fortune Journals

Research Article

ARCHIVES OF INTERNAL MEDICINE RESEARCH

ISSN: 2688-5654

# Therapeutic Use of Medical Cannabis Beyond Pain Management in Physical Medicine and Rehabilitation

**Andrew Cameron[1], Marcel P. Fraix[2], Devendra K. Agrawal[1]***


## Abstract

Medical cannabis has emerged as a rapidly evolving therapeutic modality with expanding clinical interest beyond its traditional role in pain management. Particularly relevant to Physical Medicine and Rehabilitation (PM&R), where the focus extends beyond symptom control to functional restoration and optimal quality of life, key non-pain indications described in the literature include management of spasticity, neurologic and seizure disorders, sleep disturbances, and chemotherapy-induced nausea and vomiting (CINV). This PM&R-centered narrative review synthesizes current evidence on the efficacy, mechanisms, and clinical implications of cannabis use for non-pain conditions, with emphasis on its interaction with the endocannabinoid system, including CB1- and CB2-receptor–mediated pathways influencing neuromodulation, inflammation, and homeostasis. Across multiple conditions, cannabinoids demonstrate modest benefits in symptom reduction, including improvements in patient-reported spasticity in multiple sclerosis, significant seizure reduction in treatment-resistant pediatric epileptic syndromes, antiemetic effects in refractory CINV, and appetite stimulation in cachectic states. Additionally, subjective improvements in sleep quality have been observed, though objective changes in sleep architecture remain inconsistent. However, there remains limited evidence supporting meaningful improvements in functional outcomes and quality of life. Cannabis use may negatively impact rehabilitation through dose-dependent cognitive impairment, sedation, impaired motor learning, and increased fall risk. Significant challenges persist, including lack of standardized dosing, variability in formulations and THC:CBD ratios, inconsistent product labeling, and limited high-quality randomized controlled trials assessing long-term functional outcomes. Regulatory barriers, including discrepancies between federal and state laws, further complicate clinical implementation and research. This review highlights the gap between symptomatic relief and functional recovery, emphasizing the need for PM&R-specific research focused on rehabilitation-relevant outcomes that objectively measure functional independence and quality of life. Bridging this gap will be critical to defining a role for medical cannabis within rehabilitation medicine and optimizing patient-centered care that maximizes function.


**Keywords:** Appetite stimulation; Cannabinoids; Chemotherapy-induced nausea and vomiting (CINV); Endocannabinoid system (ECS); Epilepsy; Medical cannabis; Physical medicine and rehabilitation (PM&R); Rehabilitation; Sleep; Spasticity.

**Affiliation:**

[1]Department of Translational Research, Western University of Health Sciences, 309 E. Second Street, Pomona, California 91766, USA

[2]Department of Physical Medicine and Rehabilitation, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, California 91766 USA

**ORCID:**
Devendra K. Agrawal: 0000-0001-5445-0013

***Corresponding author:**
Devendra K. Agrawal, MSc, PhD (Biochem), PhD (Med Sci), MBA, MS (ITM), FAAAAI, FAHA, FAPS, FIACS Director and Professor, Department of Translational Research, Western University of Health Sciences, 309 E. Second Street, Pomona, California 91766, USA.

**Citation:** Andrew Cameron, Marcel P. Fraix, Devendra K. Agrawal. Therapeutic Use of Medical Cannabis Beyond Pain Management in Physical Medicine and Rehabilitation. Archives of Internal Medicine Research. 9 (2026): 156-167.

**Received:** May 24, 2026
**Accepted:** May 27, 2026
**Published:** July 01, 2026

Cameron A, et al., Arch Intern Med Res 2026
DOI:10.26502/aimr.0246

## Introduction

Medical cannabis refers to the therapeutic use of cannabinoids derived from the Cannabis plant (Cannabis sativa and Cannabis indica) or synthetic analogs for medical purposes. Cannabis contains over 500 chemical compounds, including terpenes, flavonoids, and more than 120 phytocannabinoids. Of these cannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) being the most extensively studied [1-3]. These compounds exert their physiological effects through interaction with the endocannabinoid system (ECS), a widespread neuromodulatory network of receptors that interact with various types of cannabinoids. The ECS is necessary for homeostasis of multiple biological processes, including neurotransmission, immune function, metabolism, and stress responses [4,5]. Through these mechanisms, cannabinoids can influence a broad range of physiological systems, which helps explain their versatile therapeutic potential.

Cannabinoids can be categorized into three groups. Endogenous cannabinoids, such as anandamide and 2-arachidonoylglycerol, are produced naturally in the body [3,5]. Phytocannabinoids are plant-derived compounds and include THC and CBD. Synthetic cannabinoids are manufactured in a lab and mimic or modify cannabinoid activity [5]. THC is the primary psychoactive component of cannabis and is responsible for effects such as euphoria, relaxation, and altered perception. In contrast, CBD is nonpsychoactive and has been associated with anti-inflammatory, anxiolytic, antioxidant, and neuroprotective properties [3]. The interplay between these compounds contributes to the clinical effects of medical cannabis, which will vary depending on the dose, specific formulation, and individual patient factors.

Interest in medical cannabis has increased significantly in recent years, largely driven by expanding legalization at the state level. Although cannabis remains classified as a Schedule I substance at the federal level, meaning it is considered to have no accepted medical use and a high potential for abuse, most states in the United States now permit some form of medical or recreational cannabis use [6]. Currently, cannabis is legal in 38 states, the District of Columbia, Puerto Rico, and 3 US territories. Idaho, Kansas, and Nebraska still maintain complete prohibition of all cannabis products [6-8]. A recent push by the Department of Health and Human Services to reschedule cannabis to Schedule III reflects the potential medical utility for cannabis and a lower potential for abuse than previously thought. Rescheduling cannabis is thought to loosen restrictions for clinical research and highlights the need to better understand the therapeutic role of cannabis beyond pain management [7]. This discrepancy between federal and state regulation has created both opportunities and challenges, particularly in the context of clinical research and standardization of care.

Routes of administration for cannabis are diverse and include inhalation (onset of action within minutes), oral ingestion (onset of action from 30 minutes to 3 hours), and less common methods such as transdermal or transmucosal delivery. The most common methods of cannabis ingestion are smoking (79.4%), followed by edibles (41.6%), then vaping (30.3%) [9]. These routes differ significantly in pharmacokinetic properties, influencing onset, duration, and bioavailability. These differences complicate dosing strategies and contribute to variability in clinical outcomes. Further complexity arises from variability in THC to CBD ratios across different cannabis products along with lack of standardized dosing, which create challenges for patients and clinicians to reliably interpret and titrate cannabis use [10,11]. Ratios of THC: CBD are highly variable depending on the specific strain of cannabis in question. Generally, the current classification system distinguishes cannabis cultivars as chemotype I (THC rich), II (THC/CBD balanced ratios), III (CBD rich), IV (cannabigerol rich), or V (cannabinoid free) [5]. Standardizing the dose of medical cannabis is difficult, which is reflected by studies demonstrating that THC levels listed on commercial cannabis products are often higher than what they contain [10,11].

From a rehabilitation perspective, a few concerns remain. Potential effects of cannabinoids include cognitive impairment, sedation, impaired motor and verbal learning, impaired working memory, impaired executive functioning, slowed processing speed and reduced attention [12-15]. These impairments have the potential to interfere with participation in various rehabilitation therapies and limit functional recovery. As a result, while cannabis has been shown to relieve symptoms for various conditions, its impact on true functional recovery and rehabilitation outcomes remains under investigation.

The evaluation of whether medical cannabis provides symptom relief versus true functional improvement forms a central theme of this narrative review. In PM&R, success is defined not only by reduction in symptoms but by meaningful gains in independence, mobility, and participation in activities of daily living (ADLs). Evidence suggests that while the use of medical cannabis may lead to reported improvements in symptom control, this does not reliably translate to meaningful functional gains [16,17]. Continued research evaluating how medical cannabis fits within a functional framework is essential for appropriate integration into clinical practice, especially in the rehabilitation space.

## II. The Endocannabinoid System: Pharmacology and Physiology

To understand the therapeutic potential of medical cannabis, it is essential to examine the structure and function of the endocannabinoid system (ECS), which plays a central

Citation: Andrew Cameron, Marcel P. Fraix, Devendra K. Agrawal. Therapeutic Use of Medical Cannabis Beyond Pain Management in Physical Medicine and Rehabilitation. Archives of Internal Medicine Research 9 (2026): 156-167.

Cameron A, et al., Arch Intern Med Res 2026
DOI:10.26502/aimr.0246

role in mediating the physiologic effects of cannabinoids. The ECS is a complex signaling network composed of cannabinoid receptors, endogenous ligands, and enzymes responsible for ligand synthesis and degradation. Notable functions of the ECS are to modulate immune function, metabolism, and stress responses. Two primary cannabinoid receptors are CB1 and CB2 [5,18-20] (Figure 1). Both CB1 and CB2 receptors are inhibitory G-protein coupled receptors that exert inhibitory effects on transmission of neurotransmitters such as dopamine, gamma-aminobutyric acid (GABA), and glutamate [5]. CB1 receptors are predominantly located in the central and peripheral nervous systems, particularly in regions involved in cognition, memory, motor control, and emotional regulation. These regions include the prefrontal cortex, hippocampus, amygdala, basal ganglia, and cerebellum. They are also found in peripheral tissues of the cardiovascular system [5]. The receptor distribution of CB1 explains many of the cognitive and motor effects associated with THC, including altered perception, impaired memory, and changes in coordination. In contrast, CB2 receptors are primarily expressed in immune cells like microglia and peripheral immune tissues. These receptors are involved in regulating inflammation and immune responses [5]. Activation of CB2 receptors has been associated with anti-inflammatory effects, which may contribute to the therapeutic potential of cannabinoids in conditions that involve inflammation, especially of the nervous system [5].

Endogenous cannabinoids, such as anandamide and 2-arachidonoylglycerol, are synthesized on demand from membrane lipids and act as signaling molecules within the ECS. These ligands are rapidly degraded by specific enzymes, allowing for tight regulation of their effects [18,19]. THC acts as a partial agonist at both CB1 and CB2 receptors, producing its characteristic psychoactive and physiological effects. In contrast, CBD has a more complex mechanism of action. CBD interacts with multiple non-cannabinoid receptors in a dose-dependent fashion–at lower concentrations CBD activates serotonin, glycine, and transient receptor potential (TRP) channels, while additionally activating PPAR-γ and vanilloid receptors at higher concentrations. [5,20]. This broad receptor activity contributes to the diverse effects of CBD, including its anxiolytic and anti-inflammatory properties [3]. Clearly, the widespread distribution of the ECS throughout the body allows cannabinoids to influence a wide range of physiological processes. However, this same complexity also contributes to variability in clinical outcomes with medical cannabis. Individual differences in receptor expression, metabolism, and underlying disease states all influence how patients will respond to medical cannabis therapy.

In the context of rehabilitation medicine, the ECS is relevant due to its diverse involvement in neuromodulation, motor control, inflammation, immune function, metabolic regulation, and stress adaptation. These processes are central to recovery following neurologic injury or chronic disease. Thus, modulating the ECS represents a promising therapeutic target, although the clinical implications remain incompletely understood.

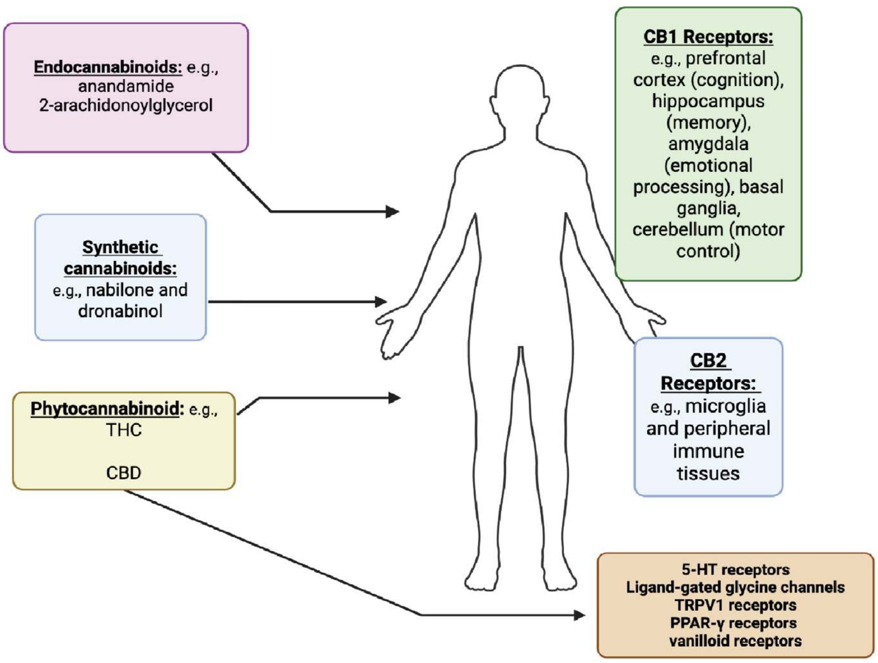


**Figure 1:** The Endocannabinoid System Overview: Endocannabinoids and cannabinoids such as THC modulate CB1 and CB2 receptors, while CBD modulates other receptors such as serotonin (5-HT), glycine, TRP, PPAR-γ and vanilloid receptors.

Cameron A, et al., Arch Intern Med Res 2026
DOI:10.26502/aimr.0246

## III. Expanding Beyond Pain: A Shift in Clinical Focus

Historically, most research on medical cannabis has focused on pain management. An ecological study of U.S. medical cannabis trends from 2020 to 2022 indicates that the most common patient-reported qualifying condition for cannabis use as of 2022 was chronic pain (48.4%) [21]. However, emerging evidence suggests potential benefits for medical cannabis across multiple non-pain conditions. The ECS's "promiscuous" pharmacology allows cannabinoids to influence diverse biological systems [3]. Of note, the current literature reflects a growing interest in medical cannabis to manage spasticity, neurologic disorders, sleep disturbances, and CINV.

Yet, a key limitation remains. Much of the current literature focuses on medical cannabis for symptom relief rather than analyzing objective functional outcomes. In PM&R, success is defined not only by symptom reduction but by improvements in mobility, independence and interdependence, and participation in daily activities.

The distinction between use of medical cannabis for symptom relief versus functional improvement is critical to understand. While cannabinoids may alleviate symptoms, their impact on rehabilitation outcomes remains uncertain and further research is needed.

## IV. Non-Pain Uses of Medical Cannabis: PM&R-Focused

Currently, the US Food and Drug Administration has approved use of medical cannabinoids for certain conditions including HIV/AIDS-related anorexia, CINV, and certain pediatric seizure disorders [22]. In addition, there is promising evidence for the use of medical cannabinoids to manage spasticity (Figure 2).

### A. Spasticity

Spasticity is a common and debilitating condition seen in neurologic disorders such as multiple sclerosis (MS), spinal cord injury (SCI), and as a sequela of stroke. Evidence supporting cannabinoid use is strongest in MS patients [22].

The American Academy of PM&R (AAPM&R) Consensus Guidance on Spasticity Assessment and Management recognizes cannabinoids for their muscle relaxant and anti-inflammatory properties [23]. Specifically, oromucosal nabiximol spray (an extract of equal THC:CBD ratio) showed improvements in patient-reported spasticity as measured by a numeric pain scale compared to placebo, though objective measures such as the Ashworth spasticity scale showed minimal improvement [22-25]. Additionally, a meta-analysis of nine trials involving 2,544 patients with multiple sclerosis found that cannabis-based therapies improved spasticity, particularly with long-term use, and were generally well tolerated. However, differences between studies and possible publication bias reduced confidence in these findings [25].

In other clinical populations, such as in people with spinal cord injury, results are mixed. A review of 34 studies on spinal cord injury suggests that cannabinoids might help reduce spasticity. However, results from these randomized trials are inconsistent and not strong enough to confirm a meaningful clinical benefit. There were also concerns about side effects like fatigue and cognitive impairment, demonstrating modest benefits for medical cannabis yet inconsistent clinical significance [26].

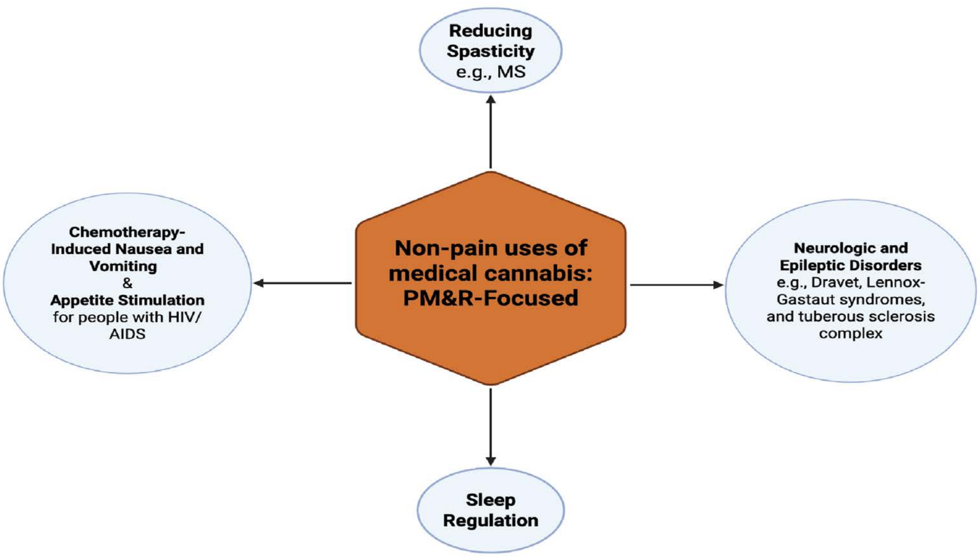


Figure 2: Leading non-pain indications for medical cannabis based on the strongest available evidence in the literature.

Cameron A, et al., Arch Intern Med Res 2026
DOI:10.26502/aimr.0246

Evidence in post-stroke spasticity remains limited. A 2022 RCT of 34 stroke patients demonstrated that an oromucosal spray of nabiximols was well tolerated but showed no significant change in spasticity, as measured by the modified Ashworth scale, electromyographic stretch reflex, numeric rating scales for pain, sleep and bladder function, and reported number of daily spasms [27]. This suggests that while cannabinoid therapy may be safe in this clinical population, its efficacy remains uncertain.

From a functional perspective, cannabinoids appear to improve subjective comfort in those living with spasticity rather than improving objective motor function [28]. This distinction highlights the role for medical cannabis as adjunctive symptom management tools for spasticity rather than primary rehabilitation interventions.

### B. Epileptic and Other Neurologic Disorders: An FDA-approved indication

The FDA has approved pharmaceutical-grade CBD (Epidolex) for treatment-resistant epilepsy syndromes such as Dravet syndrome,

Lennox-Gastaut syndrome, and tuberous sclerosis complex in patients older than one year of age. These epileptic disorders have high-quality RCT evidence that shows meaningful seizure reduction when cannabinoids are utilized for treatment-resistant seizures [29]. Dravet syndrome is a developmental epileptic encephalopathy starting in infancy that involves treatment-resistant seizures. A double-blind clinical trial on 199 children with Dravet syndrome demonstrated that CBD at both 10mg/kg/day and 20 mg/kg/day significantly reduced convulsive seizure frequency by at least 50% compared to placebo. Furthermore, researchers of the study were able to demonstrate a positive change in the Caregiver Global Impression of Change score in the cannabinoid group [30].

The characteristic features of Lennox-Gastaut Syndrome epileptic seizures, often an atonic or “drop” seizure, cognitive impairment, and slow spike-wave pattern on EEG. Phase 3 trials (GWPCARE3 and GWPCARE4 studies) demonstrated that 14 weeks of adjunctive oral cannabidiol at 20 mg/kg daily significantly reduced drop seizure frequency in Lennox–Gastaut syndrome compared to placebo, with effects observed early and sustained over time [31,32].

Tuberous sclerosis is an autosomal dominant disease that causes hamartomas in multiple organ systems, especially in the brain and eyes. Characterized by primarily focal seizures, tuberous sclerosis patients experience severe refractory neurological symptoms that require novel therapeutic interventions. A randomized controlled trial (GWPCARE6 study) demonstrated that cannabidiol significantly reduced seizure frequency in patients with tuberous sclerosis complex compared to placebo, with the 25 mg/kg/day dose showing a more favorable safety profile than the 50 mg/kg/day dose [33].

The positive impacts of medical cannabinoids on people with neurologic and epileptic disorders have profound functional implications, including reduced fall risk, improved participation in therapy, and decreased caregiver burden. From a functional perspective, seizure reduction has profound implications for quality of life. Reducing the frequency of drop seizures in this population prevents falls and injury and promotes mobility and independence. Thus, medical cannabinoid therapy is a useful adjunct in addition to other first-line therapies for seizure control [31].

In movement disorders such as Parkinson’s disease, cannabinoids may improve non-motor symptoms such as sleep, appetite, spasticity, lack of appetite, tremor and dystonia, but overall cannabinoids have demonstrated limited impact on motor function in people with Parkinson’s disease [34,35].

Emerging data suggests a neuroprotective effect of medical cannabinoids for people with traumatic brain injury (TBI). Preclinical data suggests that cannabinoids interact with neurons, microglia, and astrocytes, and they have anti-inflammatory and neuroprotective effects, which makes cannabis a promising tool for the management of traumatic brain injury [36,37].

Cannabinoids may provide neuroprotection via modulation of the ECS, reducing neuroinflammation, preventing neuronal cell loss, and decreasing the blood-brain barrier permeability [37]. In mice models, cannabinoid type-2 receptor (CB2R) activity was shown to support post-stroke neurogenesis and neuroblast migration, with receptor blockade impairing neuronal regeneration and worsening functional recovery. However, these findings have not translated to human clinical benefit and research is preliminary [38]. A retrospective cohort study of TBI patients found that pre-injury cannabis use was associated with similar mortality but improved functional outcomes, shorter hospital stays, and higher rates of discharge home, suggesting a potential neuroprotective effect of cannabinoids in TBI recovery [39].

From a functional perspective, medical cannabinoids may additionally have relevance for patients with acquired seizure disorders who are undergoing rehabilitation. However, further research is necessary within these populations, as they currently lack FDA-approved indications for cannabis-based therapies.

### C. Appetite stimulation in cachetic patients with HIV/AIDS and nausea management in chemotherapy-induced nausea and vomiting (CIMV): An FDA-approved indication

Currently, the FDA has approved use of medical cannabis for both CIMV and for cachexia in patients with HIV/AIDS.

Cameron A, et al., Arch Intern Med Res 2026
DOI:10.26502/aimr.0246

The approved dosage for anorexia due to AIDS is dronabinol, a synthetic THC cannabinoid, dosed at 2.5 mg orally twice daily, one hour before lunch and dinner, with max dose at 10 mg daily [40]. The pathophysiology is mediated by THC activating CB1 receptors in the mediobasal hypothalamus which attenuates the normal inhibitory signal to the hunger-promoting Agouti-Related Peptide (AgRP) neurons. Also, THC modulates the mesolimbic reward system and increases food-seeking behavior and meal frequency [41,42]. Further, clinical benefit stems from the fact that there is an absence of tachyphylaxis regarding the appetite-stimulating effects of cannabinoids on the ECS. This is reflected by clinical studies in people with AIDS, showing that appetite stimulation was sustained for up to 5 months with doses of 2.5mg-20mg/day [40]. Despite these findings, research shows no significant improvements in objective measures such as weight gain in this patient population, and research remains limited to whether appetite stimulation from medical cannabis leads to actual increased quality of life [43].

Regarding CINV, cannabinoids exert their antiemetic effects through CB1 receptors, activating the dorsal vagal complex within the brainstem which is responsible for controlling neurocircuitry involved in the emesis response. When bound to CB1 receptors, THC modulates the area postrema and the nucleus tractus solitarius found within the chemoreceptor trigger zone controlling the vomiting reflex [44]. Both the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) recommend dronabinol and nabilone synthetic cannabinoids but only if refractory to first and second-line antiemetics or as salvage therapy [23, 45,46]. The Cannabis CINV Phase II/III trial included 147 patients whose CINV did not improve despite receiving the standard guideline-recommended antiemetic treatment. The study found that 24% of patients receiving an adjunctive THC: CBD combination had a complete response, meaning no vomiting and no need for rescue medications for up to 120 hours, compared with only 8% having complete response in the placebo group receiving methylcellulose capsules [47]. When comparing medical cannabinoids to other treatments, a 2025 meta-analysis found that while cannabinoids were superior to placebo, there was no difference in efficacy when compared with active first-line treatments like prochlorperazine and chlorpromazine [48]. Furthermore, a cost-effectiveness analysis demonstrated that using medical cannabinoids in addition to standard antiemetic prophylaxis was less expensive and more effective than antiemetic prophylaxis alone, with a quoted mean total healthcare cost saving of $1,261 per patient in the patients who supplemented their CINV treatment with medical cannabis [49].

From a functional perspective, CINV directly affects participation in cancer rehabilitation by causing dehydration, electrolyte imbalances, nutritional depletion, and fatigue [50-54]. Thus, the role of the clinician in controlling CINV is critical and medical cannabinoids are valuable as an adjunct to standard first-line antiemetics for CINV.

### D. Sleep Regulation

Because most cannabis research focuses on pain, the strongest evidence for sleep improvement is found in patients with pain-related disorders, rather than primary sleep, neurological, or psychiatric conditions affecting sleep [55]. Evidence suggests that cannabinoids are associated with improvements in subjective sleep quality, particularly in individuals with insomnia [40]. A 2025 meta-analysis involving 6 RCTs showed that cannabinoids significantly improved subjective sleep quality compared to placebo in those with insomnia, with THC therapy being superior to CBD therapy [56]. While subjective reports of sleep quality have improved with medical cannabinoids, objective measures of sleep architecture show inconsistent findings. A meta-analysis involving cannabinoid therapy in mostly cannabis-naive subjects found negligible impact in objective measurements of sleep architecture such as sleep duration, latency, wake time, or sleep staging [1, 57].

Sleep disruption is common across rehabilitation populations, but research involving cannabinoids to manage sleep disturbances in patients with MS, TBI, and other chronic neurologic diseases is lacking. In MS spasticity trials sleep quality was a secondary outcome that consistently improved in treatment groups in those using nabiximols [58]. Tolerance and withdrawal effects further complicate use, potentially leading to disrupted sleep over time [43].

From a functional perspective, sleep is critical for recovery. While cannabinoids have been shown to have short-term self-reported benefits in sleep quality, their long-term role in sleep management remains uncertain. Clinicians must consider the potential for tolerance and more importantly possible withdrawal-related sleep disruption. Sleep disturbances were reported in 60% of those experiencing cannabis withdrawal, including disturbing dreams, REM rebound, and worsening insomnia. All of these factors may complicate successful rehabilitation [1, 58,59].

## V. Adverse Effects of Medical Cannabinoids and Rehabilitation Implications

### Va. Risk of dependence and strategies for the clinician

Cannabinoids are associated with a range of dose-dependent adverse effects, and these effects are particularly relevant in PM&R. Regarding rehabilitation, common adverse effects of medical cannabinoids include the risk of addiction in heavy users, cognitive impairment, sedation, anxiety, psychosis, impaired participation in rehabilitation therapy, and potential drug-drug interactions [22].

Cameron A, et al., Arch Intern Med Res 2026
DOI:10.26502/aimr.0246

Approximately 29% of people who use cannabis for medicinal purposes meet criteria for cannabis use disorder, defined as a problematic pattern of cannabis use causing clinically significant impairment or distress, defined by at least two symptoms within 12 months such as impaired control, increased cravings, continued use despite harm, tolerance, or withdrawal [59]. At higher doses, cannabis may also induce psychiatric symptoms including anxiety, panic attacks, paranoia, and hallucinations, which can further limit functional recovery. Chronic heavy use has been associated with cannabinoid hyperemesis syndrome (CHS), which is becoming increasingly recognized in the setting of rising commercial availability of medical cannabis. Characteristic features of CHS include cyclic nausea, vomiting, and abdominal pain [60].

To mitigate the risk of dependence, the American College of Physicians recommends clinicians exercise caution or avoid recommending cannabis in the following vulnerable populations: anyone under 25 years of age due to potential long-term cognitive effects and increased risk of psychosis; pregnant, breastfeeding individuals or individuals trying to conceive due to reproductive risks; those with underlying mental health or substance use disorders due to increased risk of psychosis and mania in susceptible populations; frail, elderly patients or any individual with an increased risk of sedation and falls; patients with current or past substance use disorder (Table 1) [61]. Clinicians should routinely incorporate screening for cannabis and other substance-use-related disorders and counsel patients on harm reduction strategies such as avoiding high-potency products and initiating therapy with products containing less than 10% THC concentration with equal or higher CBD content [1]. If the risks of continued use begin to outweigh the benefits, a gradual taper is recommended rather than abrupt cessation to minimize withdrawal symptoms [1].

**Table 1:** List of increased risks with caution or avoidance of Cannabis according to the American College of Physicians.

| Population | Increased Risks |
|---|---|
| Anyone under 25 years old | • Long term cognitive effects on the developing brain<br>• Increased risk of psychosis |
| Pregnant, breastfeeding individuals, or individuals trying to conceive | • Reproductive risks including preterm birth, small-for-gestational-age births, and increased perinatal mortality |
| Anyone with serious mental illness | • Risk of acute psychosis leading to hospitalization in genetically susceptible individuals<br>• Increased incidence of manic episodes in Bipolar I |
| Frail, elderly, or patients at increased risk of falling | • Fall risk due to increased sedation, dizziness, and postural hypotension |
| Patients with current or prior substance use disorder | • Cannabis use disorder |

### Vb. Neurocognitive and psychiatric effects

Cannabinoid use is associated with important neurocognitive and psychiatric adverse effects. High-potency cannabis has been linked to increased rates of psychosis (12.4% vs 7.1%) and generalized anxiety disorder (19.1% vs 11.6%) compared to low-potency formulations [22]. THC intoxication may impair verbal learning, working memory, executive functioning, and processing speed, which tend to be already compromised in patients undergoing rehabilitation, particularly those with traumatic brain injury. These effects raise concerns that cannabis use may hinder neuroplasticity, motor learning, and overall cognitive recovery, thereby limiting the effectiveness of rehabilitation interventions [12].

### Vc. Functional and safety implications in rehabilitation

The sedative and fatiguing effects of cannabinoids have direct implications for patient safety and rehabilitation outcomes. Sedation, dizziness, and fatigue can impair participation in therapy sessions and increase the risk of falls, especially in the elderly or those with neurologic impairments [22,61]. Additionally, cannabis is known to alter reaction time and increase the risk of harm when driving or operating heavy machinery [22].

To mitigate these risks, clinicians should counsel patients on harm reduction strategies. These strategies include avoiding concurrent use of cannabis with other central nervous system depressants such as alcohol, benzodiazepines, or barbiturates, using the lowest effective dose possible, and refraining from cannabis use during activities that require full cognitive and motor function [22].

### Vd. Drug-drug interactions

Cannabinoids may also pose risks through clinically significant drug–drug interactions. Preliminary evidence suggests that cannabinoids interact with hepatic cytochrome P450 enzyme systems and uridine

The 5’-diphospho-glucuronosyltransferase pathways, which are involved in the metabolism of many commonly prescribed medications [5]. As a result, cannabis use may alter serum levels of drugs such as warfarin, certain antiarrhythmics, sedatives, and anticonvulsants, potentially leading to toxic effects or reduced therapeutic efficacy [19]. Therefore, clinicians should exercise caution, especially in medically complex patients, when prescribing or recommending medical cannabis to those who rely on medications metabolized through these hepatic pathways.

## VI. Legal and Clinical Considerations

Conflicting state and federal classification of cannabis remains a major barrier to universal dosing standards, research efforts, and quality control of cannabis cultivation

Cameron A, et al., Arch Intern Med Res 2026
DOI:10.26502/aimr.0246

between state lines [6,9,10]. When recommending medical cannabis, clinicians must use appropriate clinical judgement and carefully adhere to institutional, state, and national guidelines.

Many clinicians report limited training and inadequate knowledge regarding medical cannabis due to minimal coverage in medical education, which can further complicate decision-making [7]. Clinicians must also account for communication barriers, as patients may underreport cannabis use due to stigma, potentially leading to incomplete clinical assessments [22].

Pharmacokinetics also play an important role in clinical use. Oral formulations have a longer duration of action, typically lasting 5 to 12 hours, and lower bioavailability due to first-pass metabolism, increasing the risk of unintentional overconsumption and prolonged adverse effects [15,59-61]. Dosing should be carefully timed to avoid peak impairment during rehabilitation therapy sessions. Safety considerations are critical, particularly in vulnerable populations. Patients at increased risk of falls or frailty should be counseled that the harms of cannabis, including central nervous system depression and impaired coordination, may outweigh potential benefits [22].

Screening for substance use disorder is recommended prior to initiation, with tools such as the CAGE-AID questionnaire, along with consideration of urine drug screening (UDS) and prescription drug monitoring program (PDMP) review [22]. Furthermore, clinicians should advise patients to avoid unregulated cannabis products due to risks of contamination, adulteration, and inconsistent potency [22]. Inhaled forms should also be discouraged, as the American College of Physicians recommends against their use due to increased respiratory risks, including chronic bronchitis and wheezing [1].

## VII. Gaps in Knowledge and Future Directions

● Significant gaps remain in medical cannabis research. These include: (i) Limited high-quality randomized controlled trials with larger sample size and longer follow-ups with the assessment of functional outcomes, (ii) Lack of standardized dosing protocols and product consistency, (iii) Insufficient long-term functional outcome data relevant to rehabilitation, (iv) Need for PM&R-specific studies focusing on function, independence, participation, and quality of life, and (v) Need for comparative effectiveness studies assessing standard rehabilitation medications and therapies to define the underlying mechanisms of action of cannabinoids in rehabilitation, and the role of cannabis in clinical practice.

## VIII. Clinical Takeaways

1. Cannabis has limited, condition-specific evidence in non-pain uses, with the strongest support for CBD in certain seizure disorders and THC-based agents for refractory chemotherapy-induced nausea and vomiting.
2. Most benefits are symptomatic, not functional. Reported improvements in spasticity, nausea, appetite, or sleep do not consistently translate into clinically meaningful gains in independence, mobility, or rehabilitation outcomes.
3. There is no standardized dosing or formulation, and wide variability in THC/CBD content, delivery methods, and product labeling makes consistent prescribing and titration difficult.
4. Cannabis can interfere with rehabilitation, particularly through cognitive impairment, sedation, impaired motor learning, reduced attention, and increased fall risk, all of which may negatively impact therapy participation.
5. Use requires careful patient selection and monitoring, including regular screening for substance use disorders and contraindications, awareness of drug interactions, and counseling on risks, as benefits are modest and often limited to symptom control rather than functional restoration.
6. Careful risk assessment, along with medical cannabis education for clinicians, are essential when considering medical cannabis in rehabilitation settings.

## IX. Conclusion

Medical cannabis represents a promising but complex therapeutic modality within PM&R. While evidence supports its use in certain non-pain conditions, benefits are largely symptom-based and do not consistently translate into functional improvement. Given the central importance of function in rehabilitation, future research must prioritize outcomes that reflect independence, mobility, and quality of life. Medical cannabis may serve as an adjunctive tool in carefully selected patients, but its role in rehabilitation remains to be fully explored.

## X. Key Points and Findings

- **Cannabis is a complex, Schedule I substance** with legal, educational, and systemic barriers to prescribing. Federal–state regulatory conflict limits prescribing, standardization, and research. Clinician knowledge gaps and limited training, along with patient stigma and underreporting, complicate clinical use.
- **Administration, formulations, and dosing are highly variable,** with multiple routes (inhaled, oral, etc.) that differ in the onset and duration.
- **High-quality evidence for non-pain uses is strongest in select conditions but overall limited.** The highest quality evidence supports cannabinoids for certain refractory

pediatric seizure disorders. Conditions for which cannabis has provided the most supportive care in the literature are for anti-seizure therapy and anti-emetic therapy as seen in chemotherapy induced nausea and vomiting.

- **Clinical benefits are generally symptom-focused rather than function-driven.** Reported improvements are seen in spasticity, seizures, nausea, appetite, and subjective sleep quality, but there is less research that explores whether these benefits translate to meaningful functional gains such as improved independence, mobility, or rehabilitation participation.
- **Rehabilitation-specific outcomes are under-studied:** There is limited data on activities of daily living, return to work, caregiver burden, and objective functional measures. Some quality-of-life improvements are reported, but functional recovery remains largely underexplored, indicating the need for further research
- **Cannabis may negatively impact rehabilitation when misused or poorly timed.**
- **Adverse effects and risks,** including cognitive impairment, anxiety, psychosis risk, sedation, fall risk, cannabinoid hyperemesis syndrome, and potential for cannabis use disorder, are significant and dose dependent.
- **Drug-drug interactions (via CYP450 pathways) and contraindications** (e.g., pregnancy, psychiatric illness, frailty) must be considered.

## Funding

The research work of DKA is supported by the R25AI179582 grant from the National Institutes of Health, USA. The contents of this research article are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

## Competing interests

All authors have read the manuscript and declare no conflict of interest. No writing assistance was utilized in the production of this manuscript.

## Consent for publication

All authors have read the manuscript and consented for publication.

## References

1. Gorelick DA. Cannabis-Related Disorders and Toxic Effects. N Engl J Med. 389 (24): 2267-2275.
2. Page RL 2nd, Allen LA, Kloner RA, et al.; American Heart Association Clinical Pharmacology Committee and Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Basic Cardiovascular Sciences; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Lifestyle and Cardiometabolic Health; and Council on Quality of Care and Outcomes Research. Medical Marijuana, Recreational Cannabis, and Cardiovascular Health: A Scientific Statement From the American Heart Association. Circulation 142 (2020): e131-e152.
3. Dos Santos RG, Hallak JEC, Crippa JAS. Neuropharmacological Effects of the Main Phytocannabinoids: A Narrative Review. Adv Exp Med Biol 1264 (2021): 29-45.
4. Aabedi A, Masiach D, Agrawal DK. Muscular Dystrophy Muscle Preservation: A Comparative Systematic Review of Exercise and Cannabidiol (CBD) Interventions. J Biotechnol Biomed 9 (2026): 77-83.
5. Testai FD, Gorelick PB, Aparicio HJ, et al.; American Heart Association Stroke Brain Health Science Subcommittee of the Stroke Council; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Lifestyle and Cardiometabolic Health; and Council on Peripheral Vascular Disease. Use of Marijuana: Effect on Brain Health: A Scientific Statement From the American Heart Association. Stroke 53 (2022): e176-e187.
6. National Conference of State Legislatures. State Medical Marijuana Laws. Available at: https://www.ncsl.org/research/health/state-medicalmarijuana-laws.aspx.
7. Zolotov Y, Mendoza Temple L, et al. Developing Medical Cannabis Competencies: A Consensus Statement. JAMA Netw Open 8 (2025): e2535049.
8. Rhee TG, Rosenheck RA. Increasing Use of Cannabis for Medical Purposes Among U.S. Residents, 2013-2020. Am J Prev Med. 2023 Sep; 65 (3): 528-533.
9. Quader ZS, Roehler DR, Vivolo-Kantor AM, Ko JY. Routes of Marijuana Use - Behavioral Risk Factor Surveillance System, 22 U.S. States and Two Territories, 2022. MMWR Morb Mortal Wkly Rep. 74 (2025): 198-204. Erratum in: MMWR Morb Mortal Wkly Rep. 74 (2025): 256.
10. Hammond D. Communicating THC levels and 'dose' to consumers: Implications for product labelling and packaging of cannabis products in regulated markets. Int J Drug Policy. 91 (2021): 102509.
11. Schwabe AL, Johnson V, Harrelson J, et al. Uncomfortably high: Testing reveals inflated THC potency on retail Cannabis labels. PLoS One. 18 (2023): e0282396.
12. Kansagara D, Terry GE, Ayers CK, et al. Cannabis and Mental Health: A Review. JAMA Intern Med 186 (2026): 618-628.

Cameron A, et al., Arch Intern Med Res 2026
DOI:10.26502/aimr.0246

13. Prashad S, Paek AY, Fournier LR. Longer chronic cannabis use in humans is associated with impaired implicit motor learning and supranormal resting state cortical activity. PLoS One. 21 (2026): e0338082.

14. Bolbecker AR, Apthorp D, Martin AS, et al. Disturbances of postural sway components in cannabis users. Drug Alcohol Depend. 2018 Sep 1; 190 (2018): 54-61.

15. Volkow ND, Swanson JM, Evins AE, et al. Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review. JAMA Psychiatry. 73 (2016): 292-297.

16. Slawek DE, Zhang C, Dahmer S, et al. Medical Cannabis and Opioid Receipt Among Adults With Chronic Pain. JAMA Intern Med. 186 (2026): 252-261.

17. Wang L, Hong PJ, May C, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. BMJ. 374 (2021): n1034.

18. Kilaru A, Chapman KD. The endocannabinoid system. Essays Biochem. 64 (2020): 485-499.

19. Page RL, Allen LA, Kloner RA, et al.; on behalf of the American Heart Association Clinical Pharmacology Committee and Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Basic Cardiovascular Sciences; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Lifestyle and Cardiometabolic Health; and Council on Quality of Care and Outcomes Research. Medical marijuana, recreational cannabis, and cardiovascular health: a scientific statement from the American Heart Association. Circulation. 142 (2020): e131-e152.

20. Lu HC, Mackie K. An Introduction to the Endogenous Cannabinoid System. Biol Psychiatry. 79 (2016): 516-525.

21. Boehnke KF, Sinclair R, Gordon F, et al. Trends in U.S. Medical Cannabis Registrations, Authorizing Clinicians, and Reasons for Use From 2020 to 2022. Ann Intern Med 177 (2024): 458-466.

22. Hsu M, Shah A, Jordan A, et al. Therapeutic Use of Cannabis and Cannabinoids: A Review. JAMA. 335 (2026): 345-359.

23. Verduzco-Gutierrez M, Raghavan P, Pruente J, et al. AAPM&R consensus guidance on spasticity assessment and management. PM&R. 16 (2024): 864-887.

24. Filippini G, Minozzi S, Borrelli F, et al. Cannabis and cannabinoids for symptomatic treatment for people with multiple sclerosis. Cochrane Database Syst Rev. 5 (2022): CD013444.

25. AlHabil Y, Saadeddin L, Ishkirat H, et al. Assessing the Role of Cannabis in Managing Spasticity in Multiple Sclerosis: A Systematic Review and Meta-Analysis. Clin Ther. 48 (2026): 13-21.

26. Nabata KJ, Tse EK, Nightingale TE, et al. The Therapeutic Potential and Usage Patterns of Cannabinoids in People with Spinal Cord Injuries: A Systematic Review. Curr Neuropharmacol 19 (2021): 402-432.

27. Marinelli L, Puce L, Mori L, et al. Cannabinoid Effect and Safety in Spasticity Following Stroke: A Double-Blind Randomized Placebo-Controlled Study. Front Neurol 13 (2022): 892165.

28. Nastatos XL, Schubert EA, Wheate NJ. Investigating the effectiveness and adverse events of medicinal cannabis for patients with muscle spasticity or spasms. J Pharmacol Exp Ther. 393 (2026): 103780.

29. FDA Orange Book. https://www.deadiversion.usdoj.gov/schedules/orangebook/orangebook.pdf

30. Miller I, Scheffer IE, Gunning B, et al; GWPCARE2 Study Group. Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial. JAMA Neurol. 77 (2020): 613-621.

31. Devinsky O, Patel AD, Cross JH, et al. ; GWPCARE3 Study Group. Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. N Engl J Med. 378 (2018): 1888-1897.

32. Thiele EA, Marsh ED, French JA, et al.; GWPCARE4 Study Group. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 391 (2018): 1085-1096.

33. Thiele EA, Bebin EM, Bhathal H, et al; GWPCARE6 Study Group. Add-on Cannabidiol Treatment for Drug-Resistant Seizures in Tuberous Sclerosis Complex: A Placebo-Controlled Randomized Clinical Trial. JAMA Neurol. 78 (2021): 285-292.

34. Oikonomou P, Jost WH. Randomized controlled trials on the use of cannabis-based medicines in movement disorders: a systematic review. J Neural Transm (Vienna). 129 (2022): 1247-1256.

35. Aladeen TS, Mattle AG, Zelen K, et al. Medical Cannabis in the Treatment of Parkinson's Disease. Clin Neuropharmacol. 46 (2023): 98-104.

36. Lins BR, Anyaegbu CC, Hellewell SC, et al. Cannabinoids in traumatic brain injury and related neuropathologies: preclinical and clinical research on endogenous, plant-derived, and synthetic compounds. J Neuroinflammation. 20 (2023): 77.

Cameron A, et al., Arch Intern Med Res 2026
DOI:10.26502/aimr.0246

37. Saulino PA, Greenwald BD, Gordon DJ. The changing landscape of the use of medical marijuana after traumatic brain injury: a narrative review. Brain Inj. 35 (2021): 1510-1520.

38. Bravo-Ferrer I, Cuartero MI, Zarruk JG, et al. Cannabinoid Type-2 Receptor Drives Neurogenesis and Improves Functional Outcome After Stroke. Stroke. 48 (2017): 204-212.

39. Szaflarski JP, Szaflarski M. Traumatic Brain Injury Outcomes After Recreational Cannabis Use. Neuropsychiatr Dis Treat. 20 (2024): 809-821.

40. Dronabinol. FDA Drug Label. Food and Drug Administration. Updated date: 2023-01-19.

41. Wheeler EC, Choi P, De Howitt J, et al. Cannabis Sativa targets mediobasal hypothalamic neurons to stimulate appetite. Sci Rep. 13 (2023): 22970.

42. Lau BK, Cota D, Cristino L, et al. Endocannabinoid modulation of homeostatic and non-homeostatic feeding circuits. Neuropharmacology. 124 (2017): 38-51.

43. Simon L, Baldwin C, Kalea AZ, et al. Cannabinoid interventions for improving cachexia outcomes in cancer: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle. 13 (2022): 23-41.

44. Van Sickle MD, Oland LD, Ho W, et al. Cannabinoids inhibit emesis through CB1 receptors in the brainstem of the ferret. Gastroenterology. 121 (2001): 767-774.

45. Braun IM, Bohlke K, Abrams DI, et al. Cannabis and Cannabinoids in Adults With Cancer: ASCO Guideline. J Clin Oncol. 42 (2024): 1575-1593.

46. Antiemesis. National Comprehensive Cancer Network. Updated 2025-05-12.

47. Grimison P, Mersiades A, Kirby A, et al. Oral Cannabis Extract for Secondary Prevention of Chemotherapy-Induced Nausea and Vomiting: Final Results of a Randomized, Placebo-Controlled, Phase II/III Trial. J Clin Oncol. 42 (2024): 4040-4050.

48. Chow R, Basu A, Kaur J, et al. Efficacy of cannabinoids for the prophylaxis of chemotherapy-induced nausea and vomiting-a systematic review and meta-analysis. Support Care Cancer. 33 (2025): 193.

49. Grimison P, Mersiades A, Kirby A, et al. Oral Cannabis Extract for Secondary Prevention of Chemotherapy-Induced Nausea and Vomiting: Final Results of a Randomized, Placebo-Controlled, Phase II/III Trial. J Clin Oncol. 42 (2024): 4040-4050.

50. Walker R, Dias S, Phillips RS. Antiemetic medications for preventing chemotherapy-induced nausea and vomiting in children: a systematic review and Bayesian network meta-analysis. Support Care Cancer. 32 (2024): 747.

51. Piechotta V, Adams A, Haque M, et al. Antiemetics for adults for prevention of nausea and vomiting caused by moderately or highly emetogenic chemotherapy: a network meta-analysis. Cochrane Database Syst Rev. 11 (2021): CD012775.

52. Antiemesis. National Comprehensive Cancer Network. Updated 2026-04-03.

53. Verzicco I, Regolisti G, Quaini F, et al. Electrolyte Disorders Induced by Antineoplastic Drugs. Front Oncol. 10 (2020): 779.

54. Encinosa W, Davidoff AJ. Changes in Antiemetic Overuse in Response to Choosing Wisely Recommendations. JAMA Oncol. 3 (2017): 320-326.

55. Velzeboer R, Malas A, Boerkoel P, et al. Cannabis dosing and administration for sleep: a systematic review. Sleep. 2022 Nov 9;45(11):zsac218. doi: 10.1093/sleep/zsac218. Erratum in: Sleep. 46 (2023): zsad008.

56. da Silva GHS, Barbosa EC, de Lima FR, et al. Effectiveness of cannabinoids on subjective sleep quality in people with and without insomnia or poor sleep: A systematic review and meta-analysis of randomised studies. Sleep Med Rev. 84 (2025): 102156.

57. Velzeboer R, Malas A, Wei S, et al. Cannabis and sleep architecture: A systematic review and meta-analysis. Sleep Med Rev. 84 (2025): 102164.

58. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 2015 Jun 23-30; 313 (24): 2456-2473. Erratum in: JAMA. 2015 Aug 4;314(5):520. Erratum in: JAMA. 2015 Aug 25;314(8):837. Erratum in: JAMA. 2015 Dec 1;314(21):2308. Erratum in: JAMA. 2016 Apr 12; 315 (14): 1522.

59. Jeste DV, Lieberman JA, Fassler D et al.: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR). Edited by the American Psychiatric Association (2022). https://doi.org/10.1176/appi.books.9780890425787.

60. Rubio-Tapia A, McCallum R, Camilleri M. AGA Clinical Practice Update on Diagnosis and Management of Cannabinoid Hyperemesis Syndrome: Commentary. Gastroenterology. 166 (2024): 930-934.e1.

61. Kansagara D, Hill KP, Yost J, et al.; Population Health and Medical Science Committee of the American College of Physicians; Dunn AS, Jackson CD, Jokela JA, Lee RA, Mackey K, Saini SD, Tschanz MP, Wilt TJ, Etxeandia-Ikobaltzeta I, Shamliyan T, Vigna C. Cannabis or

Cannabinoids for the Management of Chronic Noncancer Pain: Best Practice Advice From the American College of Physicians. Ann Intern Med. 2025 May; 178 (2025): 714-724.



**Citation:** Andrew Cameron, Marcel P. Fraix, Devendra K. Agrawal. Therapeutic Use of Medical Cannabis Beyond Pain Management in Physical Medicine and Rehabilitation. Archives of Internal Medicine Research 9 (2026): 156-167.