases includes posttraumatic stress disorder, Tourette syndrome, and epilepsy, because there were some studies identified that did not meet inclusion criteria for this review.

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