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Review Article

Practical considerations in medical cannabis administration and dosing

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ABSTRACT

Cannabis has been employed medicinally throughout history, but its recent legal prohibition, biochemical complexity and variability, quality control issues, previous dearth of appropriately powered randomised controlled trials, and lack of pertinent education have conspired to leave clinicians in the dark as to how to advise patients pursuing such treatment. With the advent of pharmaceutical cannabis-based medicines (Sativex/nabiximols and Epidiolex), and liberalisation of access in certain nations, this ignorance of cannabis pharmacology and therapeutics has become untenable. In this article, the authors endeavour to present concise data on cannabis pharmacology related to tetrahydrocannabinol (THC), cannabidiol (CBD) et al., methods of administration (smoking, vaporisation, oral), and dosing recommendations. Adverse events of cannabis medicine pertain primarily to THC, whose total daily dose-equivalent should generally be limited to 30 mg/day or less, preferably in conjunction with CBD, to avoid psychoactive sequelae and development of tolerance. CBD, in contrast to THC, is less potent, and may require much higher doses for its adjunctive benefits on pain, inflammation, and attenuation of THC-associated anxiety and tachycardia. Dose initiation should commence at modest levels, and titration of any cannabis preparation should be undertaken slowly over a period of as much as two weeks. Suggestions are offered on cannabis-drug interactions, patient monitoring, and standards of care, while special cases for cannabis therapeutics are addressed: epilepsy, cancer palliation and primary treatment, chronic pain, use in the elderly, Parkinson disease, paediatrics, with concomitant opioids, and in relation to driving and hazardous activities.

1. Introduction

Cannabis has a history of medical application likely exceeding that of the written word, including mainstream usage in Europe and North America for a century between 1840 and 1940 [1,2]. It is only in the last century that quality control issues, the lack of a defined chemistry, and above all, politically and ideologically motivated prohibition relegated it *planta non grata*. The discovery and elucidation of the endocannabinoid system [3], coupled with a popular tidal wave of anecdotal accounts and renaissance of therapeutic clinical trials renders that *status quo ante* untenable.

One preparation, Sativex® (USAN: nabiximols), an oromucosal cannabis-based medicine with 2.7 mg of THC and 2.5 mg CBD plus terpenoids per spray has attained regulatory approval in 29 countries for treatment of spasticity in multiple sclerosis, having met the standards of safety, efficacy and consistency required of any pharmaceutical. The problem for physicians with respect to treatment with herbal cannabis remains acute, however: How does the responsible healer and medical scientist approach the desperate patient for whom conventional medicine has failed and wishes to avail themselves of a purportedly healing herb that has been an international societal outlaw for decades? The answer is simple: educational and scientific standards apply to the cannabis controversy equally with that of any other putative therapy.

Unfortunately, physicians of the world remain profoundly uneducated with respect to cannabis and the endocannabinoid system (ECS) that underlies much of its activity. A recent USA study [4] documented that 89.5% of surveyed residents and fellows felt unprepared to prescribe, while only 35.3% even felt ready to answer cannabis questions. Additionally, only 9% of American medical schools

Abbreviations: 5-HT_{1A}, serotonin 1A receptor; AE, adverse events; AIDS, acquired immunodeficiency syndrome; CB_1, cannabinoid-one receptor; CB_2, cannabinoid-two receptor; CBD, cannabidiol; CBDA, cannabidiolic acid; CRISP-R, Clustered Regularly Interspaced Short Palindromic Repeats; ECS, endocannabinoid system; GAP, Good Agricultural Practice; GCP, Good Clinical Practice; GMP, Good Manufacturing Practice; HIV, human immunodeficiency virus; MS, multiple sclerosis; PAH, polycyclic aromatic hydrocarbon; RCT, randomised controlled trial; THC, Δ^9-tetrahydrocannabinol; THCA, tetrahydrocannabinolic acid; TRPV1, transient receptor potential cation channel vanilloid subfamily receptor 1; USAN, United States Adopted Name

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documented pertinent clinical cannabis content in their curricula.

While it remains a common complaint that cannabis therapeutics lacks adequate documentation, according to a recent publication [5], scientist and clinicians are recognising the limitations of randomised controlled studies in their generalisability to populations vs. customisation of best evidence based practices for individual patients. Individualized evidence based medicine may be delivered to a patient using an N-of-1, or single clinical trial, whereby the patient is the sole unit of observation for efficacy and side effects of various interventions. This method can be applied to a medical cannabis patient to find an optimal intervention or "sweet spot" combination of plant varieties and dosage forms that provide superior symptom control.

In this article, two experienced clinicians, internist and neurologist, respectively, offer their review of the literature and personal observations that might serve as an initial guide to suggested Good Clinical Practice (GCP) as applied to cannabis. These include our opinion that cannabis medicines, whether prescription or over-the-counter, should be ideally cultivated organically according to Mendelian selective breeding techniques without the necessity of genetic modification or CRISPR technology according to Good Agricultural Practice (GAP), be extracted and processed under Good Manufacturing Practice (GMP) [6], and be made available to consumers with full information as to cannabinoid and terpenoid profiles, and certification that the material is free of pesticide [7], microbial or heavy metal contamination.

2. Cannabis pharmacology in brief

Cannabis produces phytocannabinoids (plant cannabinoids) in greatest abundance in the unfertilised female flowers in acid form, most abundantly tetrahydrocannabinolic acid-A (THCA-A) and cannabidiolic acid (CBDA), which are most frequently utilised after heating either by smoking, vaporisation, or baking in confections to produce decarboxylation of the more familiar neutral cannabinoids, tetrahydrocannabinol (THC) and cannabidiol (CBD) (see graphical abstract) [8].

THC is the primary psychoactive component of cannabis, working primarily as a weak partial agonist on CB_1 and CB_2 receptors with well-known effects on pain, appetite, digestion, emotions and thought processes mediated through the endocannabinoid system, a homeostatic regulator of myriad physiological functions [9], found in all chordates. THC can cause psychoactive adverse events depending on dose and patient previous tolerance. Its use is applicable for many symptoms and conditions including; pain, nausea, spasticity/spasms, appetite stimulation, anxiety, depression, post-traumatic stress disorder (PTSD), insomnia et al.

CBD, in contrast, has little affinity for these receptors directly, but rather is a negative allosteric modulator of CB_1 [10], with protean pharmacological effects on various other receptor systems including TRPV1, 5-HT_{1A}, adenosine A2A and non-receptor mechanisms (reviewed [11]), productive of analgesic, anti-inflammatory, anti-anxiety, and anti-psychotic effects among many others. CBD is non-intoxicating, and has been shown to help with similar symptoms, with added benefit as an anticonvulsant, anti-psychotic, neuroprotectant, and anti-inflammatory (including autoimmune conditions). Cannabis is a multimodal treatment. It can be used to treat multiple symptoms and conditions concurrently, which can therefore help to reduce polypharmacy burden.

There are thousands of individual cannabis types, which patients and purveyors may erroneously refer to as 'strains', whereas the preferred term is chemical variety or 'chemovar' [12]. Each chemovar contains varying concentrations of cannabinoids and other components with important pharmacological and modulatory effects include the monoterpenoids [8,11] myrcene (analgesic, sedating), limonene (antidepressant and immune-stimulating), pinene (acetylcholinesterase inhibitor alleviating short-term memory impairment from THC) and the sesquiterpenoid beta-caryophyllene (anti-inflammatory analgesic and selective full agonist at the CB_2 receptor). The relative proportions of these and other components are the primary determinants of the pharmacological effects and adverse events associated with a particular cannabis chemovar, and is critical information that should be available to patients and physicians recommending such treatment. Until recent years, the vast majority of chemovars in Europe [13] and North America [14] were THC-predominant (Type I cannabis). Contemporaneously, there has been greater interest in mixed THC:CBD (Type II) and CBD-predominant (Type III cannabis) chemovars with broader mechanisms of action and improved therapeutic indexes [12].

The acid cannabinoids have received much less research interest, but possess fascinating pharmacological properties. THCA has been noted to produce anti-inflammatory effects via antagonism of tumour necrosis factor-alpha (TNF-α) [15], to be a strong anti-emetic [16] and was recently demonstrated to be an agonist of the PPAR-γ nuclear receptor with neuroprotective effects [17], as well as anticonvulsant efficacy [18]. CBDA is also a powerful anti-emetic [19] and anti-anxiety agent [20] in rodents, and both acid cannabinoids have prominent anecdotal reports of benefit on skin and other tumors.

3. Pharmacokinetic considerations

Absorption, distribution, and metabolism determine the onset and duration of action of each dosage form. Absorption has the most variability, and is affected by product lipophilicity, bioavailability as well as the inherent organ tissue differences (i.e., alveolar, dermal vs. gastric). Cannabinoids are lipophilic and have low water solubility. Therefore, for topical or oral routes, they are best absorbed in the presence of fat, oils or polar solvents, such as ethanol. There is suggestion that newer technology such as using nano- or ionized particles or the use omega fats in carrier oil can enhance absorption; or for topicals preparations, using ingredients to mildly disrupt the skin barrier may allow greater absorption of active ingredient. Factors such as recent meals, depth of inhalation, duration of breath holding, temperature of vaporizer all affect cannabis absorption, which can vary from 20%–30% orally, up to 10–60% for inhalation [21]. Clinicians will benefit from an understanding of these factors to prescribe or recommend cannabis to enable estimation of a target quantity of dried product for their patients. See Dosing strategies and clinical pearls section for more details.

4. Modes of administration

This information is summarised (Table 1, Table 2) [7,21–27].

5. Therapeutic uses

Cannabis can be a useful tool in the treatment of many complex diseases or rare conditions which lack effective conventional therapeutic options, or where the side effects burden of such treatments outweigh the benefits, for example, central sensitivity syndromes (fibromyalgia, chronic fatigue syndrome, migraines, irritable bowel), or multiple sclerosis, neuropathic pain, and refractory nausea. An assessment of current evidence in various indications is summarised (Table 3) [28–33].

6. Dosing strategies and clinical pearls

- There is insufficient evidence to support the necessity of a trial of synthetic cannabinoids prior to initiating cannabis-based medicine treatment, unless legal availability is not an option.
- General approach to cannabis initiation is 'start low, go slow, and stay low'.
- For cannabis inhalation, patients should start with 1 inhalation and wait 15 min. Then, they may increase by 1 inhalation every 15–30 min until desired symptom control has been achieved.