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Dr. Gupta summarizes the evidence on medical marijuana

Medical marijuana: Do the benefits outweigh the risks?

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Limited evidence supports its use for treating some conditions, but risks may be substantial

There is a need for additional treatment options to improve symptoms, enhance the quality of life (QOL), and reduce suffering among patients who have chronic medical illness. Medical marijuana (MM) has the potential to help patients who have certain medical conditions in states where it is legal for prescription by a licensed medical provider.

Cannabis has a long history of medicinal use (***Box 1,***[1-12] ***page 35***). Two derivatives of the *Cannabis* plant—cannabinoid delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)—are responsible for most of its effects. Some of these effects, including analgesia, decreased muscle spasticity, and reduced eye pressure, have been harnessed for their potential therapeutic effects (***Box 2,***[13-19] ***page 36***). As of November 2017, 29 states had legalized *Cannabis* for medical use, and several had legalized its recreational use.[12]

With the increasing availability of MM, psychiatrists are likely to encounter patients who are using it or who will ask them about it. This article reviews evidence related to using MM to treat patients with neuropathic pain; chemotherapy-induced nausea and vomiting (CINV); epilepsy; multiple sclerosis (MS); glaucoma; Crohn's disease; Parkinson's disease; amyotrophic lateral sclerosis; dementia-related behavioral disturbances; posttraumatic stress disorder (PTSD); and anxiety.

Medical illnesses

Neuropathic pain. Chronic neuropathic pain affects an estimated 7% to 8% of adults.[20] Patients with neuropathic pain

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Box 1

Cannabis: A history of medicinal use

Cannabis has been cultivated since ancient times, beginning in China and India. The earliest reference of its use for healing purposes may have been in the Chinese Pharmacopeia, circa 1500 BC.[1] In 1839, Dr. William Brooke O'Shaughnessy introduced *Cannabis* Indica, or "Indian hemp," to the western world after a professorship in Calcutta, India.[2] In the early 1840s, an English physician, Dr. John Clendinning, prescribed *Cannabis* for migraine headache.[3] In the 19th and early 20th centuries, several prominent physicians advocated using *Cannabis* for migraines; Sir William Osler did so in his textbook, *The principles and practice of medicine*.[4] It was listed in the U.S. Pharmacopeia in 1850 but removed in 1942.[5,6]

Until 1937, *Cannabis* was used in the United States for medicinal purposes, such as for treating inflamed skin, incontinence, and sexually transmitted diseases.[7] In 1937, the Marihuana Tax Act, which prohibited the production, importation, possession, use, and dispersal of *Cannabis*, was passed.[8] *Cannabis* became a Schedule I drug under the Controlled Substance Act of 1970.[9]

In 1999, based on available evidence, the Institute of Medicine (IOM) concluded *Cannabis* had less likelihood of dependence than benzodiazepines, opiates, cocaine, or nicotine. The IOM also concluded that the symptoms of withdrawal were mild in comparison with benzodiazepines or opiates. Finally, the IOM stated that *Cannabis* was not a "gateway" drug.[10]

In 1996, California was the first state to reimplement medicinal use of *Cannabis* under the Compassionate Use Act, also known as Proposition 215.[11] This act allowed individuals to retain or produce *Cannabis* for personal consumption with a physician's approval. Many states eventually followed California's lead. As of November 2017, 29 states, the District of Columbia, Guam, and Puerto Rico had regulated *Cannabis* use for medical purposes,[12] and recreational use had been approved in 7 states and the District of Columbia.

Clinical Point

THC and CBD can improve central and peripheral neuropathic pain

are often treated with anticonvulsants, antidepressants, opioids, and local anesthetics[21]; however, these medications may not provide substantial relief. Research has revealed that THC and CBD can improve central and peripheral neuropathic pain, as well as pain associated with rheumatoid arthritis and fibromyalgia.[22]

Wilsey et al[23] evaluated the analgesic effects of smoked MM for neuropathic pain in a small (N = 38) double-blind, randomized controlled trial (RCT). Patients in this study had a preexisting diagnosis of complex regional pain syndrome, spinal cord injury, peripheral neuropathy, or nerve injury. To prevent any unforeseen adverse outcomes related to *Cannabis* use, participants were required to have previous exposure to *Cannabis*. Patients were excluded if they had major mental illness, substance abuse, or other major medical ailments.

Participants smoked high-dose *Cannabis* cigarettes (7% THC), low-dose *Cannabis* cigarettes (3.5% THC), or placebo cigarettes. Pain was measured on a visual analog scale (VAS) that ranged from 0 (no pain) to 100 (worst possible pain). Compared with the placebo group, significant analgesia was achieved in both *Cannabis* groups (P = .016). The high-dose group had greater neurocognitive impairment.

Ware et al[24] conducted a crossover RCT (N = 23) to determine the efficacy of smoked MM for neuropathic pain. Participants had neuropathic pain for at least 3 months that was caused by trauma or surgery, with an average weekly pain intensity score >4 on scale of 0 to 10. Patients with pain due to cancer, nociceptive causes, unstable medical conditions, current substance abuse, history of a psychotic disorder, or suicidal ideation were excluded. Participants were assigned to a 9.4% THC group or a 0% THC group. Pain intensity was evaluated daily via telephone. Participants in the 9.4% THC group had statistically lower pain intensity compared with the 0% THC group (P = .023). Common adverse effects reported by those in the 9.4% group included headache, dry eyes, burning sensation, dizziness, numbness, and cough.

In an RCT of vaporized *Cannabis*, 39 patients with a diagnosis of complex regional pain syndrome, thalamic pain, spinal cord injury, peripheral neuropathy, radiculopathy, or nerve injury were assigned

Medical marijuana

Clinical Point

Two synthetic cannabinoids are FDA-approved for treating chemotherapy-induced nausea and vomiting

Box 2

The effects of *Cannabis*

Marijuana is harvested from the plant *Cannabis sativa* and composed of 400 lipophilic chemical compounds, including phytocannabinoids, terpenoids, and flavonoids.[13] The plant contains compounds termed "cannabinoids." Two of these derivatives in particular are responsible for most of the effects of marijuana: cannabinoid delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC has a comparable structure and binding mechanism to anandamide, a naturally occurring fatty acid neurotransmitter present within the human brain.[14-16] The endogenous endocannabinoid system and its receptors are found throughout the entire body (brain, organs, glands, immune cells, and connective tissues).

THC binds to cannabinoid receptors CB_1 and CB_2. CB_1 is found predominantly in the CNS. CB_2 is found predominantly outside the CNS and is associated with the immune system.[14-16] The effects of THC include euphoria, relaxation, appetite stimulation, improvement of nausea and vomiting, analgesia, decreased muscle spasticity, and reduced eye pressure.[14,15] CBD may have anxiolytic, antipsychotic, anticonvulsive, and analgesic effects.

The rate of absorption of THC and CBD depends both on the potency of the cannabinoid as well as the mechanism of consumption. *Cannabis* can be administered by multiple routes, including via smoking, oral ingestion, or IV.[16] When *Cannabis* is smoked (the route for the most rapid delivery), THC is transported from the lungs to the bloodstream and reaches peak concentrations in 3 to 10 minutes. Oral ingestion (capsules, tinctures, sprays, and edibles) has a more flexible onset of action, usually occurring in 30 to 120 minutes, with effects lasting 5 to 6 hours. IV administration has rapid effects; the onset can occur within seconds to minutes, and effects can last 2 to 3 hours. The IV form allows 90% of THC to be distributed in plasma and can rapidly penetrate highly vascularized tissues, such as the liver, heart, fat, lungs, and muscles.

Pharmaceutical manufacturers have used cannabinoid derivatives to produce *Cannabis*-based medications for treating medical conditions. Nabilone, a potent agonist of the CB_1 receptor, became available as a Schedule II medication in 1981 and was approved for patients with chemotherapy-induced nausea and vomiting (CINV).[17] In 1985, dronabinol was introduced as an antiemetic for CINV as well as an appetite stimulant for patients with conditions associated with excessive weight loss.[18] Another option, nabiximols, is an oral mucosal spray that consists of THC and CBD in a 1:1 ratio.[19] Nabiximols is approved in Canada for pain relief in end-stage cancer patients and pain associated with multiple sclerosis.[19]

to a medium-dose (3.53% THC), low-dose (1.29% THC), or placebo group.[25] Serious mental illness, substance abuse, and medical conditions were cause for exclusion. Participants received vaporized marijuana (average 8 to 12 puffs per visit) over 3 sessions. A 30% pain reduction was achieved by 26% of those in the placebo group, 57% of those in the low-dose group, and 61% of individuals in the high-dose group; the difference between placebo and each *Cannabis* group was statistically significant.

Chemotherapy-induced nausea and vomiting. Up to 80% of patients who receive chemotherapy experience CINV, which occurs from 24 hours to 7 days after receiving such therapy.[26] CINV negatively influences a patient's QOL and may impact the decision to continue with chemotherapy. Use of MM can help to diminish vomiting by binding to central CB_1 receptors and averting the prometic effects of dopamine and serotonin.[27] Two synthetically derived cannabinoids, dronabinol and nabilone, are FDA-approved for treating CINV.

In a small (N = 64) parallel-group RCT, Meiri et al[27] compared dronabinol with the commonly used antiemetic ondansetron and with a combination of dronabinol and ondansetron for treating CINV in adults. The primary outcome was prevention of delayed-onset CINV. Patients were eligible for this study if they had a malignancy that did not involve bone marrow, were receiving treatment with a moderately to highly emetogenic regimen, were not pregnant, and had an estimated life expectancy of at least 6 weeks after chemotherapy. The patients were randomized to 1 of 4 treatment groups: dronabinol alone, ondansetron alone, dronabinol plus ondansetron, or placebo. Overall, 47% to 58% of the active treatment groups improved, compared with 20% of the placebo group. Combination therapy did not provide any benefit beyond any single agent

alone. All active treatments reduced nausea compared with placebo; there was no difference between active treatment groups. This study was limited by low enrollment.

Tramèr et al[28] conducted a systematic review of 30 randomized comparisons of MM with placebo or antiemetics. The reviewed studies were completed between 1975 to 1997 and analyzed a total of 1,366 patients. Nabilone was evaluated in 16 trials; dronabinol was utilized in 13 trials; and IM levonantradol, a synthetic cannabinoid analog of dronabinol, was used in 1 trial. These agents were found to be more effective as an antiemetic compared with prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, or alizapride. In addition, 38% to 90% of patients in these studies preferred MM over the traditional antiemetics.

A Cochrane review[29] suggested that MM may be a viable option for treatment-resistant CINV; however, further studies are needed because current studies have methodological limitations.

Epilepsy. Maa and Figi[30] reported a case of a 5-year-old girl who had Dravet syndrome, which resulted in 50 generalized tonic-clonic seizures daily; multiple anticonvulsants did not alleviate these seizures. Because of her recurring seizures, the patient had multiple cognitive and motor delays and needed a feeding tube. In addition to her existing antiepileptic drug regimen, she was started on adjunctive therapy with a sublingual *Cannabis* extract containing a high concentration of CBD. Her seizures decreased from 50 per day to 2 to 3 nocturnal convulsions per month. The treatment enabled her to stop using a feeding tube, resume walking and talking, and sleep soundly.

dos Santos et al[31] reviewed studies of MM for treating epilepsy. One was a double-blind, placebo-controlled trial that included 15 patients ages 14 to 49 who had secondary generalized epilepsy with a temporal lobe focus. Eight patients received 200 to 300 mg/d of oral CBD for 8 to 18 weeks, and 7 received placebo. Seven patients had fewer seizures and 4 had no seizures. Only 1 patient in the placebo group demonstrated any improvement. Another study in this review included 19 children with treatment-resistant epilepsy: Dravet syndrome (n = 13), Doose syndrome (n = 4), Lennox-Gastaut syndrome (n = 1), or idiopathic epilepsy (n = 1). These patients experienced various types of seizures with a frequency ranging from 2 per week to 250 per day. Overall, 84% of children treated with CBD had fewer seizures: 11% were seizure-free, 42% had a >80% reduction in seizures, and 32% had a 25% to 60% reduction in seizures. Parents also noted additional benefits, including increased attention, improved mood, and improved sleep. CBD was well tolerated in most patients in both studies.

Despite these results, a Cochrane review[32] found that no reliable conclusions can be drawn regarding the efficacy of MM for treating epilepsy.

Multiple sclerosis. According to American Academy of Neurology guidelines, physicians may provide MM as an alternative treatment for patients with MS-related spasticity.[33] Multiple studies have tested MM and MM-related extracts for treating spasticity related to MS.[34,35] In a placebo-controlled crossover study, Corey-Bloom et al[34] reported a significant reduction in spasticity, measured using the modified Ashworth scale, in MS patients receiving *Cannabis* cigarettes vs placebo cigarettes ($P < .0001$). However, compared with the placebo group, patients who received MM had significant adverse effects, primarily cognitive impairment ($P = .003$).

In a multicenter RCT (N = 572 patients with refractory MS spasticity), Novotna et al[36] evaluated nabiximols, an oral mucosal spray of a formulated extract of *Cannabis* that contains THC and CBD in a 1:1 ratio. They assessed spasticity using the Numerical Spasticity Rating Scale (NRS). Results were confirmed by measuring the number of daily spasms, self-report of sleep quality, and activities of daily living. After 4 weeks of single-blind treatment, patients who responded to nabiximols (≥20% improvement in spasticity) were randomized to a placebo group or nabiximols group for 12 additional weeks. After 12 weeks, compared with those who received placebo, those in the nabiximols group experienced a statistically significant

Clinical Point

According to the American Academy of Neurology, medical marijuana may be considered an alternative treatment for MS-related spasticity

Medical marijuana

Clinical Point

Evidence suggests that cannabinoids may facilitate the extinction of aversive memories

Box 3

Cannabis for treating glaucoma, Crohn's disease, Parkinson's disease, and amyotrophic lateral sclerosis

Glaucoma. In a placebo-controlled study, oromucosal administration of medical marijuana (MM) reduced intraocular pressure from 28 mm Hg to 22 mm Hg, with a duration of action of 3.5 hours.[37] However, the American Academy of Ophthalmologists does not recommend treating glaucoma with MM because the effect is short-lasting, and MM causes significant cognitive impairment compared with other standardized treatments.[38] MM also leads to decreased blood pressure, which lowers blood flow to the optic nerve, thus increasing the risk of blindness.

Crohn's disease. A randomized controlled trial (RCT) of MM for Crohn's disease was conducted using the Crohn's Disease Activity Index (CDAI) to assess for remission. In this 8-week study, 21 individuals with Crohn's disease were administered smoked MM (115 mg of delta-9-tetrahydrocannabinol [THC]) or placebo.[39] Eligible patients were at least 20 years old, had active Crohn's disease (CDAI >200), and had not responded to medical treatment for the illness. Compared with those who received placebo, patients who received MM experienced a statistically significant reduction in CDAI scores ($P < .05$). However, at follow-up 2 weeks after the study, when MM was no longer administered, there was no difference in mean CDAI scores between the 2 groups. Five of the 11 patients in the MM group achieved clinical remission, compared with 1 of 10 in the placebo group, but this difference was not statistically significant.

Parkinson's disease (PD). According to the American Academy of Neurology, oral *Cannabis* extracts are "probably ineffective" for levodopa-induced dyskinesia in patients with PD.[40] Reported benefits have come mainly from self-report studies. A 2014 survey (22 patients) found a significant reduction in PD symptoms—mainly relief from drug-induced tremor and pain—when measured using the Unified Parkinson's Disease Rating Scale (UPDRS). Patients also reported better sleep and reduced pain (measured with a visual analog scale [VAS]). An exploratory double-blind placebo trial (N = 119) found no difference in mean UPDRS and no difference in any neuroprotective measures.[41] However, the experimental group had a significantly higher quality of life (QOL; $P = .05$). A similar double-blind crossover study that included 19 patients found no significant difference in dyskinesia, as measured with the UPDRS, in the group receiving oral *Cannabis* extract compared with the placebo group.[42]

Amyotrophic lateral sclerosis (ALS). A randomized double-blind crossover trial of 27 ALS patients found that an oral THC extract (dronabinol, 5 mg, twice daily) had no significant effects on spasticity, as measured with the VAS.[43] There was also no significant difference between the experimental and placebo groups on number of spasms (also measured with a VAS), quality of sleep (measured with the Sleep Disorders Questionnaire), or QOL (measured with the Amyotrophic Lateral Sclerosis Assessment questionnaire).

reduction in spasticity based on NRS score ($P = .0002$).

For a summary of evidence on MM for treating glaucoma, Crohn's disease, Parkinson's disease, and amyotrophic lateral sclerosis, see ***Box*** [37-43]).

Psychiatric illnesses

Dementia-related behavioral disturbances. A few clinical trials with small sample sizes have found evidence supporting the use of MM compounds for alleviating neuropsychiatric symptoms of patients with dementia. An open-label pilot study of 6 individuals with late-stage dementia who received dronabinol, 2.5 mg/d, for 2 weeks, found a significant reduction (compared with baseline) in nighttime motor activity as measured with an actometer ($P < .0028$).[44] The secondary Neuropsychiatric Inventory (NPI) assessment found reductions in aberrant motor behavior ($P = .042$), agitation ($P = .042$), and nighttime behaviors ($P = .42$).

A 2014 retrospective analysis of 40 inpatients with dementia-related agitation and appetite loss who were treated with dronabinol (mean dosage: 7.03 mg/d) found reductions in all aspects of agitation, including aberrant vocalization, motor agitation, aggressiveness, and treatment resistance, as measured with the Pittsburgh Agitation Scale ($P < .0001$).[45] The study found no significant improvements in appetite, Global Assessment of Functioning mean score, or number of times patients awoke during the

night. Adverse effects included sedation and delirium.

A RCT of 50 dementia patients with clinically relevant neuropsychiatric symptoms found no significant difference in mean NPI scores between patients given placebo and those who received nabiximols, 1.5 mg, 3 times daily.[46] There were no significant differences found in agitation, QOL, life activities, or caregiver-scored Caregiver Global Impression of Change scale.

In a small RCT, THC was safe and well tolerated in 10 older patients with dementia.[47] A 2009 Cochrane review[48] concluded that there was no evidence for the efficacy of MM in treating the neuropsychiatric symptoms related to dementia.

PTSD. Preclinical evidence shows that the endocannabinoid system is involved in regulating emotional memory. Evidence also suggests that cannabinoids may facilitate the extinction of aversive memories.[49,50]

In 2009, New Mexico became the first state to authorize the use of MM for patients with PTSD. In a study of patients applying for the New Mexico Medical Cannabis Program, researchers used the Clinician Administered Posttraumatic Scale (CAPS) to assess PTSD symptoms.[51] A retrospective chart review of the first 80 patients evaluated found significant ($P < .0001$) reductions of several PTSD symptoms, including intrusive memories, distressing dreams, flashbacks, numbing and avoidance, and hyperarousal, in the group using MM vs those not using MM. There also was a significant difference in CAPS total score ($P < .0001$). Patients reported a 75% reduction in PTSD symptoms while using MM. This study has several limitations: It was a retrospective review, not an RCT, and patients were prescreened and knew before the study began that MM helped their PTSD symptoms.

In another retrospective study, researchers evaluated treatment with nabilone, 0.5 to 6 mg/d, in 104 incarcerated men with various major mental illnesses; most (91%) met criteria for *Cannabis* dependence.[52] They found significant improvements in sleep and PTSD symptoms.

A double-blind RCT evaluated MM in 10 Canadian male soldiers with PTSD who experienced nightmares despite standard medication treatment. Adjunctive nabilone (maximum dose: 3 mg/d) resulted in a reduction in nightmares as measured by the CAPS recurrent distressing dream of the event item score.[53]

Currently, there are no adequately powered RCTs of MM in a diverse group of PTSD patients. Most studies are open-label, enriched design, and included white male veterans. No well-conducted trials have evaluated patients with noncombat-related PTSD. Most of the relevant literature consists of case reports of *Cannabis* use by patients with PTSD.

continued

Related Resources

- Nguyen DH, Thant TM. Caring for medical marijuana patients who request controlled prescriptions. Current Psychiatry. 2017;16(8):50-51.
- National Institute on Drug Abuse. Marijuana as medicine. https://www.drugabuse.gov/publications/drugfacts/marijuana-medicine.

Drug Brand Names

Alizapride • Litican, Superan
Chlorpromazine • Thorazine
Domperidone • Motilium
Dronabinol • Marinol, Syndros
Haloperidol • Haldol
Metoclopramide • Reglan
Nabilone • Cesamet
Nabiximols • Sativex
Ondansetron • Zofran, Zuplenz
Prochlorperazine • Compazine
Thiethylperazine • Torecan

Clinical Point

Patients indicate that *Cannabis* relieves anxiety, but there is no replicated evidence based on RCTs to support this

Bottom Line

Limited evidence suggests medical marijuana (MM) may be beneficial for treating a few medical conditions, including neuropathic pain and chemotherapy-induced nausea and vomiting. There is no clear and convincing evidence MM is beneficial for psychiatric disorders, and *Cannabis* can impair cognition and attention and may precipitate psychosis. The risk of deleterious effects are greater in adolescents.

Medical marijuana

Clinical Point

Heavy *Cannabis* use impairs motivation and could precipitate psychosis in vulnerable individuals

Anxiety disorders. Patients frequently indicate that smoking *Cannabis* helps relieve their anxiety, although there is no replicated evidence based on double-blind RCTs to support this. However, in rat models CBD has been shown to facilitate extinction of conditioned fear via the endocannabinoid system.[54-56] The mechanism of action is not completely understood. CBD has been shown to have antagonistic action at CB_1 and CB_2 receptors. It may have similar effects on memory extinction and may be an adjunct to exposure therapies for anxiety disorders.

Das et al[57] studied the effects of CBD (32 mg) on extinction and consolidation of memory related to contextual fear in 48 individuals. They found that CBD can enhance extinction learning, and suggested it may have potential as an adjunct to extinction-based therapies for anxiety disorders.

Caveats: Adverse effects, lack of RCTs

Cannabis use causes impairment of learning, memory, attention, and working memory. Adolescents are particularly vulnerable to the effects of *Cannabis* on brain development at a time when synaptic pruning and increased myelination occur. Normal brain development could be disrupted. Some studies have linked *Cannabis* use to abnormalities in the amygdala, hippocampus, frontal lobe, and cerebellum. From 1995 to 2014, the potency of *Cannabis* (THC concentration) increased from 4% to 12%.[58] This has substantial implications for increased abuse among adolescents and the deleterious effects of *Cannabis* on the brain.

Heavy *Cannabis* use impairs motivation and could precipitate psychosis in vulnerable individuals. *Cannabis* use may be linked to the development of schizophrenia.[59]

There are no well-conducted RCTs on the efficacy of MM, and adequate safety data are lacking. There is also lack of consensus among qualified experts. There is soft evidence that MM may be helpful in some medical conditions, including but not limited to CINV, neuropathic pain, epilepsy, and MS-related spasticity. Currently, the benefits of using MM do not appear to outweigh the risks.

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