

Current Status of Cannabis Treatment of Multiple Sclerosis with an Illustrative Case Presentation of a Patient with MS, Complex Vocal Tics, Paroxysmal Dystonia, and Marijuana Dependence Treated with Dronabinol

By Stephen I. Deutsch, MD, PhD, Richard B. Rosse, MD, Julie M. Connor, BS, Jessica A. Burket, BS, Mary E. Murphy, APRN, BC, and Fiona J. Fox, MD

ABSTRACT

Pain, spasticity, tremor, spasms, poor sleep quality, and bladder and bowel dysfunction, among other symptoms, contribute significantly to the disability and impaired quality of life of many patients with multiple sclerosis (MS). Motor symptoms referable to the basal ganglia, especially paroxysmal dystonia, occur rarely and contribute to the experience of distress. A substantial percentage of patients with MS report subjective benefit from what is often illicit abuse of extracts of the *Cannabis sativa* plant; the main cannabinoids include delta-9-tetrahydrocannabinol (Δ^9 -THC) and cannabidiol. Clinical trials of cannabis plant extracts and synthetic Δ^9 -THC provide support for therapeutic benefit on at least some patient self-report measures. An illustrative case is presented of a 52-year-old woman with MS, paroxysmal dystonia, complex vocal tics, and marijuana dependence. The patient was started on an empirical trial of dronabinol, an encapsulated form of synthetic Δ^9 -THC that is usually prescribed as an adjunct-

Needs Assessment

Multiple sclerosis (MS) is a demyelinating disorder that is associated with several disabling core symptoms, including pain, spasms, spasticity, weakness, poor sleep quality, and bladder and bowel dysfunction; patients complain that these symptoms interfere with their quality of life. Many patients self-report that illicit use of cannabis provides them with subjective relief from many of these symptoms. Data is emerging that is consistent with benefit on subjective patient self-report measures; unfortunately, objective assessments do not consistently corroborate these self-reports of MS patients. Subjective assessments by patients often reflect integrated impressions of benefit experienced by patients over the course of 1 day, week, or longer period, whereas objective assessments by "blinded" examiners may "miss" evidence of benefit that may be most apparent at different times and in other contexts. The data support continued clinical investigation of cannabis-based medicines for the treatment of some of the core disabling symptoms of MS.

Learning Objectives

At the end of this activity, the participant should be able to:

- List some of the core disabling symptoms of multiple sclerosis.
- Recognize that symptoms referable to dysfunction or involvement of the basal ganglia occur in patients with multiple sclerosis.
- Identify core disabling symptoms that may benefit from therapeutic administration of cannabis-based medicines.

Target Audience: Neurologists and psychiatrists

CME Accreditation Statement

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Mount Sinai School of Medicine and MBL Communications, Inc. The Mount Sinai School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation

The Mount Sinai School of Medicine designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This activity has been peer-reviewed and approved by Eric Hollander, MD, chair at the Mount Sinai School of Medicine. Review date: April 7, 2008. Dr. Hollander does not have an affiliation with or financial interest in any organization that might pose a conflict of interest.

To Receive Credit for This Activity

Read this article and the two CME-designated accompanying articles, reflect on the information presented, and then complete the CME posttest and evaluation found on page 437. To obtain credits, you should score 70% or better. Early submission of this posttest is encouraged: please submit this posttest by May 1, 2010, to be eligible for credit. Release date: May 1, 2008. Termination date: May 31, 2010. The estimated time to complete all three articles and the posttest is 3 hours.

Dr. Deutsch is associate chief of staff for mental health in the Mental Health Service Line at the Department of Veterans Affairs Medical Center (VAMC) and Professor and Associate Chairman for the Clinical Neurosciences in the Department of Psychiatry at Georgetown University School of Medicine, both in Washington, DC. Dr. Rosse is chief of psychiatry in the Mental Health Service Line at the VAMC, and Professor of Psychiatry in the Department of Psychiatry at Georgetown University School of Medicine. Mses. Connor and Burket are members of the Mental Health Service Line at the VAMC. Ms. Murphy is the program coordinator of the Intensive Outpatient Substance Abuse Rehabilitation Program of the Mental Health Service Line at the VAMC. Dr. Fox is a staff psychiatrist in the Mental Health Service Line and Instructor of Psychiatry in the Department of Psychiatry at Georgetown University School of Medicine.

Faculty Disclosures: The authors do not have an affiliation with or financial interest in an organization that might pose a conflict of interest.

Submitted for publication: January 28, 2008; Accepted for publication: April 7, 2008.

Please direct all correspondence to: Stephen I. Deutsch, MD, PhD, Department of Veterans Affairs Medical Center, 50 Irving Street NW, Washington, DC 20422; Tel: 202-745-8156, Fax: 202-745-8169; E-mail: stephen.deutsch@med.va.gov.

tive medication for patients undergoing cancer chemotherapy. The patient reported a dramatic reduction of craving and illicit use; she did not experience the “high” on the prescribed medication. She also reported an improvement in the quality of her sleep with diminished awakenings during the night, decreased vocalizations, and the tension associated with their emission, decreased anxiety and a decreased frequency of paroxysmal dystonia.

CNS Spectr. 2008;13(5):393-403

INTRODUCTION

Survey Data of Cannabis Use among Patients with Multiple Sclerosis

Data were obtained from 112 male and female patients with multiple sclerosis (MS) from the United States and the United Kingdom, who (illicitly) smoked cannabis to self-treat their symptoms; patients responded anonymously to a 68-item questionnaire that was distributed to 230 patients enquiring about cannabis use and its benefits.¹ Given the high placebo-response rates in this disorder (approaching 70%), it is of interest that >70% of the responders reported improvement in some of the most disabling and difficult-to-treat symptoms, including spasticity, pain, tremor, weakness, depression, anxiety, and altered sensations, such as numbness and tingling. The patients surveyed in this study were contacted by the Alliance for Cannabis Therapeutics in the US and UK and, thus, could be biased, rationalizing a therapeutic benefit from cannabis use. However, the inconsistency of magnitude and profile of therapeutic responses, including responses of “not changed” and worsening argue for the validity of the data. Nonetheless, this may not be a representative sample of all patients with MS. Whereas bowel and bladder dysfunction and tiredness were also reported to improve, they were reported by <70% of all respondents. Using the criterion of 70% of respondents reporting improvement as significant, weakness in legs (72.9%) may also be a potential therapeutic target. Importantly, the highest percentage of respondents rated the

symptoms of spasticity and pain as “much better.” Thus, clinical trials to evaluate the response of these therapeutic targets to cannabis extracts and synthetic delta-9-tetrahydrocannabinol (Δ^9 -THC) should be pursued.¹

In spite of its classification as a Schedule 1 drug in the UK that prohibits the prescription of cannabis for medical purposes, an impression that it was used for symptom relief was supported by a survey of patients with MS in South East London and surroundings.² Of the 254 survey respondents, 59 reported that they first used cannabis after their diagnosis, and 90% of them did so because of the diagnosis. Forty-six patients were using cannabis at the time of the survey, most of the current users were using multiple times per week, specifically, in an attempt to relieve MS-related symptoms, primarily pain and spasms. The risk of cannabis use increased with greater disability and dysfunction of the lower and upper limbs. Increased risk of cannabis use was also associated with being married or having a long-term partner and tobacco smoking. Although rare among cannabis users for MS, three patients reported feeling “paranoia” and one reported hallucinations; thus, careful monitoring, including evaluation of treatment-emergent psychiatric symptoms, would be necessary if cannabis were prescribed therapeutically for MS.²

A cross-sectional questionnaire designed to assess the prevalence and pattern of cannabis use was distributed to 220 patients with MS in Halifax, Nova Scotia, Canada.³ Ninety-three percent of the patients responded and 19 of them (~9%) reported using cannabis for medical purposes at least weekly and more frequently; an additional 15 patients reported rare use for medicinal purposes. Of the 34 patients who used cannabis for medical purposes, 20 of them reported it as “very effective” when rating the overall effectiveness of cannabis. Self-reported moderate to complete relief was reported for almost all of the 34 patients experiencing the following symptoms: stress (20 out of 21), sleep (17 out of 18), stiffness (16 out of 17), mood (16 out of 16), muscle spasm (14 out of 15), and pain (10 out of 12). Patient characteristics that were associated with medical use of cannabis included male gender, tobacco use and its recreational use. Although only ~9%

of the respondents were frequent users, it is clear that symptoms that interfere with function and quality of life, such as pain, spasticity, mood, sleep, and stress, were not adequately addressed in this clinical-practice setting.³

Therapeutic Effects of Cannabis on Some Core Disabling Symptoms of Multiple Sclerosis: Clinical Trials

Δ^9 -THC and an identically encapsulated extract of the Cannabis sativa plant that contained a standardized amount of Δ^9 -THC and 20% to 30% cannabidiol—the latter interferes with the liver's metabolism of Δ^9 -THC and, thereby, raises its concentration within the central nervous system (CNS)—showed no superiority over placebo in a randomized placebo-controlled, double-blind crossover study⁴ in 16 adult patients with progressive MS and severe spasticity; each treatment condition lasted 4 weeks with a 4-week washout between conditions. In both of the active medication conditions, the Δ^9 -THC content was initiated at a dose of 2.5 mg BID for 2 weeks, which, if tolerated, could be doubled to 5.0 mg BID for the final 2 weeks. Treatment with active medication did not improve muscle tone, nor were any clearly beneficial effects noted on a variety of objective and subjective measures of muscle function, cognition, fatigue, and general well-being.⁴

As discussed, the survey data showed that nonprescribed cannabis use is associated with patient-reported subjective benefit in a variety of disease-related symptoms in MS, including pain, bladder symptoms, tremor, ataxia, and spasticity. These symptoms often worsen over time, are associated with progressive disease, and interfere with activities of daily living and quality of life.⁵ Because of the illicit cannabis use and its reported subjective benefit, a 15-week, double-blind, placebo-controlled clinical trial was conducted⁵; 657 outpatients with MS and problematic spasticity (Ashworth score of ≥ 2 in two or more lower-limb muscle groups) recruited from 33 sites in the UK were randomly assigned to one of three groups: encapsulated Δ^9 -THC (n=216), an encapsulated cannabis extract containing an equivalent amount of Δ^9 -THC and cannabidiol as the principal cannabinoid (n=219), and matching encapsulated placebos (n=222). The medica-

tion was dosed according to bodyweight and 25 mg in a divided dose was the maximum allowable dose; medication was titrated over the first 5 weeks, maintained on a stable dose through week 13, tapered and discontinued during week 14, and patients were fully withdrawn during week 15. The primary outcome measure was the clinician-assessed Ashworth score of spasticity, which assessed spasticity in 10 muscle groups on a 5-point scale, in addition to a variety of objective and subjective secondary measures. Data were analyzed using an analysis of variance with an intention-to-treat and carrying forward the last Ashworth score during the treatment phase. With and without adjustment for ambulatory status and treatment site, neither Δ^9 -THC nor the cannabis extract significantly differed from placebo in terms of the change of the total Ashworth score or its upper-body and lower-body muscle-group components from baseline to the end of maintenance treatment at the end of week 13.5. Δ^9 -THC significantly improved the median time taken to walk 10 meters, whereas there was no significant effect of the cannabis extract on this measure. Importantly, while the active-medication conditions were not associated with clear objective evidence of therapeutic benefit, with the exception of median time taken to walk 10 meters, patients subjectively reported improvement of symptoms of pain, sleep quality, spasms, and spasticity.⁵ Although the assessors that blindly performed the objective outcome ratings without access to any information about dose and side effects were not able to correctly distinguish between patients in the active-medication and placebo conditions, the patients themselves were significantly better at identifying whether they were assigned to the active-medication, as opposed to placebo, conditions in spite of the blind. Importantly, the treatment conditions did not differ in terms of the occurrence of serious adverse events. Although there were a large number of minor adverse events across all groups, certain minor adverse events occurred more frequently in the active-cannabis conditions that could have improved the patients' discriminability of treatment assignment: gastrointestinal tract, vision, dizzy or lightheadedness, and dry mouth; however, these more

commonly occurring minor adverse events were also reported by patients in the placebo conditions. Once again, a dissociation between the objective assessments performed by clinicians and the subjective self-reports of patients was observed, which may reflect the variability of symptom severity over time and the fact that clinicians perform their assessments cross-sectionally at one point in time, whereas patient self-reports are an integrated, albeit biased, assessment of changes in symptom severity that usually occur over of ≥ 1 week.⁵

A blinded, continuation phase that lasted up to 52 weeks suggested that Δ^9 -THC, as compared with the cannabis extract and placebos, had a small, but statistically significant, effect on two clinician-rated, objective measures: the Ashworth score, the primary efficacy measure, and the Rivermead Mobility Index.⁶ The doses were selected on the basis of the original 15-week trial. There was also subjective self-report of benefit in a variety of measures that evaluated differences between the three groups in categorical improvement and deterioration at the end of the 52 weeks; the suggestion of subjective benefit was obtained for the following: pain, shaking, spasm, spasticity, sleep, energy, and tiredness. A higher percentage of the patients in the placebo groups that decided to discontinue treatment did so because they felt the medication produced no benefit (74% of those that discontinued), compared with the percentage of patients that discontinued due to no benefit in the cannabis extract (45%) and Δ^9 -THC (42%) groups. Thus, rater-assessed, objectively small and significant benefits were observed on measures associated with disability, which may be clinically significant from the perspective of the patients. The data supported continued long-term exploration of cannabis in MS.⁶

Action tremor that typically involves the upper limbs occurs in $>50\%$ of randomly selected clinic patients with MS and is associated with disability in $\sim 25\%$ of the diagnosed patients.⁷ The severity of tremor is correlated with severity of cerebellar signs, suggesting that the cerebellum or its connections is involved in its pathogenesis. As many as 50% of patients experiencing tremor self-report that they feel "much better" in response to cannabis use.¹ Data analyzed on 13 of 14 patients with

MS and visible upper-limb tremor randomized to a placebo-controlled, crossover trial of an encapsulated ethanolic extract of *Cannabis sativa*, standardized to 2.5 mg of Δ^9 -THC per capsule, failed to show objective evidence of tremor improvement on clinical ratings and other objective measures, including an automated one⁷; each treatment phase lasted 2 weeks and final active doses ranged from 7.5–10.0 mg BID. Although they were blinded, patients showed good discriminability with respect to distinguishing between the cannabis and placebo phases (nine of 14 patients correctly identified treatment condition) and were more likely to report subjective benefit during the cannabis, as opposed to placebo, phase (five patients reported improvement of their tremors on cannabis, whereas only one did so on placebo). Thus, although objective benefit on tremor was not shown, patient subjective self-report favors a beneficial effect. Adverse events were rated as mild.⁷

Route of administration may influence bioavailability and efficacy of whole-plant cannabis-based medicinal extracts as well as the ease of dose titration by the patient.⁸ Also, efficacy may be more apparent (and clinically relevant) when patients rate themselves, selecting the primary target symptoms that are most troublesome for them. Because of these considerations, a 6-week, double-blind, parallel-group, placebo-controlled clinical trial⁸ of whole-plant extract containing the Δ^9 -THC 2.7 mg and cannabidiol 2.5 mg and matching placebo was conducted in 160 patients with MS that were randomly assigned to one of the two treatment conditions, each patient chose one of the following five primary target symptoms: spasticity, spasms, bladder problems, tremor or pain. A fixed amount of medication (2.7 mg of Δ^9 -THC and 2.5 mg of cannabidiol) or placebo was delivered by a pump action spray to the oromucosa with each actuation. The patients rated the severity of their chosen primary target symptoms on a 100 mm Visual Analogue Scale with anchors ranging from "no problem" to "very bad;" at least one of these symptoms had to be recorded at ≥ 50 mm on the 100 mm Visual Analogue Scale on baseline in order to be eligible to participate. Patients could not exceed the maximum allowable dose of 120 mg of Δ^9 -THC

per day. At the end of 6 weeks, the active medication was associated with a statistically significant improvement among patients selecting spasticity as their primary symptom; spasticity was also the largest primary symptom category selected by 39 patients.⁸

One hundred thirty-seven of the 160 patients enrolled in the 6-week, randomized, placebo-controlled, parallel-group clinical trial^{8,9} of the oromucosal spray of the whole-plant extract of *Cannabis sativa* (0.1 mL of each spray contained 2.7 mg of Δ^9 -THC and 2.5 mg of cannabidiol) entered a long-term, open-label extension trial of active medication; data for 73 patients completing at least 1 year of treatment were presented. Once again, changes of severity on primary target symptoms of spasticity, spasms, bladder-related problems, tremor, or pain were measured with 100 mm Visual Analogue Scales and served as the outcome efficacy measures. Although not intended to be an efficacy trial, these self-selected patients showed dramatic improvements in pain, spasm, spasticity, and bladder problems of ~30–40 mm reductions at ~10 weeks that were sustained.⁹ Although a placebo-comparison group did not exist in the open-label, extension study as it was not intended to be an efficacy study, the data suggest that 6 weeks may be insufficient time to experience maximum benefit. In the open-label extension study,⁹ the maximum benefit emerged at ~10 weeks following the acute study, was reported for a variety of measures in addition to spasticity (including pain, spasm, and bladder problems) and, importantly, was sustained for >1 year. Again, there was a biased self-selection for enrollment into the extension phase because many patients elected to continue because they thought they had benefited from participation in the acute trial^{8,9}; patients considering themselves to be nonresponders declined enrollment in the open-label, extension study. Although serious adverse events were rare, there were two reports of seizures (one of the patients with seizures died from subsequent aspiration pneumonia) and one patient had a loss of balance resulting in an ankle injury. A subset of 25 patients was asked to undergo abrupt withdrawal for a period of 2 weeks; 17 of them reported worsening of their symptoms. A consistent abrupt-withdrawal syndrome was

not observed; however, a variety of complaints were reported by several patients, including interrupted sleep, hot and cold flushes, tiredness, low mood, decreased appetite, emotional lability, vivid dreams, and intoxication.⁹

Adjunctive administration of an encapsulated extract of *Cannabis sativa* that contained Δ^9 -THC 2.5 mg and cannabidiol 0.9 mg was shown to reduce patient-recorded frequencies of spasms at effective doses ranging from 7.5–27.5 mg in a randomized, placebo-controlled crossover study¹⁰ that enrolled 57 patients into a 14-day active-treatment phase; 50 patients were analyzed with an intention-to-treat having a minimal data set for the second phase of the crossover and 37 patients “completed” the trial having taken 90% or more of the prescribed doses. In addition, after exclusion of a patient who fell and stopped walking, objective assessment of mobility showed improvement (ie, Rivermead Mobility Index) in the intention-to-treat analysis. The active medication was rated as tolerable and no serious adverse events emerged.¹⁰

The characterization of central neuropathic pain, which derives from sclerotic plaque lesions affecting central pain pathways, is difficult and often vague in patients with MS. In spite of the difficulty, a randomized, double-blind, placebo-controlled crossover study of dronabinol, an encapsulated synthetic Δ^9 -THC (maximum dose: 10 mg/day),¹¹ showed a reduction in median pain-intensity scores in 24 patients; each active-treatment condition lasted 3 weeks with a 3-week washout period in between. Patients rated their pain at a maximal pain site using a 10-point numerical rating scale (0=no pain; 10=worst imaginable pain) that was further characterized by abnormal sensations to pinprick, touch, warmth, or cold. As noted, median spontaneous pain-intensity scores in the third week of each treatment phase served as the primary outcome measure of efficacy. Patients with pain due to musculoskeletal disorders, peripheral neuropathic pain, or visceral pain were excluded from the trial. There were no carryover effects between treatment conditions, consistent with a cannabinoid (CB)₁ receptor-mediated therapeutic effect that was detectable only when agonist was present. In addition to the statistically significant reduction

of the median pain-intensity score, dronabinol improved median rating pain-intensity and pain-relief scores.¹¹ Dronabinol also raised the threshold for patients' perception of pressure pain that was administered with an automated device. Finally, dronabinol improved the "bodily pain" and "mental health" items on the Short-Form 36, a health-related, quality-of-life questionnaire. The data supported a clinically relevant, therapeutic effect of dronabinol on central neuropathic pain.¹¹ A meta-analysis¹² supported the therapeutic effect of cannabis-based treatments, in general, on MS-related, presumably largely neuropathic pain.

The most common manifestation of central pain in MS is nonparoxysmal extremity pain that is often accompanied by "dysesthetic" qualities, such as burning, aching, pricking, stabbing, or squeezing.¹³ Painful spasms of the extremities have also been classified as a central pain phenomenon. The reported prevalence rates for central pain in MS vary widely (range: 17% to 52%) with about one third of the patients reporting it to be severe and contributing to disability.⁶⁶ Patients with central neuropathic pain primarily involving their legs and feet and either dysesthetic qualities or painful tonic spasms were randomized to a 5-week, double-blind clinical trial of either active cannabis-based medicine delivered via oromucosal spray (one spray: Δ^9 -THC 2.7 mg and cannabidiol 2.5 mg) or placebo spray administered as adjunctive analgesic treatment¹³; 64 patients completed the study. One female patient discontinued because of the emergence of agitation with tachycardia and hypertension after four sprays and one female patient was withdrawn by the investigators in the second week of active treatment due to the emergence of paranoid ideation. A numerical rating (0=no pain; 10=worst possible pain) was used to rate the severity of the patients' most troublesome neuropathic pain at the time of day when it was expected to be most severe. Patients receiving the active cannabis-based medicine showed significant improvement of their mean pain-intensity scores, especially the patients with the painful spasms, and mean pain-related sleep disturbance scores that were also rated between 0 and 10.¹³ In week 4, the mean number of daily sprays of the active cannabis-based medicine was 9.6, corresponding

to a mean dose of ~26 mg of active Δ^9 -THC daily (range: 5.4–67.5 mg/day). The active cannabis-based medicine condition was well-tolerated, but the very rare emergence of serious adverse events, including confusion, crying, disorientation, paranoia, and hallucination, emphasizes the need for careful monitoring.

Cannabinoids act via receptor-mediated mechanisms to regulate urinary-bladder motility and the urge to micturate; receptors sensitive to cannabinoids are located on the bladder itself and suburothelium as well as throughout areas of the CNS involved in regulation of bladder function.¹⁴ Lower urinary tract symptoms (LUTS), especially urinary urgency and urge incontinence, occur in $\geq 90\%$ patients with MS of >10-years duration that often necessitates "clean intermittent self-catheterization." With progressive disability, long-term in-dwelling catheterization is often required, which is associated with chronic urinary tract infections. The cause of the most common symptoms of LUTS (ie, urgency, urge, and reflex incontinence) in a majority of patients with MS is "neurogenic detrusor overactivity" due to demyelination in the cervical spinal cord.¹⁵ Detrusor overactivity co-exists with "detrusor-sphincter-dyssynergia" in a high percentage of patients resulting in incomplete bladder emptying and associated infection. Some patients also show "detrusor areflexia/acontractility" due to damage to the lower spinal cord.¹⁵ However, in the majority of patients the consequences of detrusor overactivity, especially damage to the upper urinary tract, and LUTS are the targets of therapy and main reasons for patient distress, disability, and impaired quality of life.¹⁵

Survey data^{1,14} revealed that many patients with MS who use cannabis illicitly report improvement of urgency, urge incontinence, and hesitancy. Fifteen patients with MS complaining of LUTS for >5 years were treated consecutively for 8 weeks with sublingual administration of one of two different extracts of cannabis sativa plants bred to contain fixed amounts of Δ^9 -THC and cannabidiol via spray¹⁴; patients self-administered Δ^9 -THC and cannabidiol in the first treatment phase (one spray: Δ^9 -THC 2.5 mg and cannabidiol 2.5 mg) and Δ^9 -THC alone in the second treatment phase (one spray: Δ^9 -THC 2.5 mg). Fourteen patients elected to continue in a long-term extension phase of treatment with Δ^9 -

THC alone; data were presented for a mean and median treatment duration of 31 and 35 weeks, respectively. The stable doses achieved via self-titration ranged between 2.5 and 97.5 mg of Δ^9 -THC and cannabidiol daily and between 2.5 and 75 mg of Δ^9 -THC alone daily in the first and second treatment phases, respectively. Each 8-week treatment phase significantly improved patients' home assessments of number of daily incontinence episodes, the volume of incontinence, nocturia, and daytime urinary frequency. The improvements reported for the number of incontinence episodes and daytime urinary frequency were sustained in the long-term extension. The beneficial treatment effect reported by patients may have been confounded, however, by a reduction in the total daily volume of urine produced. Nonetheless, patients reported that there was a decreased sensation of "urgency" for a higher proportion of their voided urines, and more of their voided urines were described as "planned or normal." Objective evidence of urodynamic improvement was also shown.¹⁴ Other troublesome symptoms such as pain, spasticity, and difficulty sleeping were also reported to improve. Dose-related emergence of hallucinations in three patients, which resolved with dose reduction, highlights the importance of careful titration and close monitoring.¹⁴

A substudy of the Cannabinoids in Multiple Sclerosis trial¹⁵ evaluated the effect of encapsulated Δ^9 -THC 2.5 mg/capsule, encapsulated cannabis extract that contained an equivalent amount of Δ^9 -THC and 1.25 mg of cannabidiol, and matching placebo capsules on urge-incontinence episodes as assessed by 3-day urinary diaries completed at baseline and end-of-study after week 13. The diaries were supplemented with specific questions about incontinence taken from established instruments for the assessment of incontinence. Five hundred twenty-two patients from 33 centers across the UK enrolled in the substudy and 255 individuals completed 13 weeks of treatment. At the end of 13 weeks, patients enrolled in all three treatment conditions showed a significant reduction of episodes of urge incontinence. However, relative to the placebo conditions, the two active-cannabis conditions showed a significant advantage over placebo. The subjective benefit of active cannabis was corroborated by significant reduc-

tions in the weight of pads that were used due to incontinence and weighed in a small number of patients in each of the three conditions. Thus, in this randomized study, active treatment with cannabis (either Δ^9 -THC and cannabidiol or Δ^9 -THC alone) was associated with patient-reported reductions in episodes of urge incontinence.¹⁵

Basal Ganglia Involvement in Multiple Sclerosis

A case¹⁶ was reported of a 31-year-old woman with a relapsing-remitting presentation of MS that responded to high-dose therapy with prednisolone with almost complete resolution of multifocal bilateral lesions of the caudate nucleus, putamen, globus pallidus, the anterior limb of the internal capsule, thalamus, and brainstem on her initial presentation. Approximately 1 year after remission while withdrawn from prednisolone, she relapsed, presenting with anorexia, impairment of recent memory, apathy, and decreased spontaneous speech. Imaging at the time of her second presentation revealed lesions of the right caudate nucleus and left frontal white matter. This disappeared after reinitiation of oral prednisolone with resolution of her symptoms.¹⁶ This patient presented with primarily cognitive and behavioral dysfunction ascribed to her basal ganglia lesions (specifically memory dysfunction and apathy with reduced spontaneity and initiative), and none of the characteristic motor symptoms, including tics, associated with basal ganglia dysfunction.

Defined tic disorders in association with MS are extremely rare, which is somewhat surprising in view of the frequent finding of demyelinating lesions in basal ganglia and thalamus.¹⁷ The patient reported in this submission showed onset of utterances at ~36 years of age that progressed to coprolalia and echolalia, in addition to paroxysmal dystonia. She had no known childhood history of tics, obsessive-compulsive symptoms, or abnormal movements related to basal ganglia dysfunction. Although basal ganglia-related movement disorders in general appear infrequently in association with MS, paroxysmal dystonia is the most commonly reported one.¹⁷ Our patient described paroxysmal contractions of her skeletal muscles that would result in a freezing of her posture lasting for a period of seconds; this occurs unex-

pectedly while walking. A case of simple phonic tic, throat-clearing sounds with no premonitory symptoms, as the sole manifestation of basal ganglia dysfunction was reported in a 34-year-old woman with progressive MS, showing demyelinating lesions of the thalamus and basal ganglia.¹⁷

Endogenous Cannabinoids Participate in Regulation of Basal Ganglia Function

The high density of the endocannabinoid CB₁ receptor and high concentrations of anandamide and 2-arachidonyl-glycerol, endogenous cannabinoids that are produced locally within the area of the synapse and can act as retrograde messengers in basal ganglia, and structures interconnected with basal ganglia support their role in basal ganglia function and pathology.^{18,19} The endocannabinoid CB₁ receptor participates in the regulation of presynaptic release and reuptake of γ -aminobutyric acid and glutamate and is co-localized with dopamine (D)₁ and D₂ receptors in the striatum, where it may engage in “cross-talk” at the level of the trimeric guanosine triphosphate-binding protein/adenylyl cyclase signal transduction cascade. Of note, the endocannabinoid CB₁ receptor is the most abundant trimeric guanosine triphosphate-binding protein-binding protein-coupled receptor in the CNS.²⁰ Behavioral experiments have shown that CB₁ receptor agonists and antagonists can affect behaviors referable to basal ganglia (eg, spontaneous locomotion, stereotypies, immobility, and catalepsy) and modulate effects of dopaminergic interventions on them.¹⁸ Thus, it is not surprising that cannabis extracts are reported to (therapeutically) influence symptoms referable to the basal ganglia, including those of Tourette syndrome (TS).¹⁹

Cannabis May Therapeutically Target Tics and Other Types of Basal Ganglia Dysfunction

A high density of the central cannabinoid CB₁ receptor is found in the output nuclei of the basal ganglia, consistent with its possible involvement in abnormal movement and other basal ganglia-related disorders, such as tics and obsessive-compulsive disorder.²¹ Furthermore, this receptor may serve as a potential therapeutic target in at least some basal ganglia-related

disorders, as it modulates glutamatergic, γ -aminobutyric acidergic, and dopaminergic neurotransmission. A single-dose, randomized, double-blind, placebo-controlled crossover trial of Δ^9 -THC,²¹ the active principal of marijuana, was conducted in 12 adult patients with TS due to favorable anecdotal reports and a patient survey suggesting beneficial effects of marijuana in TS. Within 3–4 hours after a morning dose of oral Δ^9 -THC that was adjusted according to weight, age, gender, and prior exposure to marijuana (range: 5.0–10.0 mg), self-reported improvements of simple and complex motor tics, complex vocal tics, and obsessions and compulsions, such as checking, washing, ordering, doing things just right, counting, doing things an exact number of times, and rituals, were noted. Importantly, 10 of 12 patients reported global improvement on the day that they received active medication, whereas only three of 12 reported global improvement on the day they received placebo.²¹ Δ^9 -THC was given after a standardized breakfast in order to improve and minimize its slow and erratic absorption, respectively; using this dosing procedure, associations between oral dose, plasma levels of 11-hydroxy- Δ^9 -THC, a metabolite of Δ^9 -THC, and tic improvement were found.

Neuroprotective, Disease-Modifying Effects of Cannabis May Not Be Clinically Relevant

In addition to the wide distribution of CB₁ receptors in the CNS, a distinct CB₂ receptor exists on cells of the immune system, notably B cells and macrophages, suggesting a role in the regulation of inflammatory processes.²² Although endocannabinoids may play a pathogenic role in neurodegenerative and demyelinating disorders, it is unlikely that the typical doses of exogenously administered (or illicitly abused) cannabis extracts used for the symptomatic treatment of MS would achieve sufficient concentrations within blood to inhibit lymphocyte and macrophage/micorglial function via CB₂ receptor-mediated mechanisms; thus, they are not expected to have a disease-modifying effect.²²

CASE REPORT

Ms. CJ is a 52-year-old left-handed white female with a history of MS and a complex vocal tic disorder, who was referred to a specialized intensive

outpatient substance-abuse rehabilitation program for evaluation and treatment of marijuana dependence. On admission to the program, the patient reported that she is “always high” for most of each day, smoking a minimum of five “joints” each day. The patient was also charged with illegal possession of marijuana that was discovered when she was stopped for a routine traffic violation, which prompted her referral for treatment.

Both of the patient’s parents suffered from chronic alcohol dependence. As a child and adolescent, she was repeatedly sexually abused by her father, including rape and molestation, and physically abused by her mother, whom patient reports was in denial about the father’s repeated sexual abuse. The patient also reported significant mercury exposure as a child because the father recycled mercury and the patient had access to it. In addition to playing with it, Ms. CJ believes that she may have ingested some as a child. Otherwise, patient reported no early-childhood history of attention, learning, or conduct problems.

The patient moved out of her parental home upon graduation from high school at 17 years of age. She also reported that she abused marijuana at this time—“I smoked pot back then.” From 17 years of age until she entered college at 28 years of age, the patient supported herself by working multiple jobs “minimum wage and minimum effort,” while engaged in serious athletic training “I was a marathon runner for 12 years... I did not smoke pot during this period.”

Patient completed an undergraduate major in exercise physiology and reported doing well until her early 30s, when she began to suffer from recurrent urinary tract infections that led to a surgical intervention for correction of congenitally misplaced ureters, a vague, but persistent complaint of “choking,” and a general feeling of “unwellness.” At about this time, she resumed illicit smoking of marijuana and sought “treatment” by attending Narcotics Anonymous because it was free.

Ms. CJ enlisted in the United States Army Reserves at 34 years of age and was mobilized for 56 weeks, working at the Walter Reed Army Medical Center in Washington, DC, as an X-ray technician, a career that she continued into her civilian life after demobilization. At ~36 years of age, while employed in an academic medical

center, the patient sought neurological consultation because of falling while running, weakness, pain in her feet, and a loss or change of sensation from her mid-chest level to her lower extremities. Ms. CJ was informed that magnetic resonance imaging findings and history were consistent with a diagnosis of MS. At ~43 years of age, Ms. CJ noted the onset of vocal tics “uncontrollable utterances of nonsense” that has progressed to frank coprolalia, often saying “Goddamn” in an uncontrollable “tic-like” manner. She also reported that she suffers from episodes of paroxysmal dystonia (ie, a brief freezing of her body that occurs while walking and lasting a few seconds), and echolalia. As noted, the family history is remarkable for alcohol dependence in both parents and her brother.

In terms of her past personal psychiatric history, Ms. CJ described discrete episodes consistent with major depression, consisting of dysphoric mood, spontaneous tearfulness, difficulty concentrating, slowed mentation, feelings of hopelessness, helplessness, and pessimism about the future, and active suicidal ideation. She was not, however, able to disentangle complaints of appetite and sleep disturbance during these discrete episodes from her persistent symptoms related to MS.

The mental status examination revealed a casually dressed white female, who walked into the office carrying a stick that she reported she uses as a cane. Ms. CJ was alert, awake, animated, likeable, engageable, and cooperative during the evaluation. Her affect was bright, showed full range and was appropriate to ideational content (eg, she became tearful when recalling her father’s repeated episodes of sexual abuse). Her mood was reported to be sad and concerned. Her speech was mildly pressured, but was of normal rhythm, loudness, and tonality. Her thinking was logical, relevant, coherent, and goal directed; she denied hallucinations and delusions. She abstracted well to simple proverbs. Her cognitive examination was essentially normal, with the exception of failing to recall one of three items after a lapse of several minutes and difficulty with serial seven subtractions; however, she later reported that her performance was adversely affected by an intense urge to urinate and concerns about urge incontinence. At the time of her evaluation, she was receiving

thyroid supplementation for hypothyroidism, a low dose of aripiprazole for her tic disorder, citalopram for her recurrent major depression, and simvastatin for hypercholesterolemia and a family history of stroke.

Dronabinol was initiated at an oral dose of 2.5 mg BID, which was well-tolerated and raised within 1 week to its maintenance dose of 5.0 mg BID. Using 100 mm Visual Analogue Scales, the patient self-reported the following improvement: reduction in the choking sensation of her throat (~26% reduction); reduction in feeling anxious (~30% reduction); improved control of vocalizations that were less frequent, associated with less "tension," and quieter (~25% reduction); fewer episodes of awakening from sleep (~20% reduction); elimination of "high" (~97% reduction); and markedly diminished craving for, and almost complete cessation of, illicit use of marijuana (~86% reduction). Unfortunately, relative to how Ms. CJ felt while illicitly using marijuana, there was a variably experienced worsening of her subjective sense of "unwellness;" however, she insisted on maintenance pharmacotherapy with dronabinol.

DISCUSSION

This patient with a positive parental history of alcohol dependence began episodic illicit use of marijuana in late adolescence. She was, however, essentially abstinent from marijuana use for a period of ~12 years while engaged heavily in athletic training as a marathon runner and triathlon participant; interestingly, the patient referred to this period of intense athletic training as an "addiction." The onset of MS was associated with falling and lower-extremity weakness, beginning in her mid 30s, which progressed to include the sensation of choking, abnormal gut motility and difficulty with control of her anal sphincter, pain in her feet and lower extremities, and episodes of paroxysmal dystonia that contributed to a subjective sense of "unwellness." Approximately 7 years after the onset of falling and lower extremity weakness, Ms. CJ noted the beginning of involuntary nonsensical utterances of stereotyped phonemes that progressed to coprolalia; she also described echolalia. With the onset and progression of her MS, Ms. CJ resumed marijuana abuse that progressed rapidly to dependence

and an almost continuous state of being "high," which interfered profoundly with her social and occupational functioning. She accepted a referral to an intensive outpatient substance-abuse rehabilitation program after being criminally charged with illegal possession of marijuana in the Commonwealth of Virginia, a charge that included the possibility of imprisonment if convicted. On admission to the program, Ms. CJ acknowledged her marijuana dependence and the social and vocational impairment associated with her state of almost continuous "high;" however, she reported her firmly held conviction that illicitly abused marijuana was the only intervention that provided her with marked subjective symptomatic relief, of the several that were medically prescribed, from many of her disabling symptoms of MS. Because of the severity of her marijuana dependence and serious nature of her legal problems, reluctantly, a cautious trial of dronabinol was begun with the patient's full voluntary consent and willing participation.

Ms. CJ tolerated the medication with diminution of craving and discontinuation of illicit cannabis abuse; she reported that she was no longer "high." Thus, the use of dronabinol in this instance is highly analogous to the use of methadone as an opiate agonist therapy for the treatment of heroin dependence. Moreover, symptoms referable to basal ganglia involvement specifically (ie, involuntary vocalizations and paroxysmal dystonia) and core symptoms of this demyelinating disorder attenuated. Clearly, interindividual variability is to be expected with respect to sensitivity to therapeutic effects of dronabinol and the profile of symptoms that will respond to this intervention.

The susceptibility of Ms. CJ to marijuana dependence may include genetic factors, given the family history of ethanol dependence. Also, this case presentation highlights the relatively rare co-occurrence of basal ganglia involvement in MS, including complex vocal tics.

CONCLUSION

This case report contributes to a growing, albeit inconclusive, literature supporting exploration of medicinal cannabis extracts for the symptomatic treatment of MS. Outstanding issues include patient selection criteria, primary target

symptoms, measurement tools, preparation, and formulation of medicinal extracts of cannabis sativa, dose, and route of administration, among other research issues. **CNS**

REFERENCES

1. Consroe P, Musty R, Rein J, Tillery W, Pertwee R. The perceived effects of smoked cannabis on patients with multiple sclerosis. *Eur Neurol.* 1997;38:44-48.
2. Chong MS, Wolff K, Wise K, Tanton C, Winstock A, Silber E. Cannabis use in patients with multiple sclerosis. *Mult Scler.* 2006;12:646-651.
3. Clark AJ, Ware MA, Yazer E, Murray TJ, Lynch ME. Patterns of cannabis use among patients with multiple sclerosis. *Neurology.* 2004;62:2098-2100.
4. Killestein J, Hoogervorst EL, Reif M, et al. Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology.* 2002;58:1404-1407.
5. Zajicek J, Fox P, Sanders H, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomized placebo-controlled trial. *Lancet.* 2003;362:1517-1526.
6. Zajicek JP, Sanders HP, Wright DE, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. *J Neurol Neurosurg Psychiatry.* 2005;76:1664-1669.
7. Fox P, Bain PG, Glickman S, Carroll C, Zajicek J. The effect of cannabis on tremor in patients with multiple sclerosis. *Neurology.* 2004;62:1105-1109.
8. Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler.* 2004;10:434-441.
9. Wade DT, Makela PM, House H, Bateman C, Robson P. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. *Mult Scler.* 2006;12:639-645.
10. Vaney C, Heinzl-Gutenbrunner M, Jobin P, et al. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. *Mult Scler.* 2004;10:417-424.
11. Svendsen K, Jensen T, Bach F. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomized double blind placebo controlled crossover trial. *BMJ.* 2004;329:253-260.
12. Rog DJ, Nurmikko M, Bereza B, Gordon A, Piwko C, Einarson TR. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. *Curr Med Res Opin.* 2007;23:17-24.
13. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology.* 2005;65:812-819.
14. Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ. An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. *Mult Scler.* 2004;10:425-433.
15. Freeman RM, Adekanmi O, Waterfield MR, Waterfield AE, Wright D, Zajicek J. The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS). *Int Urogynecol.* 2006;17:636-641.
16. Hashiguchi S, Ogasawara N, Mine H, Kawachi Y. Multiple sclerosis with caudate lesions on MRI. *Intern Med.* 2001;40:358-362.
17. Lana-Peixoto MA, Teixeira AL. Simple phonic tic in multiple sclerosis. *Mult Scler.* 2002;8:510-511.
18. Fernandez-Ruiz J, Lastres-Becker I, Cabranes A, Gonzalez S, Ramos JA. Endocannabinoids and basal ganglia functionality. *Prostaglandins, Leukotrienes and Essential Fatty Acids.* 2002;66(2-3):257-267.
19. Muller-Vahl KR. Cannabinoids reduce symptoms of Tourette's syndrome. *Expert Opin Pharmacother.* 2003;4:1717-1725.
20. Wilson RI, Nicoll RA. Endocannabinoid signaling in the brain. *Science.* 2002;296:678-682.
21. Muller-Vahl KR, Schneider U, Koblenz A, et al. Treatment of Tourette's syndrome with Δ^9 -tetrahydrocannabinol (THC): a randomized crossover trial. *Pharmacopsychiatry.* 2002;35:57-61.
22. Baker D, Jackson SJ, Pryce G. Cannabinoid control of neuroinflammation related to multiple sclerosis. *Br J Pharmacol.* 2007;152:649-654.