

Dosing Strategies for Medical Cannabis

A commentary on MacCallum CA, et al. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med. 2018;49:12-19.

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The key takeaway from the review article by MacCallum and Russo¹ is that there is a space for cannabis in medicine, but more training and educational opportunities are needed. Although cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) are well known, many other cannabinoids that contribute to the benefits of cannabis are being discovered daily. Starting with a low dosage is always the best approach, and the dosage can be titrated up as provider and patients feel more comfortable. Qualifying sources for patients is absolutely imperative to avoid any setbacks with new therapies being introduced into regimens.

Introduction

The article begins with a brief history of cannabis and its different uses through hundreds of years, dating back to 1840. The endocannabinoid system is a relatively recent discovery, and education around cannabis has been limited. As the review authors note, survey findings show that 89.5% of medical residents and fellows do not feel prepared to prescribe cannabis-based products (like the FDA-approved agent nabiximols), and only 9% of US medical schools cover clinical cannabis in their curricula.²

It is well known that double-blind and controlled studies of cannabis are lacking, and the authors, therefore, suggest the use of individual patient case studies to begin accumulating evidence-based data. MacCallum and Russo suggest that all cannabis-based products come from facilities that are Good Agricultural Practice (GAP) certified and extracted under certified Good Manufacturing Practice (GMP). Additionally, consumers should be provided with full access to information highlighting the cannabinoid and terpene profile as well as confirmation of absence

of heavy metals, pesticides, and other contaminants, the authors wrote.

Mechanism of Action

A brief pharmacology review in the article underlines the strong phytocannabinoid presence in cannabis, particularly within the unfertilized female flowers. THC is, of course, known for its psychoactive effects and is a weak partial agonist of CB₁ and CB₂ receptors. Evidence suggests that THC has effects on pain, appetite, digestion, emotions, and mental health.^{3,4} Depending on the dose, it can have euphoric effects through its psychoactivity.

CBD, on the other hand, actually has a low affinity for the CB₁ and CB₂ receptors directly, but has pharmacologic effects on other families of receptors, including 5-HT_{1A} and adenosine A_{2A}. CBD is also known for its activity in nonreceptor mechanisms, which has led to positive effects on pain, inflammation, anxiety, and mental health.^{4,5}

Cannabis comes in thousands of different “chemovars,” which can vary in different phytocannabinoid profiles, the review authors noted. This phytocannabinoid diversity is what can lead to different portfolios of benefits, and ideally reduce the need for prescription drugs.

Pharmacokinetics

Absorption of cannabis-based products is variable and depends on the products’ lipophilicity, bioavailability, and organ tissue differences, according to MacCallum and Russo. Cannabinoids are lipophilic and are best absorbed in the presence of fats, oils, and polar solvents both topically and orally. Recent meals, depth of inhalation, and temperature can affect absorption both orally (20%–30%) and in inhalation (10%–60%).⁶

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Table. Efficacy of Cannabis-Based Treatment in Various Conditions

Level of evidence	Benefits
Conclusive/Substantial	<ul style="list-style-type: none"> • Adult chronic pain • MS spasticity • Chemotherapy-induced nausea and vomiting • Seizures in Dravet and Lennox-Gastaut syndromes (CBD)
Moderate evidence	<ul style="list-style-type: none"> • Sleep disturbance from chronic pain, MS, fibromyalgia, obstructive sleep apnea • Decreasing intraocular pressure in glaucoma
Limited evidence	<ul style="list-style-type: none"> • Symptoms of dementia • Symptoms of Parkinson’s disease • Schizophrenia • PTSD • Appetite and decreasing weight loss associated with HIV/AIDS • MS spasticity • Anxiety (CBD) • Tourette syndrome • Depressive symptoms in patients with chronic pain or MS
Insufficient evidence	<ul style="list-style-type: none"> • Addiction abstinence • IBS • Cancer • Lateral sclerosis • Chorea • Dystonia

CBD, cannabidiol; **IBS**, irritable bowel syndrome; **MS**, multiple sclerosis; **PTSD**, post-traumatic stress disorder.

Table adapted from MacCallum et al.¹

low and go slow. Other recommendations from MacCallum and Russo include the following:

- Inhalation should be spaced in 15-minute intervals until desired symptom control is achieved
- Higher THC concentrations generally allow for lower dosage amounts
- THC-mediated side effects are better controlled when starting with a lower dose
- Medical cannabis patients prefer chemovars with lower THC to gain full symptom control with the least amount of adverse events
- Long-acting, oral preparations are better received for chronic conditions
- Vaporization can be used as an add-on therapy as needed for symptom exacerbation
- Physicians must clearly communicate potential risks and safety considerations of cannabis
- Patients must keep a symptom inventory chart to

document response and efficacy

- THC oral preparation should be uptitrated starting at 2.5 mg once daily in the first 2 days and then twice daily on days 3 and 4; uptitrated to 15 mg THC-equivalent daily over 3 doses in 1 day as needed

Cannabis should not be used in patients who are pregnant or nursing, the authors noted. It has a relatively good safety profile overall, with no reported deaths due to overdose. THC side effects can be controlled with low dosing and are further controlled in CBD and THC combinations. The most commonly reported side effects of cannabis-based medications include the following:

- Drowsiness
- Anxiety
- Dizziness
- Nausea
- Dry mouth
- Cognitive effects
- Cough

The article briefly mentions drug interactions and that cannabis is metabolized by cytochrome P450: 2C9, 2C19,

and 3A4, yet there seems to be no drugs that have been reported specifically as contraindicated, with the exception of concomitant treatment with clobazam.⁷ Patients should be followed every 1 to 6 months, depending on their familiarity with cannabis.

The authors presented levels of efficacy of cannabis-based treatment in various conditions (Table 1). The authors also highlighted the following special cases in which cannabis has shown efficacy.

- Epilepsy: CBD shows anticonvulsant properties, as Epidiolex is an FDA-approved medication
- Cancer: THC has accumulating data supporting its use in cancer and diverse phytocannabinoid preparations can help with malignancies
- Pain: Strong data has accumulated to support the use of cannabis in chronic pain
- Geriatrics: THC can treat agitation in dementia
- Parkinson's disease: CB₁ saturation in the basal ganglia can be supportive
- Pediatrics: Data is building to support the use of CBD in mental health
- Opioid: Cannabis may be helpful for patients with chronic pain who are tapering off opioids

Furthermore, the authors presented tables delineating administration factors in various cannabis delivery methods as well as routes of administration.

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—Cobin Kakar, PharmD, MBA

Commentary

This review article is a good introduction to cannabis and its forms of administration in the medical setting. However, it lacks strong data to support the claims and disease states that are mentioned. The dosing guidance is general and hard to follow without a clear description of specific products available. Clinicians can benefit from education on the effects of specific products (as opposed to general cannabinoid formulations) on specific symptoms. As the science advances, clinicians could further benefit from the

Clinical Takeaways

- Cannabis education is in severe shortage in the US medical field, and must be qualified from advanced professionals familiar in the space
- THC- and CBD-dominant formulations can be effective in symptom control if managed carefully
- Cultivation, extraction, manufacturing, and packaging of sources must always be verified to assure a safe cannabis-based product
- Data is accumulating to support the use of cannabis in epilepsy, stress, anxiety, PTSD, pain, inflammation, and cancer
- Dosing should always start low and titrate up slowly
- Routes of administration include inhalation, oral, oromucosal, and topical

ability to match chemovars to diseases and prescribe/advise accordingly.

I agree with MacCallum and Russo's belief that cannabis can be an effective alternative to prescription drugs. THC formulations should be dosed low and slow to control any risk for adverse events. The most effective formulations combine a variety of cannabinoids, addressing different receptors and mechanisms that can achieve relief.

In addition, a key aspect of the cannabis market that is overlooked is the qualification of material. All plants should be organically grown with no presence of contaminants. Finished products should be created under stringent quality guidelines and facilities must have all certifications in place.

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